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Predicting neuroimaging eligibility for extended-window endovascular thrombectomy

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Abstract

OBJECTIVE—Endovascular thrombectomy (EVT) and tissue plasminogen activator (tPA) are effective ischemic stroke treatments in the initial treatment window. In the extended treatment window, these treatments may offer benefit, but CT and MR perfusion may be necessary to determine patient eligibility. Many hospitals do not have access to advanced imaging tools or EVT capability, and further patient care would require transfer to a facility with these capabilities. To assist transfer decisions, the authors developed risk indices that could identify patients eligible for extended-window EVT or tPA.

METHODS—The authors retrospectively identified stroke patients who had concurrent CTA and perfusion and evaluated three potential outcomes that would suggest a benefit from patient transfer. The first outcome was large-vessel occlusion (LVO) and target mismatch (TM) in patients 5–23 hours from last known normal (LKN). The second outcome was TM in patients 5–15 hours from LKN with known LVO. The third outcome was TM in patients 4.5–12 hours from LKN. The authors created multivariable models using backward stepping with an α -error criterion of 0.05 and assessed them using C statistics.

RESULTS—The final predictors included the National Institutes of Health Stroke Scale (NIHSS), the Alberta Stroke Program Early CT Score (ASPECTS), and age. The prediction of the first

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outcome had a C statistic of 0.71 (n = 145), the second outcome had a C statistic of 0.85 (n = 56), and the third outcome had a C statistic of 0.86 (n = 54). With 1 point given for each predictor at different cutoffs, a score of 3 points had probabilities of true positive of 80%, 90%, and 94% for the first, second, and third outcomes, respectively.

CONCLUSIONS—Despite the limited sample size, compared with perfusion-based examinations, the clinical variables identified in this study accurately predicted which stroke patients would have salvageable penumbra (C statistic 71%–86%) in a range of clinical scenarios and treatment cutoffs. This prediction improved (C statistic 85%–86%) when utilized in patients with confirmed LVO or a less stringent tissue mismatch (TM < 1.2) cutoff. Larger patient registries should be used to validate and improve the predictive ability of these models.

Keywords

acute ischemic stroke; large-vessel occlusion; endovascular thrombectomy; tissue plasminogen activator; perfusion imaging; target mismatch; vascular disorders

Stroke is one of the leading causes of long-term disability and preventable death in the United States.¹ The development of tissue plasminogen activator (tPA) and endovascular thrombectomy (EVT) for acute ischemic stroke have significantly improved survival and functional outcome.² The efficacy of these treatments is strongly influenced by the amount of salvageable brain and the time from stroke onset to intervention.^{3–5} The DEFUSE 3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke) trial demonstrated benefit for EVT up to 16 hours after the last known normal (LKN) in large-vessel occlusion (LVO) patients with a perfusion imaging finding called target mismatch (TM), which involves a mismatch in the volume of ischemic tissue on perfusion imaging and infarct volume.⁶ TM is measured with CT perfusion (CTP) or MRI and is processed with quantitative algorithmic software. The EXTEND (Extending the Time for Thrombolysis in Emergency Neurological Deficits) trial recently showed a benefit of tPA administered in an extended time window to patients with a slightly modified version of TM, also measured using perfusion imaging and quantitative software.⁷ The EXTEND trial enrolled patients within 4.5–9 hours from LKN or, for wake-up strokes, up to 9 hours from the midpoint of sleep, which would mean that a patient with an 8-hour sleep time could be administered tPA up to 13 hours from LKN.

Neither the technical capability to perform perfusion imaging nor its processing technology is widely available, because of substantial hardware and software costs and recurring annual fees.⁸ In contrast, noncontrast CT of the head and CTA of the brain are available at most emergency departments in the United States.⁹ Acknowledging this disparity and the need to optimize the hub-and-spoke model of stroke care,¹⁰ we sought to develop simple risk indices that could be used to reliably identify patients eligible for extended-window EVT or tPA using CT/CTA and clinical information available on admission to the emergency department. Such a tool could allow effective screening of patients for extended-window EVT or tPA and appropriate transfer to a perfusion imaging– and EVT-capable facility.

Methods

We retrospectively identified patients seen in our emergency department from 2007 through 2014 who had concurrent CTA and CTP within 4.5–23 hours from LKN. The study was approved by the local institutional review board with a waiver of informed consent, and data are available upon reasonable request. CTA/CTP was performed with a 64-section scanner (Definition or Definition AS, Siemens) using a 4D spiral technique described previously.¹¹ Using validated methodology,¹² two board-certified neuroradiologist raters graded the CT images with the Alberta Stroke Program Early CT Score (ASPECTS), a 10-point score of early ischemic change. We report a weighted Cohen's kappa for their agreement. The CTA source images were used to assess for LVO, which included the internal carotid artery or proximal segment (M₁) of the middle cerebral artery. For volumetric CTP analysis, we used the FDA-approved Olea Sphere software (Olea Medical) to generate perfusion maps with a Bayesian-based probabilistic deconvolution method, which recent data suggest is superior to other delay-insensitive methods.¹³

On the basis of the criteria validated for Olea, we defined lesion core as relative cerebral blood flow (CBF) < 40% with absolute arterial tissue delay > 2 seconds and hypoperfused tissue as relative mean transit time > 135%.^{13–15} To determine inter-software stability, we compared the Olea measurements with those of a subset of patients in our cohort that were processed with RAPID software (IschemaView), which defines core as relative CBF < 30% and hypoperfused as time to peak of the residue function (Tmax) > 6 seconds.¹⁶ The CTP data were used to determine whether patients met criteria for TM, which was defined using the DEFUSE 3 criteria (core < 70 ml, mismatch ratio < 1.8, and mismatch volume < 15 ml) and the EXTEND criteria (core < 70 ml, mismatch ratio > 1.2, and mismatch volume > 10 ml).^{6,7}

We used three potential outcomes that would suggest a benefit from transfer to an advanced center. The first outcome was both LVO and TM in all stroke patients in the 5–23 hours from the LKN time window. This outcome combines TM with a window of 6–24 hours from LKN, using a maximum of 23 hours from LKN to provide 1 hour or more to transfer the patient and activate an EVT team.^{6,17} The second outcome was TM alone in stroke patients with known LVO on CTA in the 5–15 hours from the LKN time window; these patients would correspond more strictly to the DEFUSE 3 time window criteria. The third outcome is the EXTEND TM for all stroke patients in the 4.5- to 12-hour time window, who could be eligible for extended-window tPA with 1 hour to transfer the patient. We chose 12 hours because in EXTEND, wake-up stroke patients could be included up to 9 hours from the midpoint of sleep. For each of the resulting cohorts, we identified candidate variables with $p < 0.2$ in a univariable logistic regression fit to the outcome of TM. We evaluated multivariable models using interactive variable selection and backward stepping with an α -error criterion of 0.05.¹⁸ If two scores had similar performance characteristics, we collapsed them in the model. Variables that consistently predicted our outcomes were used as predictors in all models. We assessed the risk indices using a C statistic with 95% confidence intervals to measure the ability of the index to discriminate between patients who had or did not have our defined outcomes. We further report the calibration of the score by reporting the predicted and observed probabilities of the outcome for individual scores.

Results

We identified 145 patients during the study period who had adequate clinical and radiographic data. Patient baseline demographics are presented in Table 1, with patients stratified by TM. The mean age was 63.9 years, and 53.8% of the patients were male. Established stroke risk factors, including hypertension, hyperlipidemia, atrial fibrillation, and diabetes mellitus, were not different between patients who had a TM and those who did not. The ASPECTS agreement between neuroradiologists was $\kappa = 0.76$, and the correlation coefficient between Olea and RAPID software for lesion volume was 0.90 and for hypoperfused tissue was 0.79. Between patients who had TM and those who did not, the median National Institutes of Health Stroke Scale (NIHSS) score (10 vs 18), median ASPECTS (8 vs 5), and mean lesion volume (24.9 ± 18.8 vs 64.0 ± 54.9 ml) were all significantly more favorable for patients with TM ($p < 0.001$), as expected. Likewise, the median 90-day modified Rankin Scale (mRS) score was lower in patients who presented with TM (2 vs 4, $p < 0.001$).

When predicting LVO and DEFUSE TM in all patients ($n = 145$) in the window of 5–23 hours from LKN, 57/145 (39.3%) were true positives. We gave 1 point for an NIHSS score < 17 , ASPECTS 5–7, or age < 55 years. The best-fit receiver operating characteristic (ROC) curve had a C statistic of 0.71 (95% CI 0.63–0.79). In this model, a score of 3 equated to an 80% probability of having a true positive (Table 2). After restriction to only patients with confirmed LVO on CTA ($n = 56$), we predicted the DEFUSE TM definition in patients 5–15 hours from LKN time and found that 28/56 (50%) were true positives. We gave 1 point for an NIHSS score < 18 , ASPECTS > 5 , or age < 65 years. The best-fit ROC curve had a C statistic of 0.85 (95% CI 0.75–0.95). This risk index had a probability of true positive of 80% for a score of 2 and 90% for a score of 3. Last, we produced a risk index that predicted the EXTEND definition of TM in a time window of 4.5–12 hours from LKN in 54 patients, of which 36/54 (67%) were true positives. We gave 1 point each for NIHSS score < 18 , ASPECTS > 5 , and age < 60 years. The best-fit ROC curve had a C statistic of 0.86 (95% CI 0.76–0.97). The risk index had a probability of true positive of 85% and 94% for scores of 2 and 3, respectively.

Discussion

Advancements in stroke interventions have drastically improved outcomes, and innovation continues at a rapid pace. EVT and tPA are reliable and effective tools in the treatment of acute stroke.^{2,19} The appropriate imaging for patient selection in the extended treatment window for both tPA and EVT is limited to major medical centers because of the necessity for perfusion imaging and separate processing software.⁶ This presents a significant challenge for stroke systems of care. Since the publication of the DAWN (DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo) and DEFUSE 3 studies, a 24-hour treatment window is the new standard of care for EVT at most centers, and EXTEND has created the possibility that tPA could be given up to 9 hours from LKN or the midpoint of sleep. This increased time window to treat acute ischemic stroke will increase the catchment area

of most centers, as the cohort of patients previously thought to be too distant may now be eligible despite long transfer times.

These results are preliminary but introduce the possibility that patients could be risk stratified before transfer to a center with perfusion imaging capability, which would be useful for decisions regarding both transfer and the transportation method of transfer. Because of practice patterns for CTP use in the emergency department, our cohort of patients had a greater proportion of LVO (39%, 56/145) than is generally reported. LVOs have been estimated to represent 11% of acute stroke, but this subgroup seems to benefit the most from thrombectomy compared with medical therapy alone.^{6,17,20} Applying our risk index to this cohort of patients would accurately capture a large portion of the 80%–90% of patients with TM using only patient age, baseline NIHSS score, and ASPECTS. We provide two risk indices, one that predicts TM and LVO and one that only predicts TM in patients with known LVO. These proposed indices take into account the real-world limitations of community hospitals, many of which do not have any access to a CTA or do not have 24/7 access. Prior reports have suggested that use of the NIHSS alone is appropriate as a triage tool, but it is not uncommon for patients with LVO to have an unexpectedly low initial NIHSS score because they maintain good collateral flow, and these patients may still benefit from timely revascularization.^{21,22}

In our last risk index evaluation, we used the EXTEND TM definition and treatment time window. In this cohort, we successfully identified true positives with 89% probability for scores of 2 or 3. The EXTEND results were recently published, and it remains uncertain whether they will change stroke patient management as profoundly as the results of the DAWN and DEFUSE 3 trials have, but many centers have started using perfusion for determining tPA eligibility after 4.5 hours from LKN. We present a novel method of identifying which of these patients may benefit from timely transfer to a facility with perfusion imaging capability.

Several prehospital LVO screening tools have been described in prior publications; however, they have several important limitations.^{23–25} First, there are wide ranges of educational standards and training among first responders who would be performing the screening tests. This situation is further complicated by the fact that strokes have varying presentations that make relying on a single clinical scale challenging. Additionally, the sensitivities and specificities of many of the proposed assignments can be prohibitively low, limiting their effectiveness.^{26,27} Last, these preclinical assessments of LVO risk do not predict eligibility for endovascular or thrombolytic interventions as our scales do. Some authors have reported the use of mobile-based imaging scanners for preclinical screening, and although they were effective at delivering patients to thrombectomy-capable centers faster, their upfront and maintenance costs limit their feasibility in the rural settings.^{28–30} Additionally, the clinical variables proposed in this analysis are already collected at most centers, limiting the training burden and cost needed to be used effectively.

Study Strengths and Limitations

Our study has several strengths, such as using the NIHSS and ASPECTS in our risk indices, which have high reproducibility and are already used in the standard-of-care treatment of

stroke patients.^{31,32} We did use the Olea software to measure TM but were able to verify that its measurements of lesion volume and hyperfused tissue had high agreement with a subset of 52 patients who were also processed with the RAPID software, which has extensive validation.^{6,17,33} The main weakness of our study is that it is a single-center, retrospective study and has a small sample size. For these results to be used in clinical practice, a large registry of patients would be needed for us to better estimate the performance of these risk scores. However, the risk indices derived from our preliminary data provide compelling evidence that after its validation in an appropriate sample size, a screening tool such as this could potentially aid in patient transfer decision making.

Conclusions

Ischemic stroke continues to cause a significant clinical and economic burden worldwide. A minority of patients who are eligible for acute stroke interventions receive them, which is problematic because advancements in endovascular and medical therapy continue to improve outcomes. One major impediment to receiving acute stroke treatment is patient selection in resource-limited environments. The risk indices we propose are hypothesis generating in nature but warrant additional prospective study to determine whether clinical, demographic, and CT or CTA imaging data can be used to accurately identify which stroke patients warrant rapid transfer to a medical center with perfusion and EVT capability.

ABBREVIATIONS

ASPECTS	Alberta Stroke Program Early CT Score
CBF	cerebral blood flow
CTP	CT perfusion
DAWN	DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo
DEFUSE 3	Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke
EVT	endovascular thrombectomy
EXTEND	Extending the Time for Thrombolysis in Emergency Neurological Deficits
LKN	last known normal
LVO	large-vessel occlusion
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
TM	target mismatch

tPA tissue plasminogen activator

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TABLE 1. Baseline demographics of the entire cohort, stratified by the presence of TM on CTP

Variable	Entire Cohort (n = 145)	TM		p Value
		Yes (n = 85)	No (n = 60)	
Age, yrs	63.9 ± 16.7	62.2 ± 17.5	66.5 ± 15.3	0.126
Male sex	78 (53.8)	44 (51.8)	34 (56.7)	0.560
Time from LKN to CT, hrs	14.1 ± 4.7	14.3 ± 4.8	13.8 ± 4.6	0.517
NIHSS score	14 (7–19)	10 (6–15)	18 (10–23)	<0.001
ASPECTS	7 (5–9)	8 (6–9)	5 (3–8)	<0.001
Occlusion of ICA or M ₁ , MCA	99 (68.3)	57 (67.1)	42 (70.0)	0.708
Hypertension	87 (60.0)	50 (58.8)	37 (61.7)	0.731
Hyperlipidemia	65 (44.8)	40 (47.1)	25 (41.7)	0.520
Diabetes	35 (24.1)	21 (24.7)	14 (23.3)	0.849
Atrial fibrillation	50 (34.5)	28 (32.9)	22 (36.7)	0.642
Lesion volume, ml	41.1 ± 42.6	24.9 ± 18.8	64.0 ± 54.9	<0.001
Hypoperfused volume, ml	72.3 ± 54.8	71.2 ± 43.3	73.7 ± 68.3	0.788
Mismatch ratio	2.8 ± 2.9	4.0 ± 3.3	1.2 ± 0.5	<0.001
90-day mRS score (n = 135)	3 (1–5)	2 (1–3)	4 (2–6)	<0.001

ICA = internal carotid artery; MCA = middle cerebral artery.

Values are presented as number (%) of patients, mean ± SD, or median (IQR) unless otherwise indicated. Boldface type indicates values that are significant at $p < 0.05$.

Predictive models for identified outcomes with C statistics and probability of true positive and 95% Cis

TABLE 2.

TM Outcome	No. of Patients	Predictors (+1 point each)	C Statistic (95% CI)	Risk Index Score	Probability of True Positive (95% CI)	No. of True Positives/Total No.
DEFUSE 3						
				0	0.12 (-0.01 to 0.25)	3/25
5- to 23-hr time window	145 (all CVA)	NIHSS score <17; CTA ASPECTS 5-7; age <55 yrs	0.71 (0.63-0.79)	1	0.53 (0.22-0.44)	23/70
				2	0.58 (0.42-0.73)	23/40
				3	0.80 (0.55-1.05)	8/10
EXTEND						
				0	0.08 (-0.07 to 0.24)	1/12
5- to 15-hr time window	56 (confirmed LVO)	NIHSS score <18; CTA ASPECTS >5; age <65 yrs	0.85 (0.75-0.95)	1	0.52 (0.11-0.53)	6/19
				2	0.80 (0.60-1.00)	12/15
				3	0.90 (0.71-1.09)	9/10
EXTEND						
				0	0.14 (-0.12 to 0.40)	1/7
4.5- to 12-hr time window	54 (all CVA)	NIHSS score <18; CTA ASPECTS >5; age <60 yrs	0.86 (0.76-0.97)	1	0.27 (0.01-0.54)	3/11
				2	0.85 (0.69-1.00)	17/20
				3	0.94 (0.82-1.06)	15/16

CVA = cerebrovascular accident.