Identifying Severe Stroke Patients Likely to Benefit From Intervention Despite a Delay of a Day

R. Gilberto González, MD[1,3*]; Gisele Sampaio Silva MD[2]; Julian He, MD[1]; Saloomeh Sadaghiani, MD[2]; Ona Wu, PhD[3]; Aneesh B. Singhal, MD[2]

Neuroradiology Division(1), Stroke Service (2), and Athinoula A. Martinos Center for Biomedical Imaging(3), Massachusetts General Hospital, Harvard Medical School, 55 Fruit St, Boston, MA 02114, USA

* Corresponding author: R. Gilberto González, MD, GRB-273A, 55 Fruit St, Boston, MA 02114

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Abstract

Background and Purpose: Severe ischemic strokes caused by large vessel occlusion (LVO) are treatable up to 24 hours after onset. But not all patients will benefit either because the infarct enlarges too rapidly or because the patient is not at center that is capable of treatment. The purpose was to find biomarkers that reliably identify patients who are likely to benefit from intervention despite long delays .

Methods: Thirty-eight acute ischemic stroke patients with LVO who did not undergo thrombolysis or thrombectomy had serial imaging with MRI at presentation and then at ~12 hours, ~1 day, & ~2 days after onset. Presenting clinical and neuroimaging predictors of a therapeutically auspicious ischemic core size (<50 ml) one day after stroke onset were identified.

Results: Ischemic core initial growth rate (IGR) was the only independent predictor of functional outcome at 3 months (P=0.002), and a receiver operator characteristics (ROC) analysis revealed that an IGR of <5.4 ml/hr had a 95% sensitivity with a low (5.6%) false positive rate for identifying patients who would have an ischemic core of <50 ml at one day *post ictus*. Selection using an initial DWI lesion volume <37 ml was similarly powerful with a 90% sensitivity and a low false positive rate. Other imaging markers derived from CT scans were less effective, but may be more practical. Published reports of over 600 LVO ischemic stroke patients disclosed that about half met the highly favorable IGR criteria of <5.4 ml/hr at presentation.

Conclusions: Ischemic core initial growth rates of <5.4ml/hr and initial ischemic cores of <37 ml are excellent biomarkers for selecting LVO patients that are likely to benefit from intervention despite long delays due to transfer to thrombectomy-capable stroke centers. Published accounts suggest that about half of all LVO stroke patients meet these criteria.

Introduction

Strokes caused by large vessel occlusions (LVOs, viz., internal cerebral artery and/or proximal middle cerebral artery occlusions) will typically produce severe neurological deficits and poor outcomes if not treated. [1] While only up to a third of all ischemic strokes are of this type, they cause the majority of deaths and poor outcomes due to stroke. Several clinical trials have demonstrated that these types of strokes may be effectively treated with thrombectomy within timeframes of 6-8 hours.[2-8] More recently, the DAWN[9] and DEFUSE-3[10] trials have proven that thrombectomy may be successful up to 24 hours *post ictus*. The widening of the thrombectomy time window presents new opportunities to treat the many LVO stroke patients that do not live in the immediate vicinity of centers capable of this procedure, or who are recognized late as having a stroke or arrive late to the hospital. The challenge is to reliably identify those patients who will benefit from thrombectomy despite delays.

The purpose of this investigation was to identify biomarkers for selecting patients who are likely to have favorable outcomes despite sustaining significant time delays before undergoing thrombectomy. It is predicated on our observation of ischemic core stability for many hours in patients with LVOs. [11] To identify effective biomarkers, we used the observation from the HERMES collaboration[12] that patients with final infarcts of <50ml after thrombectomy had an ~80% probability of living independently at 3 months irrespective of initial symptom severity. We searched for presentation biomarkers that identify LVO patients that would have ischemic cores of <50ml one day after stroke onset.

Methods

Patient selection and evaluation

This study was compliant with the Health Insurance Portability and Accountability Act (HIPAA) and was approved by our institutional review board (IRB). The data are from the Normobaric Oxygen Therapy (NBO) in Acute Ischemic Stroke Trial (see http://clinicaltrials.gov/show/NCT00414726 for the complete trial inclusion and exclusion criteria). We included patients who met the following criteria: 1) MR imaging including a DWI scan showing acute ischemic injury; 2) CT angiography (CTA) or MR angiography (MRA) of the head; 3) three or more MRIs performed within ~2 days of stroke onset. Of the 60 subjects who underwent serial MRI in the clinical trial, 50 met inclusion criteria for this analysis. For patients whose stroke onset was not witnessed, onset time was estimated as midway between last seen well and first seen with stroke symptoms. [13] National Institutes of Health Stroke Scale (NIHSS) scores were recorded at all time points, and the modified Rankin Scale (mRS) was recorded 3 months after admission, by investigators blinded to MRI lesions and treatment assignment. In patients with arterial occlusions, a LVO was defined as occlusion of the terminal ICA and/or proximal MCA (M1 and/or M2 origin). A favorable outcome was defined as living independently (mRS score of 2 or less) at 3 months.

Imaging Techniques

MRI scans were obtained at admission and repeated after ~12 hours, ~1 day and ~2 days after onset using a clinical 1.5-T (General Electric, Waukesha, Wisconsin) MRI system. Sagittal T1, axial DWI, Fluid-attenuated inversion recovery (FLAIR) T2, and

gradient-echo sequences were performed at each time point. In addition, head MRA was obtained with the first three MRI scans.

DWI were acquired using the following median values: field of view of 220 mm, 25 slices, thickness of 5 mm, gap of 1 mm, TR of 5 seconds, TE of 85.3 ms, acquisition matrix 128x128, and with b=0 s/mm2 and b=1000 s/mm2 in at least 6 diffusion-gradient directions. Isotropic DWI and apparent diffusion coefficient (ADC) maps were calculated using techniques previously described.[14] FLAIR imaging were performed with a fast-spin echo sequence, with the following median values: 10s TR, 145ms TE, 2200ms TI, 256x192 matrix, 220mm FOV, 25 5mm slices with 1mm gap. Gradient-echo T2* imaging median values included TR/TE of 817/25ms, 20^{o} flip angle, 256x192 matrix, 220 mm FOV, 25 5mm thick slices and 1 mm gap. Perfusion MRI data were acquired using the following median values: field of view of 220 mm, 15 slices, thickness of 5 mm, gap of 1 mm, TR of 1.5 seconds, TE of 40 ms, flip angle 60 degrees, acquisition matrix 128x128. 80 data points were acquired using gradient-echo echo planar imaging readout. Mean-transit time (MTT) and Tmax (time at which the tissue response function reached maximum value) perfusion maps were calculated using automated oscillation index regularized deconvolution. [15]

The 3D time-of-flight MRA consisted of a 7cm-thick slab positioned over the circle of Willis. The median imaging parameters were TR/TE=36/6.8 ms, 25° flip-angle, 180 mm FOV, 320x192 matrix, 101 axial images, 1.4-mm-thick with 0.7-mm overlap. The MRA source images were post-processed into maximum intensity projection images.

CT angiography was performed using multi-detector scanners (GE Medical Systems, Milwaukee, WI) from the vertex to the aortic arch following injection of 65–

140 ml of a nonionic contrast agent (Isovue; Bracco Diagnostics, Princeton, NJ) at a rate of 3 to 4 ml/s. The median parameters were 1.25-mm slice thickness, 220 mm reconstruction diameter, 120 kV, and 657 mA.

Image Analysis

DWI abnormalities were outlined visually using both the DWI and ADC maps from the same time-point. Tmax lesions were outlined visually with knowledge of DWI and ADC, while MTT abnormalities were outlined visually with knowledge of DWI, ADC and Tmax maps. Analysts blinded to treatment assignment, time-point and clinical information performed all outlines. All outlines were performed using semi-automated, open-source software (Display, Montreal Neurologic Institute, Montreal). Lesion growth was calculated as the DWI lesion volume divided by the time in hours from last seen well or from the prior measurement.

Statistical Analysis

All values are reported as percentage, mean (standard error), or median. Mann-Whitney, Kruskal-Wallis, ANOVA, or Friedman Test, as appropriate, was used to assess changes in lesion volumes across the 4 time points. Correlation analyses were performed between DWI volumes and time as well as between DWI volumes and natural logarithm of time. Simple and multivariable regression analyses were used to assess the relationship of clinical and imaging variables measured at the time of admission with functional outcomes at 3 months. P-values of less than 0.05 were considered statistically significant. Receiver operator characteristic (ROC) analyses were performed to evaluate the sensitivity and specificity of presenting variables. Analyses described were performed

using MedCalc version 14.8.1 and SPSS statistical software (release 20.0 for Windows; SPSS, Chicago, IL). ROC analyses were performed using MedCalc.

Results

We present a study of 50 patients with acute ischemic stroke that had serial MRI scans. No patient received thrombolytic therapy or thrombectomy; 24 were treated with NBO and 26 with medical air for 8 hours. Demographic and clinical information is displayed in Table 1. Initial MRI scans (MRI-1) were obtained at a mean time after stroke onset of 5.0 hours (range, 1.6-9.5 hours). Subsequent scans (MRI-2, MRI-3 and MRI-4) were acquired at a mean of 11.7 hours (range, 7-15 hours), 1 day (mean 25.8 hours; range, 22-33 hours), and 2 days (mean 49.7 hours; range, 43-57 hours) following stroke onset.

Table 1. Baseline Variables and Stroke Etiology

	All (N=50)	LVO (N=38)	Non LVO (N=12)	p Value *
Age	71	72	66	0.19
Sex				0.14
Female	24	16	8	
Male	26	22	4	
Mean NIHSS score	12	14	8	0.003
Mean Glucose (mg/dl)	134	137	127	0.42
Treatment type				0.87
NBO	24	18	6	
Medical air	26	20	6	
Site of arterial occlusion				< 0.0001
ICA	8	8	0	
M1	17	17	0	
M2	13	13	0	
none of the above	12	0	12	
24-hour recanalization				0.27
Complete	5	5	0	
Partial	10	8	2	
None	29	22	7	
Unavailable	6	3	3	
Stroke Etiology				0.09
Large artery atherosclerosis	5	5	0	
Cardio-aortic embolism	30	23	7	
Small artery occlusion	2	0	2	
Other uncommon causes	7	5	2	
Undetermined causes	6	5	1	

* LVO vs Non LVO Student T test or Chi-Square test as appropriate, significant if <0.05; LVO: large vessel occlusion. NBO: Normobaric Oxygen Therapy; NIHSS: National Institutes of Health Stroke Scale.

Selected diffusion and perfusion images from a patient who presented with an initial DWI lesion volume of <50ml and a large diffusion/perfusion mismatch are shown in Figure 1. Despite persistence of arterial occlusion and a large mismatch in this patient, the ischemic core grew slowly over 48 hours and remained <50ml.

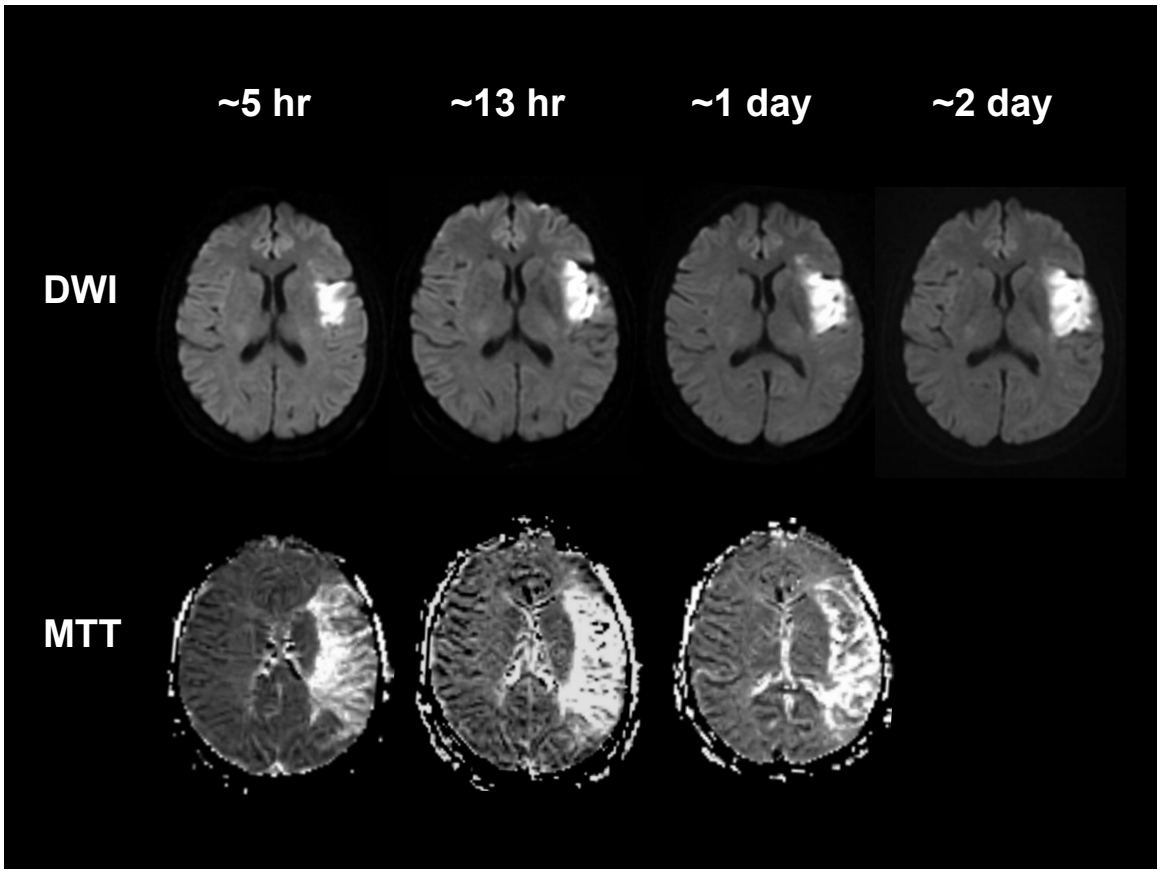

Figure 1. Diffusion and perfusion images of patient with a left MCA mainstem occlusion that persisted at 24 hours. Diffusion/perfusion MRI was performed at ~5 hours, ~ 13 hours, ~1 day and ~2 days from last seen well.

Patient outcomes with respect to baseline clinical and imaging measures

Functional outcomes at 3 months were documented in 43 patients. The relationships between measures obtained on the day of admission and functional outcomes were evaluated using regression analysis. The admission measures evaluated included age, serum glucose, sex, treatment, NIHSS, the use of NBO, DWI lesion volume, estimated initial lesion growth rate, MTT volume and MTT-DWI mismatch volume. Favorable outcomes included patients with an mRS of 0-2. Only NIHSS, DWI lesion volume, initial lesion growth rate and MTT volume were found to be predictors of functional outcome by univariable regression analysis; the data for these variables are displayed in Figure 2. A multivariable regression analysis was then performed on these 4 variables that revealed that IGR was the only independent predictor of a favorable outcome (P = 0.002).

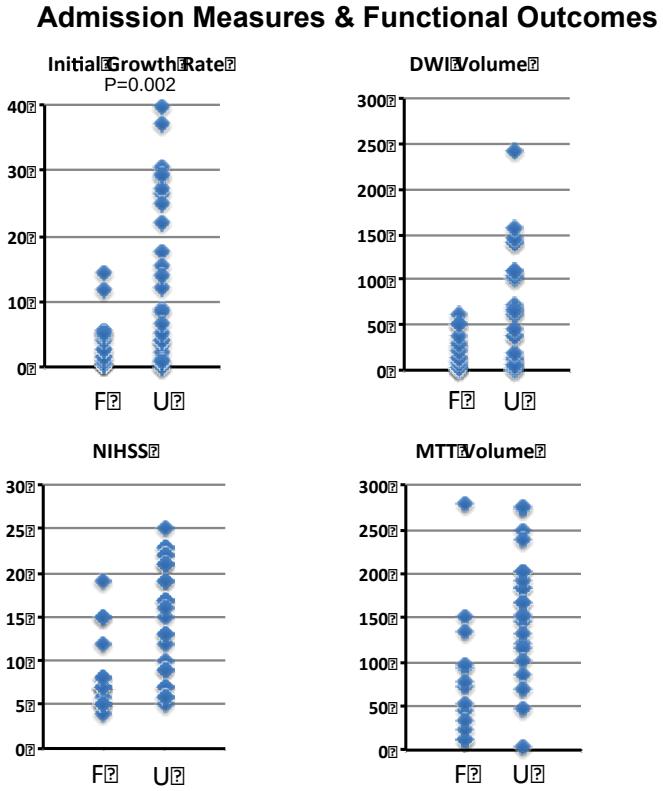

Figure 2. Admission measures and functional outcomes. The graphs depict the relationships between favorable (F) and unfavorable (U) patient outcomes to their initial DWI lesion volume growth rate, baseline DWI lesion volume, admission NIH stroke scale score, and mean transit times lesion volume at time of admission. These were the only measures that were found to be statistically significant by univariable regression analysis. * Multivariable regression analysis revealed that initial lesion growth was the only independent predictor of 3-month mRS (P = 0.002).

Temporal Ischemic Core Volume Changes in Patients with LVOs

Thirty-eight patients had LVOs and Figure 3 displays the changes in ischemic core volumes, grouped by baseline DWI lesion volumes. Patients with small initial ischemic cores (<50ml) at baseline had slower core growth compared to patients with large baseline cores (>100ml). Inspection of the figure reveals that there are outliers from these general patterns.

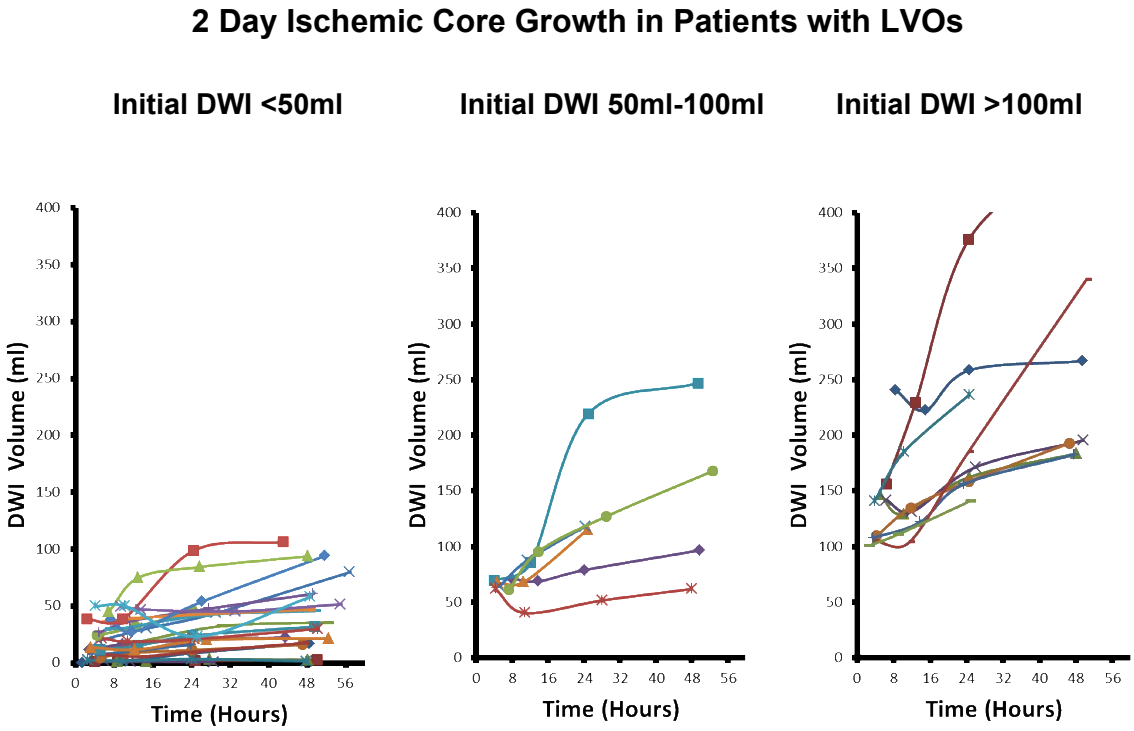

Figure 3. Ischemic core growth in 38 patients with LVO. Left. 23 patients with LVO and baseline DWI lesion volume less than 50 ml. Middle. 6 patients with LVO and DWI lesion volume of between 50 and 100 ml. Right. 9 patients with LVO and DWI lesion volume greater than 100 ml.

Ischemic core volume growth rates in patients with LVOs

Table 2 displays the average ischemic lesion growth in LVO patients grouped by initial DWI lesion volume. The highest average growth occurred during the initial period between stroke onset and the time of the first imaging. In all groups, the second period (~5-12 hours) the average growth of the core was 10% less than the initial period. The

lesion growth during the other periods was also much lower than the initial period for all groups. Ischemic core growth is nonlinear: linear regression resulted in a poor correlation coefficient between lesion volumes and time (R^2<0.6). Conversely, correlation coefficients were high (R^2≥0.96) between lesion volumes and the natural logarithm of time, suggesting logarithmic growth of the ischemic core over 2 days.

Table 2. Diffusion Lesion Growth Rates

Group	MRI-1 lesion volume ml(SE)	Symptom Onset to MRI-1 growth rate ml/hr(SE)	MRI-1 to MRI-2 growth rate ml/hr(SE)	MRI-2 to MRI-3 growth rate ml/hr(SE)	MRI-3 to MRI-4 growth rate ml/hr(SE)	P value*
All patients (n=50)	43 (8)	8.9 (1.5)	0.7 (0.3)	1.5 (0.4)	0.7 (0.2)	<0.01
LVO patients grouped by admission DWI lesion volume						
<50 mL (n=23)	20 (3.5)	4.0 (0.8)	0.4 (0.3)	0.6 (0.2)	0.4 (0.1)	<0.01
50-100 mL (n=6)	66 (1.7)	12.5 (1.4)	1.2 (1.3)	3.3 (1.5)	1 (0.3)	0.08
>100 mL (n=9)	139(14.5)	29.5 (1.9)	1.8 (1.6)	4.3 (1.1)	2 (0.8)	<0.01
*P value**	<0.01	<0.01	0.74	<0.01	<0.01	
LVO patients with persistent occlusions at 1 day grouped by admission DWI lesion volume						
<50mL (n=14)	15 (3.5)	3.4 (1.1)	0.1 (0.2)	0.8 (0.3)	0.5 (0.1)	<0.01
50-100 mL (n=3)	66 (2.4)	13.3 (2.7)	2.4 (1.5)	5.3 (2.6)	1.4 (0.3)	0.24
>100 mL (n=5)	138 (8.7)	28.1 (2.6)	2.6 (2.8)	5.5 (1.9)	2.8 (1.2)	0.01
*P value**	<0.01	<0.01	0.38	<0.01	<0.01	

*Mann-Whitney, Kuskal-Wallis, ANOVA, or Friedman Test, as appropriate.
Abbreviations: NBO, normobaric oxygen therapy; ICA, internal carotid artery; MCA, middle cerebral artery; DWI, diffusion lesion volume. MRI-1 performed at mean 5.0 hours (range, 1.6-9.5 hours) after stroke onset; MRI-2, 11.7 hours (range, 7-15 hours); MRI-3, 25.8 hours (range, 22-33 hours); and MRI-4, 49.7 hours (range, 43-57 hours) after stroke onset.

Ischemic core volume growth rates in patients without LVOs

Twelve patients did not have anterior LVOs. These included 2 involving the PCA, one ACA, one M3, and no occlusion was identified in the other patients. All of these patients had very small DWI lesions at baseline (mean baseline DWI volume 4.2 (1.2) ml). The initial growth rate was 0.9 (0.3) ml/hr, after which the growth rates dropped significantly to 0.1 ml/hr, 0.1 ml/hr, and 0.04 ml/hr ($p<0.01$).

Biomarkers of Slow Progressors Likely to Benefit From Delayed Thrombectomy

To find the best identifiers of slow progressors who are likely to benefit from delayed thrombectomy, receiver operator characteristic (ROC) analyses were performed. The target was an ischemic core size of <50ml at the time of the 1-day scan. Figure 4 displays the ROC graph showing the sensitivity versus the false positive rate for predicting this target for IGR, initial core volume, TTP, Tmax, mismatch volume and the NIHSS. Details of the ROC analyses are shown in Table 3. IGR and initial core volume were the best performing markers with the highest sensitivities and the lowest false positive rates.

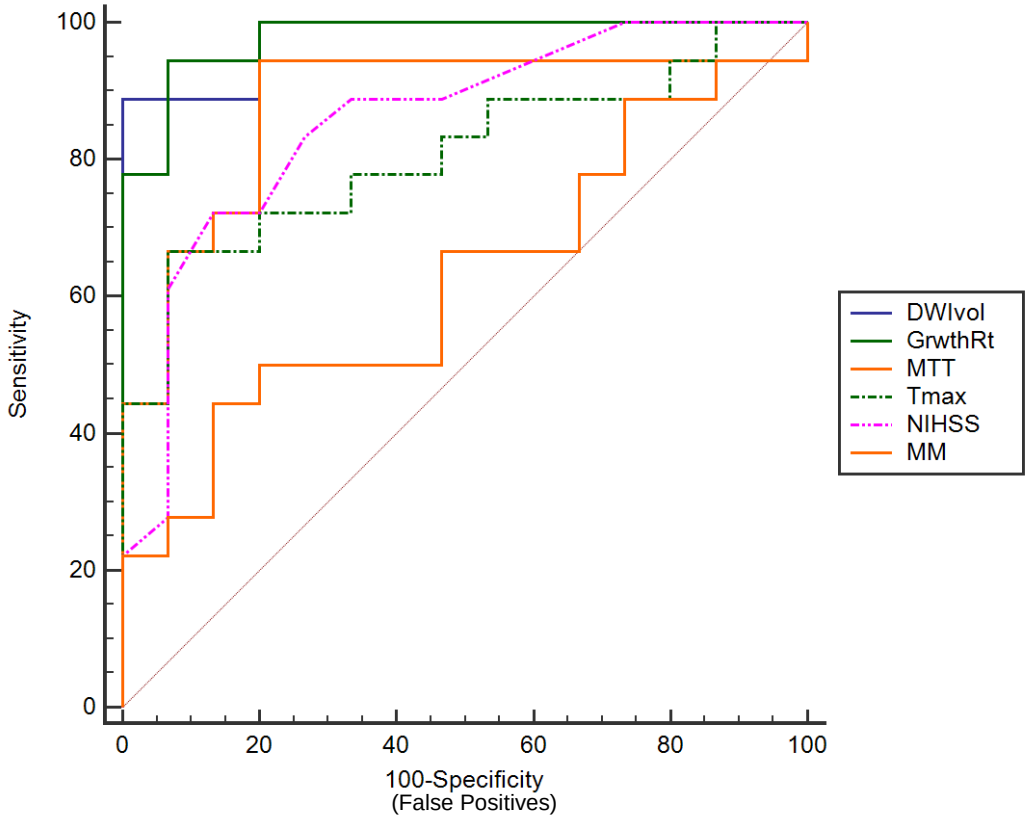

Figure 4. Receiver operator characteristic (ROC) curves of variables predicting ischemic core volumes <50 ml one day after stroke onset. Data is from all 38 patients with an LVO identified on CT or MR angiography. Presentation variables include ischemic stroke initial growth rate (GrwthRt), initial core volume (DWIvol), MR perfusion mean transit time (MTT) and time to maximum signal change (Tmax), diffusion/perfusion mismatch (MM) and NIH stroke scale (NIHSS).

Table 3. ROC Analyses of Baseline Variables To Predict Ischemic Core of < 50ml One Day *Post Ictus*

Variable	Criteria	Sensitivity	Specificity	AUC (95% CI)
Initial Core Growth Rate	<5.4 ml/hr	95%	94%	0.98 (0.87-1.0)
Baseline DWI Volume	<37 ml	90%	100%	0.98 (0.88-1.0)
MTT	<150 ml	94%	80%	0.88 (0.72-0.96)
NIHSS	<13	75%	89%	0.87 (0.72-0.95)
Tmax	<128 ml	67%	93%	0.81 (0.63-0.92)
Diff/Perf Mismatch	<50 ml	44%	87%	0.63 (0.44-0.79)

Discussion

We found that LVO ischemic stroke patients with ischemic core IGR of <5.6 ml/hr or an initial ischemic core volume of <36 ml have a high probability of having an ischemic core size of less than 50 ml one day after stroke onset. This is highly significant because a 50 ml final infarct volume after thrombectomy results in favorable functional outcomes at 3 months even in patients who present with severe neurological deficits. [12] The reliable identification of LVO patients likely to have ischemic cores of this size or smaller despite delays of many hours could expand the use of thrombectomy, and more widely apply the lessons from the recent successful DAWN [9] and DEFUSE 3[10] thrombectomy trials.

The reliability of a low IGR to predict a small ischemic core many hours later may be explained by the nonlinearity in the growth of the ischemic core. In animal stroke models, the ischemic core typically grows in a logarithmic fashion. [16] This appears to be

the case in people as well: Wheeler et al. [17] deduced logarithmic infarct growth rates using baseline and 1-week core volumes in LVO patients. This type of growth is supported by our data. In our cohort, most of the core growth occurred by the time of the first imaging session, with less than 10% further growth over remainder of the first day. Comparison of line fits of core volume with respect to time or the natural logarithm of time favored logarithmic growth. However, we also observed a high variability in lesion growth in patients with the occlusion of the same artery or arterial segment. This is best explained by the differences in the collateral circulation. [18-20]

We found a low IGR in the majority LVO patients that were recruited into the NBO clinical trial. From the multicenter DEFUSE 2 trial, Wheeler et al. [17] reported that the median IGR was also low at 3.1 ml/hr in 65 patients. This raises the question of how commonly a low IGR occurs in patients with LVO that were not part of clinical trials. Some have speculated that number of patients that might benefit from thrombolysis beyond 6 to 8 hours is small, perhaps 5%.[21] However, the published evidence suggests otherwise. Desai, et al.[22]reported on 185 consecutive LVO ischemic stroke patients evaluated at the University of Pittsburgh, and found a median IGR of 2.6 ml/hr. Olivot et al. [23] reported a median IGR of 6.1 ml/hr in 166 patients in a study from Toulouse, France. Finally, in the study reported by Hakimalahi [20] the median IGR was 4.2 ml/hr in 186 LVO patients who presented to the Massachusetts General Hospital emergency department. Taken together, published evidence from over 600 LVO patients suggest that around half of such patients are slow progressors.

An important consideration is whether LVO slow progressors still need thrombectomy after a many-hour delay. After all, these patients must have a robust

collateral circulation that may persist until there is spontaneous recanalization. But we found that over half of slow progressors still had the occlusion 1 day after stroke onset (Table 2). Also, only 50% of slow progressors had favorable functional outcomes at 3 months indicating that not undergoing thrombectomy may be hazardous (Figure 2).

Our study also suggests that there may be more practical but still effective alternatives to MRI. The ROC analyses (Figure 4, Table 3) hint at several approaches, and there may be others. This is critical because most centers where patients first present may not have MRI available. A suitable alternative to MRI may be CT perfusion. For example, the MR perfusion measurement MTT performed well with an AUC of 0.89. An MTT lesion criterion of <150ml would identify over 90% of patients destined to have a small core despite a long delay, and would result in only 2 false positives for every 10 patients selected for transfer. It is likely that a CT perfusion MTT measurement would be similarly effective. Another approach is the use of the NIHSS score of <13 in patients with an LVO identified by CTA. Using this approach, three-quarters of slow progressors would be identified, and the false positive rate would be low, only 1 in 10. There may be other effective imaging biomarkers such as CT perfusion measurements (CBV or CBF estimates of the ischemic core). Other possibilities include collateral assessment of CT angiography images and evaluation of CTA source images. Finally, developments in artificial intelligence assessment of neuroimaging may yield rapid, reliable assessments based on CT/CTA data.

A unique aspect of this study is that it documented the natural history of ischemic core evolution, without confounders such as thrombolytic use or thrombectomy. There is the potential confound of NBO therapy on the NBO-treated arm; however we did not find

any difference between the NBO and room air treated groups on any variable that was measured including outcomes. Another possible limitation is the use of midway time between last known well and symptom discovery for estimation of stroke. The effect would be that the true optimal IGR might be higher than calculated here. In any case, prospective studies are needed to determine the value of imaging biomarkers in making triage decisions for transport of patients for thrombectomy.

In conclusion, ischemic core initial growth rates of <5.4 ml/hr and ischemic core volumes of <36 ml are excellent biomarkers for selecting LVO patients that are likely to benefit from transfer to thrombectomy-capable stroke centers despite a substantial delay. Published accounts suggest that about half of all LVO stroke patients meet these criteria. Imaging biomarkers based on CT scans are slightly less effective, but may be more practical. These observations herald an opportunity to treat many more severe ischemic stroke patients with thrombectomy by transporting patients identified with imaging biomarkers.

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