A Clinical Paradigm for Classifying Neurologic Symptoms to Screen for Emergent Large Vessel Occlusions

Rebecca Pollard, MD,* Michelle Leppert, MD, MBA,* Charles Rawson, MD,† Mitchell Boehnke, MD,† Justin Honce, MD,† Lidia Nagae, MD,† Sharon Poisson, MD, MAS,* and Eric Nyberg, MD†

Background: With newly-extended treatment windows for endovascular therapy in emergent large vessel occlusions, it is increasingly important to identify thrombectomy-eligible patients without overwhelming resources dedicated to acute stroke care. We devised a simple paradigm to classify patient's presenting neurologic symptoms to screen for large vessel occlusions. *Methods:* We reviewed the presenting symptoms, imaging findings, and final diagnoses of consecutive emergency department stroke alert cases. Patients were classified based on their neurologic exams as focal objective, focal subjective, or nonfocal. Outcomes of final diagnoses of acute ischemic stroke and large vessel occlusions were compared across groups. Comparisons were made to other large vessel occlusion prediction scales. *Results:* Of 521 patients, 342 (65.6%) were categorized as focal objective, 142 (27.2%) as focal subjective, and 37 (7.1%) as nonfocal. Ischemic stroke and large vessel occlusions were diagnosed in 114 (21.9%) and 27 (5.2%) of patients, respectively. Classification as focal objective significantly predicted stroke (odds ratio 3.77; 95% confidence interval 2.17-6.55) and captured all large vessel occlusions (P = .0001). The focal objective categorization was the only tool which achieved 100% sensitivity for large vessel occlusions (with a specificity of 36%) compared to other large vessel occlusion prediction tools. *Conclusions:* Patients who presented as stroke alerts without focal neurologic symptoms were unlikely to have large vessel occlusions. With high sensitivity, classifying patients' neurologic exams into focal objective versus subjective or nonfocal categories may serve as a useful tool to screen for large vessel occlusions and prevent unnecessary emergent workup in patients unlikely to be endovascular candidates.

Key Words: Stroke—large vessel occlusion—thrombectomy—acute stroke

Introduction

Rapid clinical assessment and expedient intervention are critical to ensuring the best outcomes in acute stroke.[1] Efforts to optimize this process have prompted many medical centers to institute "stroke alert" or "stroke code" systems.[2] However, despite efforts at optimization, stroke alerts remain resource intensive,[3] often requiring the immediate involvement of a neurologist, an emergency department (ED) physician, a pharmacist, a neuroradiologist, an ED nurse, and an ED technician, as well as immediate access to a computed tomography (CT) scanner. With the advent of endovascular thrombectomy as standard of care for emergent large vessel occlusions (LVO), the stroke alert process no longer ends after the noncontrast CT scan to inform the decision to administer

From the *Department of Neurology, University of Colorado School of Medicine, Aurora, Colorado; and †Department of Radiology, University of Colorado School of Medicine, Aurora, Colorado.

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Address correspondence to Rebecca Pollard, MD, University of Colorado School of Medicine, Department of Neurology, Mail Stop L950, 12401 East 17th Avenue, Aurora, CO 80045. E-mail: rebecca.pollard@ucdenver.edu.

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intravenous tissue plasminogen activator but also includes further evaluation for endovascular candidacy.[4] Screening for and intervening on patients with emergent LVO mobilize additional resources and increase the stroke alert resource burden.

The results of the recent "Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention with Trevo" (DAWN) and "Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke" (DEFUSE-3) trials have further extended the window of eligibility for emergent endovascular therapy to 24 hours from the time of symptom onset in the setting of an LVO.[5,6] While this extended eligibility window holds the promise of treating more patients, it also comes with the increased burden on stroke centers to screen a greater number of candidates for LVO. Rather than calling a stroke alert on every patient who presents with acute neurologic symptoms within a 24-hour window from symptom onset, an ideal "LVO alert" system would accurately capture all or nearly all potential LVO cases while optimizing stroke resource utilization. Although there have been several diagnostic scales developed to screen for LVO, these were mostly designed to inform transport decisions made by emergency medical services in the field [7-12] rather than to activate an LVO stroke alert in the ED; moreover, none of these scales has been reliable enough to preclude intracranial arterial imaging.[13] For example, a common surrogate marker for LVO is a National Institutes of Health Stroke Scale (NIHSS) score cutoff of 6 points; however this has been shown to be inaccurate with high rates of both false positives and false negatives.[14,15] In order to optimize stroke alert resource usage given the increasing number of eligible LVO patients, we analyzed acute stroke alerts at our institution to create a simple clinical algorithm based on the NIHSS items to aid clinicians in determining which patients should receive emergent angiographic imaging in consideration for endovascular therapy. We hypothesized that patients without focal objective neurologic symptoms would be unlikely to have LVO and would not require emergent vessel imaging to determine eligibility for endovascular therapy.

Material and Methods

Institutional review board approval was obtained for this retrospective cohort study. We reviewed consecutive ED stroke alerts from January 1, 2016 to December 31, 2016 at our high-volume comprehensive stroke center. Patients were included if they initially presented to our institution's ED, were examined by a neurologist, had a documented NIHSS score during the stroke alert, and received an emergent noncontrast CT brain scan. Patients were excluded if they were less than 18 years of age, initially presented to another facility prior to transferring to our institution, had intracranial hemorrhage on the noncontrast CT scan, had no documentation of an NIHSS score, were not examined by a neurologist, or if the stroke alert was cancelled after it was initially called.

We collapsed the items on the NIHSS into an intuitive categorical system to characterize each patient's presenting deficits as focal objective (FO), focal subjective (FS), or nonfocal (NF) (Table 1). FO symptoms must be localizable and verifiable by the examiner when performing the NIHSS; these include gaze preference or deviation, visual field deficits, hemiparesis, ataxia, aphasia, and neglect. FS symptoms are localizable but cannot be objectively verified by the examiner on testing; these include numbness and paresthesias. NF symptoms are not clearly localizable; these include altered level of consciousness, dysarthria, or bilateral symmetric weakness or numbness. A patient is classified as FO if any FO symptoms are present

Table 1. *Clinical paradigm classification*

NIHSS item	Description	Classification
1a. Level of consciousness	Alert, arousable to minor simulation, or unarousable	Nonfocal
1b. Level of consciousness—questions	Answers 2 simple questions	Nonfocal
1c. Level of consciousness—commands	Follows 2 simple commands	Nonfocal
2. Best gaze	Eyes able to track horizontally	Focal objective
3. Visual fields	Partial hemianopia to complete blindness	Focal objective
4. Facial palsy	Minor to complete paralysis of the face	Focal objective
5. Motor arm	Drift to complete paralysis of 1 arm	Focal objective
6. Motor leg	Drift to complete paralysis of 1 leg	Focal objective
7. Limb ataxia	Ataxia present in any limb	Focal objective
8. Sensory	Decreased to absent sensation to any body part	Focal subjective
9. Best language	Any loss of fluency or comprehension	Focal objective
10. Dysarthria	Slurred to unintelligible speech	Nonfocal
11. Extinction	Inattention to any modality, ie, visual or tactile	Focal objective

The NIHSS items classified as focal objective, focal subjective, or nonfocal.

and are localizable. Alternatively, a patient is classified as FS if at least 1 FS symptom is present and localizable in the absence of any FO symptoms. Lastly, a patient is categorized as NF if there are neurological changes without satisfying either FO or FS criteria. Of note, we intentionally focused on localizing focal symptoms to the anterior circulation, as current evidence has focused on endovascular therapy for anterior circulation strokes.[5,6] As such, patients with any combination of symptoms that crossed midline were considered nonfocal as this is a fairly rare presentation of stroke related to large vessel occlusion. We reasoned that while some posterior circulation strokes can present with crossed midline findings (eg, left facial weakness and right body weakness), these are very unlikely to be related to an LVO which would be amenable to evidence-based intervention. In the case of bilateral weakness, symptoms were considered FO if there was 1 side that was consistently documented as weaker.

Each patient's initial NIHSS score, laterality of symptoms, diffusion-weighted imaging findings (if MRI was obtained), presence of LVO in the subset of patients who received vascular imaging (CTA or magnetic resonance angiogram), and final diagnosis at discharge were recorded. Patients were considered positive for LVO if they were found to have an internal carotid artery, proximal middle cerebral artery, ie, M1 or M2, or basilar artery occlusion on vascular imaging. Patients' NIHSS components were also used to calculate their equivalent scores of existing LVO prediction tools that are also based on the NIHSS, including the Cincinnati Prehospital Stroke Severity Scale;[10] Prehospital Acute Stroke Severity Scale,[11] Stroke Vision, Aphasia, Neglect Assessment,[12] and the 3-Item Stroke Scale.[16] The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of FO categorization in detecting LVO were calculated and compared to those of existing LVO scales applied to our cohort of patients. Pearson's chi-squared test for goodness of fit and Fisher's exact test were used to compare variables of proportions across the 3 groups. The student's t test was used to compare means. An alpha level of .05 was used for all statistical testing.

Results

A total of 561 stroke alerts were reviewed within the inclusion dates of the study. Per the exclusion criteria, 40 stroke alerts were excluded. Of these, 18 were excluded due to acute hemorrhage on head CT, 13 were cancelled by the ED physician prior to examination by a stroke neurologist, 8 had no documentation of an NIHSS score, and 1 was under the age of 18. A total of 521 stroke alerts were included in the final data analysis. Of these, 342 stroke alerts were categorized as FO, 142 as FS, and 37 as NF. The average age for the study population was 59 years, and 43.4% of the patients were male. There were no significant differences between groups in terms of age, sex, or history of hypertension, hyperlipidemia, type II diabetes, atrial fibrillation, or prior stroke or transient ischemic attack. The average NIHSS score of patients in the FO group was 7, which was significantly higher than the average scores for the FS group of 0 ($P < .0001$) and the NF group of 4 ($P < .0001$). The average NIHSS score of the NF group was also significantly higher than that of the FS group ($P < .00001$). Patient demographics and characteristics are shown in Table 2.

By the time of hospital discharge, 21.9% of all patients were diagnosed with acute ischemic stroke and 5.2% of all patients were diagnosed with LVO. Within the FO group, 27 patients (8%) were diagnosed with LVO. Importantly, no patients in either the FS or NF groups had LVO. When the FS and NF groups were combined as a composite group to compare FO versus non-FO patients, the FO group had significantly more diagnoses of stroke and LVO ($P < .0001$ and $P = .0001$, respectively; Table 3).

Within the subgroup of patients with the final diagnosis of acute ischemic stroke on discharge, 85% were classified as FO, 13% as FS, and 2% as NF. The average NIHSS score of patients with acute ischemic stroke was 7. The average NIHSS of patients with LVO was 15.

The sensitivity of the FO categorization for detection of LVO was 100%, with a specificity of 36%, PPV of 8%, and NPV of 95%. Using optimal thresholds for other existing LVO prediction scales,[14] we calculated the number of patients with stroke and LVO that these scales would have captured in our cohort, as shown in Table 4. Compared to other prediction scales, our FO rating system captured the most patients with stroke (85.1%) and LVO (100%) and had the highest sensitivity (100%).

Discussion

In this study, all patients who were found to have an emergent LVO presented with focal objective neurologic symptoms. While acute ischemic stroke was diagnosed in patients without focal objective symptoms, these were less common than in the FO group and were less likely to be due to LVO. Our hypothesis that it would be highly unlikely for a patient presenting with an LVO to have purely subjective findings on physical exam was supported by our data, and the presence of at least 1 focal objective finding was 100% sensitive for the presence of an LVO.

Our system outperformed other LVO prediction scales, including those used for prehospital assessments, in capturing patients with stroke and LVO with the highest sensitivity for LVO prediction while retaining a comparable NPV. This is likely attributable to the greater number of focal neurologic signs included that would qualify a

Table 2. *Patient characteristics*

	All subjects	Focal objective	Focal subjective	Nonfocal	*p*FO versus FS	*p*FO versus NF	*p*FS versus NF
Total (% of total)	521	342 (65.6)	142 (27.2)	37 (7.1)	<.0001*	<.0001*	<.00001*
Average age (range)	59 (20-96)	60 (22-96)	57 (20-88)	56 (33-84)	.17	.68	.70
% Male	43.4	42.4	44.4	48.6	.69	.47	.49
Average NIHSS (range, ±SD)	5 (0-36, ±6.7)	7 (1-36, ±6.7)	0 (0-9, ±.9)	4 (1-13, ±3.5)	<.0001*	<.0001*	<.00001*
Hypertension (%)	143 (27.4)	101 (29.5)	31 (21.8)	11 (29.7)	.08	.98	.31
Hyperlipidemia (%)	74 (14.2)	52 (15.2)	16 (11.3)	6 (16.2)	.26	.87	.42
Type II diabetes (%)	52 (10)	38 (11.1)	10 (7.0)	4 (10.8)	.17	.97	.45
Atrial fibrillation (%)	16 (3.1)	13 (3.8)	1 (.7)	2 (5.4)	.06	.63	.05
Prior stroke/TIA (%)	66 (12.7)	45 (13.2)	15 (10.6)	6 (16.2)	.43	.61	.34
CTA obtained (%)	265 (50.9)	189 (55.3)	56(39.4)	20 (54.0)	.0002*	.742	.091
MRA obtained (%)	74 (14.2)	48 (14.0)	22 (15.5)	4 (10.8)	.68	.59	.48

Stroke risk factors were obtained from patients' past medical history and had been diagnosed prior to the stroke alert presentation. Except for the top row in which percentage indicates percentage of 521 total patients, the other percentages reported indicate percentage of each respective subgroup. Abbreviations: CTA, computed tomography angiography; FO, focal objective; FS, focal subjective; MRA, magnetic resonance angiography; NF, nonfocal; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation; TIA, transient ischemic attack.
*Denotes significant values less than .05.

patient as "positive," or FO, in our system compared to positive in other scales. For example, scales such as the Los Angeles Motor Scale,[7,8] Cincinnati Prehospital Stroke Severity Scale,[10] Prehospital Acute Stroke Severity Scale,[11] Vision, Aphasia, Neglect[12], and 3-Item Stroke Scale[11,16] assess for only 3 clinical symptoms each, while our proposed FO classification considers 8 of the NIHSS items. Although this may seem disadvantageous in terms of efficiency, our scale was derived from ED encounters with the intent of triaging patients for endovascular therapy and, unlike others, is not intended for prehospital assessment in order to triage patients in the field for higher-level stroke centers. Moreover, in the ED stroke alert context, each patient should have a full NIHSS assessment performed already, and the additional time required to then classify the NIHSS items as FO positive or negative should be negligible. The proposed FO classification is intuitive and retains simplicity; rather than adding up numbers or remembering an optimal threshold, patients are simply positive (focal objective) or negative (focal subjective or nonfocal). The 100% sensitivity of our system is critical for minimizing the number of LVO cases that might be missed.

Certainly the FO system is limited by its low specificity and PPV. This can be attributed to its inclusion of multiple focal neurologic symptoms, none of which are specific for strokes caused by LVO but carries a broad differential diagnosis of stroke mimics. However, the FO system's intended use is to support the decision to stop a stroke alert from proceeding down the route of emergent endovascular intervention and utilizing unnecessary resources, and therefore the system is more useful when patients are FO negative. For those who are FO positive, as with any scale, clinical judgment is advised to evaluate if further workup for endovascular therapy is indicated. Therefore the FO classification's strength and utility lie in its sensitivity and NPV rather than its specificity or PPV for LVO.

Several other limitations of this study should be addressed. First, our hypothesis could have been strengthened if every patient assessed had vessel imaging performed, whereas only 62% had intracranial vessel imaging in our study. Had we only analyzed patients with vessel imaging, we could have addressed if FO-negative patients could be safely excluded from vessel imaging without missing LVO candidates. By including patients who did not have intracranial vascular imaging performed, it is conceivable that we missed additional patients with LVO. However, at our institution the standard practice is to obtain intracranial vascular imaging in nearly all patients with suspected stroke, either acutely at stroke alerts (usually with CTA) or later during the hospital course to evaluate for etiology of stroke (usually with magnetic resonance angiogram). The patients who did not have vascular imaging performed were, in almost all cases, deemed by the neurologists unlikely to have ischemic stroke, let alone LVO. In most of these cases there were

Table 3. *Comparison of stroke diagnosed and LVO diagnosed within each subgroup*

Category	Total (% of total)	FO (%)	FS (%)	NF (%)	Contrast	*P* value	OR (95% CI)
Stroke diagnosed	114 (21.9)	97 (28.4)	15 (10.6)	2 (5.4)	FO versus FS	<.0001*	3.35 (1.87-6.01)
					FO versus NF	.003*	6.93 (1.72-60.24)
					FS versus NF	.531	2.07 (.45-19.42)
					FO versus not FO	<.0001*	3.77 (2.17-6.55)
LVO diagnosed	27 (5.2)	27 (7.9)	0 (.0)	0 (.0)	FO versus FS	.0006*	†
					FO versus NF	.093	†
					FS versus NF	†	†
					FO versus not FO	.0001*	†

Except for the first column in which percentage indicates the percentage of 521 total patients, the other percentages reported indicate the percentage within each respective subgroup. In the contrasts comparing FO versus not FO, the "not FO" group is the composite group consisting of FS plus NF. Abbreviations: CI, confidence interval; FO, focal objective; FS, focal subjective; LVO, large vessel occlusion; NF, nonfocal; OR, odds ratio.

*Denotes significant values less than .05.

†Note that in these cases of LVO, the statistical calculations could not be performed due to the 0 values of the FS and NF groups.

signs and symptoms favoring an alternative etiology; some examples include fever and hypotension suggesting sepsis, functional deficits suggesting conversion disorder, and neurologic symptoms consistent with peripheral nerve lesions such as Bell palsy or radial nerve palsy. Such patients were unlikely to have LVO; therefore it was considered prudent to not proceed with vascular imaging in order to reduce costs and to spare patients from exposure to radiation and contrast. Therefore, although there is some potential bias toward obtaining vessel imaging in FO patients, in the patients without vascular imaging, LVO and in most cases ischemic stroke, were excluded on clinical grounds, and this was unlikely to change the conclusions of our study.

Second, our methods focused on LVO primarily in anterior circulation strokes. While current American Heart Association stroke guidelines recommend that mechanical thrombectomy may be reasonable for LVO in the posterior circulation (vertebral, basilar, or posterior cerebral arteries),[17] we chose to include only those patients in the focal objective group whose symptoms did not cross midline, which necessarily biased the categorization towards anterior circulation strokes. Despite this limitation we did capture one basilar artery LVO in this cohort. This decision was made to allow for ease of usage by practitioners who do not specialize in neurology and we will revisit this issue in planned prospective trials.

Finally, our exclusion criteria do bias the data slightly toward classifying patients as FO. Patients were excluded if the stroke alert was cancelled after it was initially called, either based on a discrepancy between their initial complaint or presenting symptom (eg, to initial ED intake or to emergency medical services) and what was actually found on assessment, or based on the initial neurologic exam by an ED or stroke physician who felt that an acute stroke was unlikely prior to proceeding with the remainder of the stroke alert pathway. In these cases the patients were unlikely to have focal neurologic deficits; had they been included in the data analysis there likely would have been greater numbers in the FS and NF categories. However, the number of excluded patients was small and unlikely to change the observed outcomes.

For patients who otherwise met the inclusion criteria, there were a high percentage of stroke alerts that were not diagnosed with acute ischemic stroke by the time of discharge. Several factors account for this, including our institution's inclusive threshold for calling a prehospital or ED stroke alert in attempts to capture as many intervenable stroke cases as possible. Additionally, for the purposes of this study we excluded stroke alerts with intracerebral hemorrhage, and we did not consider patients with final diagnoses of transient ischemic attack or recrudescence of old stroke symptoms as acute ischemic strokes.

The strong sensitivity and negative predictive value of the FO system carries several important implications. Simple and reliable methods for screening patients for potential escalation of care are needed for efficiency and sustainability. The presence or absence of focal objective findings on clinical exam may serve as a useful proxy for excluding LVO when patients present to an ED as acute stroke alerts and a decision must be made as to whether to proceed toward emergent endovascular therapy. This intuitive paradigm for classifying the items within the established NIHSS protocol implemented in many stroke alert systems may help clinicians be mindful of the necessity of additional resource utilization in patients unlikely to have LVO. We intend to build on our findings from this retrospective study and conduct a prospective study to implement the FO scale with standard ED stroke alerts to assess patients for LVO candidacy. The aim of such a study would be to devise an alert system for suspected LVO cases that would accurately screen for LVO while optimizing costs and resource burden.

Table 4. *Application of different stroke severity scales to our cohort of patients*

	Total	Focal objective	NIHSS ≥ 6	CPSS ≥ 2	VANS positive	3ISS ≥4	PASS ≥2
Total number of patients (%)	521	342 (65.6)	152 (29.2)	133 (25.5)	94 (18.0)	29 (5.6)	74 (14.2)
Stroke diagnosed (% of all strokes)	114	97 (85.1)	43 (37.7)	57 (50.0)	34 (29.8)	13 (11.4)	24 (21.1)
LVO diagnosed (% of all LVO)	27	27 (100)	20 (74.1)	23 (85.1)	19 (70.4)	11 (40.7)	17 (63.0)
Sensitivity for LVO (%)		100	74	85	70	41	63
Specificity for LVO (%)		36	73	78	85	96	89
PPV for LVO (%)		8	13	17	20	38	23
NPV for LVO (%)		95	98	99	98	97	98

The calculations for the focal objective column are based on the contrast of focal objective group versus the composite group of focal subjective plus nonfocal groups. The statistical calculations for the remaining scales are based on the number of LVO cases that would have been captured in our cohort based on optimal thresholds for each scale. Abbreviations: CPSS, Cincinnati Prehospital Stroke Scale; LVO, large vessel occlusion; NIHSS, National Institutes of Health stroke scale; NPV, negative predictive value; PASS, Prehospital Acute Stroke Severity Scale; PPV, positive predictive value; VANS, Vision, Aphasia, Neglect; 3ISS, 3-Item Stroke Scale.

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