Large Vessel Occlusion Scales Increase Delivery to Endovascular Centers Without Excessive Harm From Misclassifications

Henry Zhao, MBBS; Skye Coote, MN; Lauren Pesavento, BN; Leonid Churilov, PhD; Helen M. Dewey, PhD; Stephen M. Davis, MD; Bruce C.V. Campbell, PhD

Background and Purpose—Clinical large vessel occlusion (LVO) triage scales were developed to identify and bypass LVO to endovascular centers. However, there are concerns that scale misclassification of patients may cause excessive harm. We studied the settings where misclassifications were likely to occur and the consequences of these misclassifications in a representative stroke population.

Methods—Prospective data were collected from consecutive ambulance-initiated stroke alerts at 2 stroke centers, with patients stratified into typical (LVO with predefined severe syndrome and non-LVO without) or atypical presentations (opposite situations). Five scales (Rapid Arterial Occlusion Evaluation [RACE], Los Angeles Motor Scale [LAMS], Field Assessment Stroke Triage for Emergency Destination [FAST-ED], Prehospital Acute Stroke Severity scale [PASS], and Cincinnati Prehospital Stroke Severity Scale [CPSSS]) were derived from the baseline National Institutes of Health Stroke Scale scored by doctors and analyzed for diagnostic performance compared with imaging.

Results—Of a total of 565 patients, atypical presentations occurred in 31 LVO (38% of LVO) and 50 non-LVO cases (10%). Most scales correctly identified >95% of typical presentations but <20% of atypical presentations. Misclassification attributable to atypical presentations would have resulted in 4 M1/internal carotid artery occlusions, with National Institutes of Health Stroke Scale score ≥6 (5% of LVO) being missed and 9 non-LVO infarcts (5%) bypassing the nearest thrombolysis center.

Conclusions—Atypical presentations accounted for the bulk of scale misclassifications, but the majority of these misclassifications were not detrimental, and use of LVO scales would significantly increase timely delivery to endovascular centers, with only a small proportion of non-LVO infarcts bypassing the nearest thrombolysis center. Our findings, however, would require paramedics to score as accurately as doctors, and this translation is made difficult by weaknesses in current scales that need to be addressed before widespread adoption. **(*Stroke*. 2017;48:568-573. DOI: 10.1161/STROKEAHA.116.016056.)**

Key Words: ambulance diversion ■ diagnosis ■ endovascular thrombectomy ■ large vessel occlusion ■ stroke ■ triage

The widespread acceptance of endovascular therapy for treatment of anterior circulation large vessel occlusion (LVO) has been an exciting advance in ischemic stroke treatment. However, the organization of systems to deliver appropriate patients to endovascular-capable centers is a serious challenge to current systems of care. Like intravenous thrombolysis, endovascular therapy is highly time dependent, with earlier reperfusion delivering substantially better outcomes.[1] Although intravenous thrombolysis is available in many centers, hospitals with around-the-clock endovascular capability are scarce in many parts of the world, including Australia. Centralizing specialist expertise and infrastructure in high-volume centers has potential to maximize quality and efficiency. However, having fewer endovascular centers results in a significant proportion of patients with LVO being transported first to a nonendovascular center. Subsequent interhospital transfer delays result in worse outcomes compared with direct transport to an endovascular center.[2]

The clinical presentation of LVO is generally more severe than that of other ischemic stroke because of the larger area of tissue hypoperfusion. This presents an opportunity to differentiate LVO from milder strokes in the prehospital setting. There is growing literature around clinical LVO triage scales that aim to allow paramedics to identify LVO in the field and bypass patients to an endovascular center. The Rapid Arterial Occlusion Evaluation (RACE),[3] Los Angeles Motor Scale (LAMS),[4] Cincinnati Prehospital Stroke Severity Scale (CPSSS),[5] Field Assessment

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Stroke Triage for Emergency Destination (FAST-ED),[6] and Prehospital Acute Stroke Severity scale (PASS)[7] are all recently published scales, using simplifications of items from the National Institutes of Health Stroke Scale[8] (NIHSS) to optimize prediction of LVO. To date, only the RACE and LAMS have undergone paramedic validation studies.[3,9]

Heldner et al[10] and Turc et al[11] evaluated the RACE and CPSSS (in addition to a host of other scales not specifically designed for LVO recognition) against data from their stroke centers and reported a false-negative rate >20% and false-positive rate >15%. Both studies concluded that LVO triage scales could not replace vessel imaging because of the potential to harm because the high false-positive rate would result in significant numbers of non-LVO stroke patients bypassing the nearest thrombolysis center (potentially delaying thrombolysis), and the high false-negative rate would miss an important proportion of LVOs. However, although current LVO triage scales do indeed suffer classification inaccuracies, the consequences of such misclassification may vary substantially. For example, misclassifying a patient with intracerebral hemorrhage (ICH) as LVO and bypassing the nearest primary stroke center would not cause any therapeutic disadvantage. Further, although previous reports would have defined a distal M2 middle cerebral artery (MCA) occlusion as LVO,[10,11] the potential benefits for endovascular treatment in this group are uncertain,[12] so it is doubtful whether misclassification as non-LVO would have ultimately resulted in harm if not transported directly to an endovascular center.

In our clinical experience, most LVOs present with a severe MCA syndrome and a high NIHSS score, but a proportion present with a much milder syndrome that may be indistinguishable from a non-LVO stroke. Conversely, non-LVO strokes (such as ICH) and stroke mimics (such as postseizure paresis) may also present with a severe MCA syndrome. We, therefore, hypothesized that these atypical presentations cause the majority of LVO scale misclassifications. We aimed to examine the diagnostic performance of published LVO triage scales in a representative Australian cohort of suspected acute stroke, with a specific emphasis on scale performance in atypical clinical presentations and the potential harm that may arise from these misclassifications.

Methods

Case Ascertainment and Scale Derivation

Patient data were prospectively collected from consecutive ambulance-initiated code stroke alerts at the emergency departments of 2 major stroke centers in Melbourne, Australia. Collection occurred at Box Hill Hospital from October 2015 to September 2016 and in Royal Melbourne Hospital from May to September 2016, representing 15 months of consecutive data from the 2 centers. Box Hill Hospital serves a population of ≈870 000 in an area of 2000 km^2 in mid- to-outer eastern Melbourne, whereas the Royal Melbourne Hospital serves a population of ≈790 000 in an area of 1600 km^2 in central and north-west Melbourne. Both centers were the primary delivery destination for their geographically independent catchment areas (no stroke bypass procedures) and were serviced by a single statewide ambulance service. The median ambulance transport time from pickup to hospital arrival for both centers is ≈19 minutes (range 2–85 minutes). All study protocols were approved by local institutional ethics committees. Inclusion criteria were age >18 years and arrival within 6 hours of symptom onset. Exclusion criteria were code stroke initiation by a general practitioner or hospital facility (thereby, biasing paramedic assessment), presence of preexisting stroke deficits scored on baseline NIHSS, or patients from a high-level care nursing facility. All records were individually checked for study eligibility. Patients were typically assessed on arrival of the ambulance (business hours) or within 15 minutes of arrival (after hours) by neurology residents or fellows certified in administering the NIHSS.

Five LVO triage scales (RACE, LAMS, FAST-ED, PASS, and CPSSS) were subsequently derived from baseline NIHSS and hand-grip data (for LAMS) according to scoring instructions and cutoffs from respective publications. We used multiple prespecified rules for derivation of the RACE because of lack of clarity from published instructions: (1) only limb weakness would determine the cortical sign scored, (2) if both sides were weak, the weaker side would determine the cortical sign scored, (3) if both sides were equally weak, no cortical sign would be scored (because scoring of all 6 items is disallowed), and (4) if the NIHSS extinction item was unable to be scored because of aphasia or conscious state, then the corresponding RACE hemi-neglect items were also negative.

LVO was defined as apparent occlusion of the common carotid, internal carotid, or proximal middle cerebral (MCA M1 or proximal M2) arteries on initial computed tomographic angiography or in rare instances (5 cases) with a clearly visible hyperdense MCA sign on noncontrast computed tomography. Basilar and vertebral occlusions were considered non-LVO for the purposes of this study because current scales were not designed to assess posterior circulation signs.

Typical and Atypical Presentation Groups

To study scale performance in atypical clinical presentations, we prospectively divided patients into 2 prespecified typical and atypical groups. We defined a clinically severe MCA syndrome as prominent arm weakness (NIHSS motor arm ≥2) plus an additional cortical sign, either severe speech disturbance (NIHSS level of consciousness commands or NIHSS language ≥2), prominent inattention (NIHSS extinction ≥2), or gaze deviation (NIHSS gaze ≥1) in line with our clinical experience with LVO symptoms. Atypical presentations, therefore, included those patients with LVO who did not present with the defined severe MCA syndrome, along with patients who presented with the severe MCA syndrome despite not having an LVO. Typical presentations, on the other hand, included the expected situations where patients with LVO presented with the severe MCA syndrome and non-LVOs did not. Initial and follow-up imaging from all atypical LVO cases was reviewed independently by 2 of the authors (H.Z. and B.C.) to determine the site and characteristics of occlusion with agreement by consensus.

Statistical Analysis and Power Calculation

We primarily compared agreement between LVO triage scales and radiological diagnosis using Cohen's kappa statistic, which takes into consideration a possibility of agreement by chance. A minimum sample size of n=541 was calculated to give 90% power to detect a kappa of 0.60 (moderate agreement) in comparison to a 2-tailed null hypothesis of 0.40 (fair agreement) assuming an LVO prevalence of 10%.[13] Prespecified analysis for overall performance also included sensitivity, specificity, positive predictive value, negative predictive value, area under the receiver-operator curve values, and diagnostic odds ratio. Areas under the receiver-operator curves for the differing scales were compared using the χ^2 test.

Results

Of 1143 screened consecutive code stroke alerts, a total of 565 patients (49%) met eligibility criteria and were included in the study. Less than 1% of patients were excluded for other reasons (such as no imaging performed). Median age was 75 years (range 19–100), and 51% were male. Final diagnoses were as follows: LVO, 82 (14.5%); non-LVO infarcts, 175 (31%); transient ischemic attack, 39 (8.7%); ICH, 59 (10.4%);

and stroke mimics, 200 (35.4%). There was no heterogeneity between the 2 centers (Fisher exact test *P*=0.50).

Overall Scale Performance

The overall diagnostic performance of the 5 LVO triage scales in recognizing LVO is shown in Table 1. Kappa agreement and diagnostic odds ratio were highest for RACE and FAST-ED and lowest for CPSSS. There was a statistically significant difference in areas under the receiver-operator curve for all 5 scales (*P*=0.003), but when CPSSS was excluded, this became nonsignificant (*P*=0.53). The negative predictive values were similar for all scales (91%–93%), but there was trend to higher positive predictive value for RACE, LAMS, and FAST-ED (48%).

Typical and Atypical Groups

Overall, atypical presentations occurred in 81/565 (14%) patients, consisting of 31 LVOs (37.8% of all LVO) and 50 non-LVOs (10.4% of all non-LVO). The distribution of site of occlusion within typical and atypical groups (Table 2) was significantly different for both LVO and non-LVO (Fisher exact test *P*<0.001, respectively). The typical group included the majority of M1 and intracranial internal carotid artery occlusions, whereas the atypical group included an over-representation of M2 occlusions (especially with NIHSS <6), ICH, and intracranial atherosclerosis.

Within the atypical LVO group, there were 4 M1/internal carotid artery occlusions with NIHSS ≥6 (4.9% of all LVO) that clearly met guideline recommendations for endovascular therapy[14] and would likely benefit based on pooled data from randomized trials.[12] Of the atypical non-LVO group, there were 9 thrombolysis-eligible ischemic stroke patients (5.1% of all non-LVO infarcts), which included 5 patients with extensive cortical embolic infarcts and 4 with large subcortical infarcts. Of the 7 stroke mimic patients who presented with severe MCA syndrome, 4 were diagnosed with postseizure paresis (witnessed seizure in 3 and suspected in 1), 1 with hyperglycemic hyperosmolar syndrome and 2 with altered consciousness because of hypoglycemia and cardiac arrest, respectively.

Most LVO triage scales were able to correctly identify >95% of typical LVO and non-LVO presentations but were only able to correctly identify <20% of atypical LVOs and <10% of atypical non-LVOs (Table 3). Even the best performing scales for each atypical group (PASS for LVO and RACE for non-LVO) misclassified over two thirds of patients.

Discussion

There is current controversy concerning the validity of using clinical LVO triage scales in comparison with the reference standard of vessel imaging, with previous reports suggesting unacceptable risks from scale misclassification. In contrast, our results suggest that the overwhelming majority of misclassifications arise from atypical clinical presentations (Non-LVO with, and LVO without, a severe MCA syndrome), but the potential harm that would arise from misclassifying atypical presentations represents a maximum of 5% of LVOs missed for bypass to the endovascular center and a maximum of 5% of non-LVO infarcts potentially directed away from the nearest thrombolysis center (thereby, potentially delaying intravenous thrombolysis). This suggests that even if LVO triage scales were able to simply identify typical clinical presentations (LVO with, and non-LVO without, a severe MCA syndrome) with a high degree of accuracy, the potential benefits of improved triage and timely transport to endovascular centers are likely to outweigh the potential harm from scale misclassification.

There are several explanations for this discrepancy with previous reports. First, our results indicate that the majority of LVOs with atypical presentation do not in fact have a vessel occlusion with clear evidence for endovascular therapy, based on current American Heart Association endovascular guidelines[14] and HERMES trials (Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke) collaboration pooled meta-analysis of endovascular trials.[12] As such, we used a differing definition of endovascular-eligible LVO from previous reports. Second, a proportion of LVO with atypical presentations in our study represent an alternative diagnosis, such as intracranial atherosclerosis and dissection, which are also outside of current endovascular guidelines and were not counted as being harmful in our study if they were misclassified as non-LVO. Further, the majority of non-LVO with atypical presentations were in fact ICH, and we would not regard bypassing these patients away from the nearest thrombolysis center to be harmful as long as the endovascular center is equipped to deal with the extra patient load. Finally, the higher stroke mimic rate in our study, in line with a more representative prehospital sample, decreases the proportion of total thrombolysis–eligible infarcts, which in turn also decreases the proportion of misclassified non-LVO infarcts.

At our institution, we would consider all patients with internal carotid artery or M1 occlusion (regardless of NIHSS) or

Table 1. Overall Agreement of LVO Scales With CT Imaging

Scale	Accuracy	Kappa (95% CI)	Sens	Spec	PPV	NPV	AUC	DOR
RACE ≥5	0.86	0.51 (0.41–0.60)	0.66	0.90	0.48	0.93	0.78	17.50
LAMS ≥4	0.83	0.43 (0.34–0.52)	0.66	0.86	0.48	0.93	0.76	11.80
FAST-ED ≥4	0.85	0.49 (0.40–0.58)	0.70	0.88	0.48	0.92	0.79	16.40
PASS ≥2	0.81	0.43 (0.34–0.52)	0.71	0.84	0.45	0.93	0.77	12.40
CPSSS ≥2	0.81	0.35 (0.26–0.45)	0.56	0.86	0.42	0.91	0.71	7.54

Prevalence =14.5%. AUC indicates area under receiver-operator curve value; CI, confidence interval; CPSSS, Cincinnati Prehospital Stroke Severity Scale; CT, computed tomography; DOR, diagnostic odds ratio; FAST-ED, Field Assessment Stroke Triage for Emergency Destination; LAMS, Los Angeles Motor Scale; LVO, large vessel occlusion; NPV, negative predictive value; PASS, Prehospital Acute Stroke Severity scale; PPV, positive predictive value; RACE, Rapid Arterial Occlusion Evaluation; Sens, sensitivity; and Spec, specificity.

Table 2. Site of Occlusion/Abnormality for Typical and Atypical Groups

	Typical Presentations	Proportion, %	Atypical Presentations	Proportion, %
LVO*				
Extracranial ICA	3/3	5.9	2/1	6.5/3.2
Intracranial ICA	5/5	9.8	1/1	3.2/3.2
Tandem occlusion	1/1	2.0	1/0	3.2/0
M1 MCA	35/35	68.6	5/2	16.1/6.5
M2 proximal MCA	6/6	11.7	18/11	58.1/35.5
Dissection	1/1	2.0	0	0
ICAD	0	0	3/1	9.7/3.2
Stent occlusion ICA	0	0	1/1	3.2/3.2
Total	51	100	31	100
Non-LVO				
M2 distal MCA	9	2.1	0	0
M3/M4 MCA or ACA	71	16.4	5	10.0
Subcortical	25	5.8	4	8.0
Basilar	1	0.2	2	4.0
Other posterior†	28	6.5	0	0
Stroke NI†	30	6.9	0	0
TIA†	49	11.3	0	0
ICH†	27	6.2	32	64.0
Stroke mimics†	193	44.6	7	14.0
Total	433	100	50	100

ICA indicates internal carotid artery; ICAD, intracranial atherosclerotic disease; ICH, intracerebral hemorrhage; LVO, large vessel occlusion; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; Stroke NI, stroke diagnosis with no abnormality on imaging; and TIA, transient ischemic attack.

*Reported as total number/number with NIHSS ≥6.

†Includes infarcts in vertebral, superior/inferior cerebellar, and posterior cerebral arterial territories.

proximal M2 occlusion with NIHSS ≥6 eligible for endovascular therapy, which is broader than AHA endovascular guidelines. This policy would increase the proportion of atypical LVO missed to 24% of total LVO. However, this would still mean that over 75% of patients with LVO would be correctly identified and triaged, compared with the current situation in many cities (including ours) in which the majority of patients are not transported directly to a 24-hour endovascular capable center. Furthermore, the potential harm from bypassing the nearest thrombolysis hospital is only relevant if the extra travel time to the endovascular center (typically not excessive in urban settings) exceeds any reduction in door-to-needle time achieved by more streamlined stroke assessment workflow at the larger endovascular center.

Although adoption of LVO triage scales is, therefore, promising, we identified significant challenges for the implementation of existing LVO triage scales for use by paramedics. In our data, apart from the CPSSS, which clearly showed poorer

Table 3. Proportion of Agreement Between LVO Scales and CT Imaging for Typical and Atypical Groups

	Typical		Atypical	
Scale	LVO (95% CI)	Non-LVO (95% CI)	LVO (95% CI)	Non-LVO (95% CI)
RACE ≥5	0.96 (0.91–1.0)	0.97 (0.95–0.99)	0.16 (0.02–0.30)	0.30 (0.17–0.43)
LAMS ≥4	0.94 (0.87–1.0)	0.95 (0.93–0.97)	0.19 (0.05–0.34)	0.08 (0.0–0.16)
FAST-ED ≥4	0.98 (0.94–1.0)	0.97 (0.96–0.99)	0.23 (0.07–0.38)	0.04 (0.0–0.10)
PASS ≥2	0.96 (0.91–1.0)	0.92 (0.90–0.95)	0.29 (0.12–0.46)	0.06 (0.0–0.13)
CPSSS ≥2	0.88 (0.79–0.97)	0.94 (0.92–0.96)	0.03 (0–0.10)	0.10 (0.01–0.19)

CI indicates confidence interval; CPSSS, Cincinnati Prehospital Stroke Severity Scale; CT, computed tomography; FAST-ED, Field Assessment Stroke Triage for Emergency Destination; LAMS, Los Angeles Motor Scale; LVO, large vessel occlusion; PASS, Prehospital Acute Stroke Severity scale; and RACE, Rapid Arterial Occlusion Evaluation.

performance, there were no statistically significant differences between the remaining scales in overall LVO identification. This is interesting because the simpler PASS and LAMS performed similarly to the more complex RACE and FAST-ED. However, to date, only the RACE and LAMS have undergone validation studies with paramedics, and these showed rather low specificities of 68%[3] and 63%[15] for RACE (despite formal paramedic training) and 58%[9] for LAMS. In comparison, the specificities for LVO identification for RACE and LAMS observed in our study where stroke doctors assessed deficits were 90% and 86%, respectively, indicating likely issues with paramedic accuracy. This is concerning because a significantly lower specificity would disproportionately lower the positive predictive value attributable to the relatively low LVO prevalence in our study. This would cause a large number of non-LVO patients to be bypassed to the endovascular center.

One reason for the observed low specificities of both the RACE and the LAMS may be the use of items that are prone to error when scored by paramedics, such as mild facial droop in both (poor interrater reliability), leg weakness in RACE (false-positive from musculoskeletal causes) or handgrip in LAMS (subjective). Similar issues are also likely to arise with the FAST-ED using bilateral simultaneous extinction (may be difficult to teach paramedics) and PASS and CPSSS using level of consciousness questions (prone to error from cognitive deficits or non-English speaking background). We also needed to set prespecified rules to interpret the RACE for specific scenarios, such as where both sides of the body may be assessed as weak (eg, left arm hemiparesis with severe right hip osteoarthritis), and these may have inadvertently improved the specificity of the scale in our study. Further clarification of these situations may have been addressed in the Spanish RACE paramedic training process but were not present in available English resources. Finally, to improve specificity, we propose that LVO triage scales require a preliminary screening procedure that excludes simple mimics, such as seizures, glycemic instability, and severely altered mentation, because these were all common causes of a false-positive scale classification in our study.

The strengths of our study are that we collected a large, consecutive sample of paramedic-initiated code stroke signals, which is representative of the true prehospital population where LVO triage scales would be applied. This is likely to be a better representation than a sample from a hospital stroke unit or stroke trial registry. We also were able to manually check progress notes and use available angiographic, computed tomography perfusion, and follow-up imaging data to correctly identify vessel occlusion and eventual diagnosis.

The limitations of our study were that medical staff rather than paramedics scored the neurological deficits. Therefore, our data presented represents a best-case scenario if paramedics were as accurate as doctors, but this is a clear prerequisite should an LVO triage scale be adopted. We were also only able to identify clinical signs at time of hospital arrival, and dynamic fluctuations in clinical severity may affect the diagnostic accuracy of LVO triage scales in the prehospital setting. We also acknowledge that there were no precedents for our definition of a severe MCA syndrome, but at the same time, we felt that this combination of symptoms was the best differentiator of LVO from milder strokes based on our clinical experience. Finally, we did not include the 3-Item Stroke Scale[16] because we did not feel that adequate validation work had been completed for this tool.

Summary

Our study shows that clinical LVO triage scales have significant potential to substantially increase delivery of patients with anterior circulation LVO to endovascular centers without excessive harm from bypassing the nearest thrombolysis hospital. Furthermore, this can be achieved simply by accurate identification of LVO presenting with a typical severe MCA syndrome (and vice versa with non-LVOs). The significant challenge for current published scales is that paramedics must score the scales as accurately as stroke doctors, and current scales either lack paramedic testing or perform inadequately in these studies. Current scales also seem to include items that may be prone to error when operationalized for scoring by paramedics, and these issues must be addressed in future research before LVO triage scales are viable for widespread adoption.

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Disclosures

None.

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