Brief Report

Prevalence of Imaging Biomarkers to Guide the Planning of Acute Stroke Reperfusion Trials

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Background and Purpose—Imaging biomarkers are increasingly used as selection criteria for stroke clinical trials. The goal of our study was to determine the prevalence of commonly studied imaging biomarkers in different time windows after acute ischemic stroke onset to better facilitate the design of stroke clinical trials using such biomarkers for patient selection.

Methods—This retrospective study included 612 patients admitted with a clinical suspicion of acute ischemic stroke with symptom onset no more than 24 hours before completing baseline imaging. Patients with subacute/chronic/remote infarcts and hemorrhage were excluded from this study. Imaging biomarkers were extracted from baseline imaging, which included a noncontrast head computed tomography (CT), perfusion CT, and CT angiography. The prevalence of dichotomized versions of each of the imaging biomarkers in several time windows (time since symptom onset) was assessed and statistically modeled to assess time dependence (not lack thereof).

Results—We created tables showing the prevalence of the imaging biomarkers pertaining to the core, the penumbra and the arterial occlusion for different time windows. All continuous imaging features vary over time. The dichotomized imaging features that vary significantly over time include: noncontrast head computed tomography Alberta Stroke Program Early CT (ASPECT) score and dense artery sign, perfusion CT infarct volume, and CT angiography collateral score and visible clot. The dichotomized imaging features that did not vary significantly over time include the thresholded perfusion CT penumbra volumes.

Conclusions—As part of the feasibility analysis in stroke clinical trials, this analysis and the resulting tables can help investigators determine sample size and the number needed to screen. **(*Stroke*. 2017;48:00-00. DOI: 10.1161/STROKEAHA.117.016759.)**

Key Words: biomarkers ■ computed tomographic angiography ■ hemorrhage ■ patient selection ■ stroke

Recent clinical trials with positive results, including MR-CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands),[1] ESCAPE (The Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke),[2] SWIFT-PRIME (Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke),[3] EXTEND-IA (Extending the Time for Thrombolysis in Emergency Neurological Deficits-Intra Arterial)[4] THERAPY (The Randomized, Concurrent Controlled Trial to Assess the Penumbra System's Safety and Effectiveness in the Treatment of Acute Stroke),[5] and REVASCAT (Revascularization With Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke),[6] have shown the efficacy of endovascular therapy in the treatment of patients with acute ischemic stroke. One major difference between these positive trials and the previous negative ones (such as IMS III-Interventional Management of Stroke III trial)[7] is the use of imaging biomarkers to select patients for randomization; the imaging biomarkers used for each trial varied from trial to trial (Table I in the online-only Data Supplement).[8] In upcoming trials, both clinical variables, such as age and National Institutes of Health Stroke Scale (NIHSS) score, and imaging biomarkers will likely be used to identify patient cohorts and determine the feasibility of these trials. To compute accurate feasibility estimates of sample size, number needed to screen, and power, it is crucial to know the prevalence of both the clinical variables and imaging biomarkers in each of the time windows after symptom onset. Although there are existing databases that describe the prevalence of clinical variables,[9] the community lacks a similar database that describes the prevalence of imaging

Received January 26, 2017; final revision received January 26, 2017; accepted February 23, 2017.

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The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.117.016759/-/DC1.

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biomarkers that could be used in conjunction with clinical databases to determine appropriate cohorts and accurately assess feasibility.

The purpose of this study is to determine the prevalence of commonly studied imaging biomarkers in different time windows after symptom onset to better facilitate the design of stroke clinical trials using such biomarkers for patient selection.

Methods

Study Population

For this study, we compiled retrospective data collected between January 2008 and June 2014 at the Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland, and the University of Pittsburgh Medical Center, Pittsburg, PA. Similar imaging workups were used to assess patients with acute ischemic stroke at both institutions and institutional review boards at each institution approved clinical and imaging data collection and analysis. All patients in this registry who fulfilled the following criteria were included in this study:

1. a clinical suspicion of acute ischemic stroke on admission,
2. up to 24 hours since symptom onset,
3. baseline imaging, including a noncontrast head computed tomography (CT), a perfusion CT (PCT), and a CT angiography,
4. no subacute/chronic/remote infarct and no hemorrhage after review of the baseline noncontrast head computed tomography.

Clinical Data

Along with imaging biomarkers, we also collected age, sex, and time from symptom onset to baseline imaging for each patient.

Imaging Biomarkers

Noncontrast Head Computed Tomography Biomarkers

Alberta Stroke Program Early CT (ASPECT) score[10] and presence or absence of a dense artery sign of middle cerebral artery.

PCT Biomarkers

Ischemic core and ischemic penumbra volume calculated automatically from the baseline PCT data using a previously described method,[11] presence or absence of target mismatch[12] ([ischemic penumbra+ischemic core]/ischemic core ratio >1.8), and presence or absence of malignant profile[13] (ischemic core >100 mL).

CT Angiography Biomarkers

Location of the clot and the collateral status (intracranial ICA, M1, M2, others, or combinations of these.), collateral circulation on thick maximal intensity projections according to the scoring system previously described by Tan et al.[14]

Statistical Analysis

The prevalence of each dichotomous imaging biomarker was described in percentages with exact binomial 95% confidence intervals and for 7 time windows (time since symptom onset). Time windows were < 3 hours, 3 to 4.5 hours, 4.5 to 6 hours, 6 to 8 hours, 8 to 12 hours, 12 to 18 hours, and 18 to 24 hours (Tables II through IV in the online-only Data Supplement).

Results

Study Population

We screened 937 patients and included a study cohort of 612 patients as depicted in Figure I in the online-only Data Supplement.

Imaging Biomarkers

The prevalence of the imaging biomarkers pertaining to the core, the penumbra, and the arterial occlusion for the different time windows is summarized in online Tables II through IV in the online-only Data Supplement. Our data are available for clinical trialists to use in the form of an interactive web application, available at https://neuroradiology.shinyapps.io/strokeimbio/, to assist with power calculations and in selecting patient cohorts.

Discussion

We examined the prevalence of imaging biomarkers in patients with acute ischemic stroke in different time windows after symptom onset and established tables to guide researchers in feasibility analysis. These tables provide a means by which to accurately estimate sample size, power, and number needed to screen for stroke clinical trials that plan to use imaging biomarkers for enrollment selection. Our data are available for clinical trialists in selecting patient cohorts and assist with power calculations in the form of an interactive web application (https://neuroradiology.shinyapps.io/strokeimbio/).

Some of the imaging biomarkers, including penumbra volume and arterial occlusions at specific sites, did not show any significant variation over time. For instance, a PCT penumbra mismatch >50% was observed in ≈80% of the patients in each time window up to 18 hours after symptom onset. This observation reinforces the concept that selection of patients using selected imaging biomarkers can be used to extend the therapeutic time window. Imaging can be used to identify patients with a positive imaging biomarker, whereas relying on time would not allow to determine whether the imaging biomarker is positive or negative.

Interestingly, some imaging biomarkers that varied over time did not follow the expected trend. As an illustration, the PCT infarct volume decreased over time. This observation is counterintuitive because it is well known that in an individual patient with a stroke caused by an arterial occlusion, the infarct volume expands over time. Although infarct volume may certainly increase over time within an individual, our time plots do not represent the time course of an infarct in one individual patient but rather, a population distribution of infarct size on admission imaging. The latter is likely to be influenced by several factors other than pathophysiology. For example, patients with a larger stroke may be more symptomatic and as a result, may present earlier for medical attention.[15]

We acknowledge several limitations to this study. First, it is retrospective in nature and our study population may not be representative of stroke clinical trial populations. The second limitation is that we did not have an equal distribution of patients in each of the different time windows we assessed. We had more patients in the earlier time windows, translating into narrow confidence intervals, and fewer patients and thus, larger confidence intervals in later time windows. For example, we only had 20 patients in the 18- to 24-hour time window, which limited our ability to make strong inferences about patients who present late. Of note, in the online tool (https://neuroradiology.shinyapps.io/strokeimbio/), the users

can define the time windows they are interested in, including wider time windows with smaller confidence intervals.

Despite these limitations, there are several notable strengths of this study. First, we had a large cohort of over 600 patients with baseline imaging in 3 commonly used imaging modalities and were able to characterize 22 imaging biomarkers, both dichotomous and continuous, in 7 time windows. A second strength of this study lies in the tables and figures of these imaging biomarkers that can guide clinical trial design and help produce accurate estimations of sample size, power, and number needed to screen. Finally, we developed an interactive web application that clinical researchers can use to select their own cutoffs and sets of imaging biomarkers from this database, thereby enabling an accurate feasibility assessment of upcoming clinical trials.

Conclusions

In conclusion, we present tables describing the prevalence of imaging biomarkers in patients with acute ischemic stroke in different time windows after symptom onset to help investigators make sample size and number needed to screen calculations as part of their feasibility. We offer a tool to facilitate the planning of the stroke clinical trials that use imaging biomarkers, and we encourage the principal investigators of the completed stroke clinical trials to contribute their data to this resource to enrich it and make it more representative of the population with stroke.

Disclosures

None.

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Stroke
Journal of the American Heart Association

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Stroke. published online April 6, 2017;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

ONLINE SUPPLEMENT

Prevalence of Imaging Biomarkers to Guide the Planning of Acute Stroke Reperfusion Trials

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Online Figures

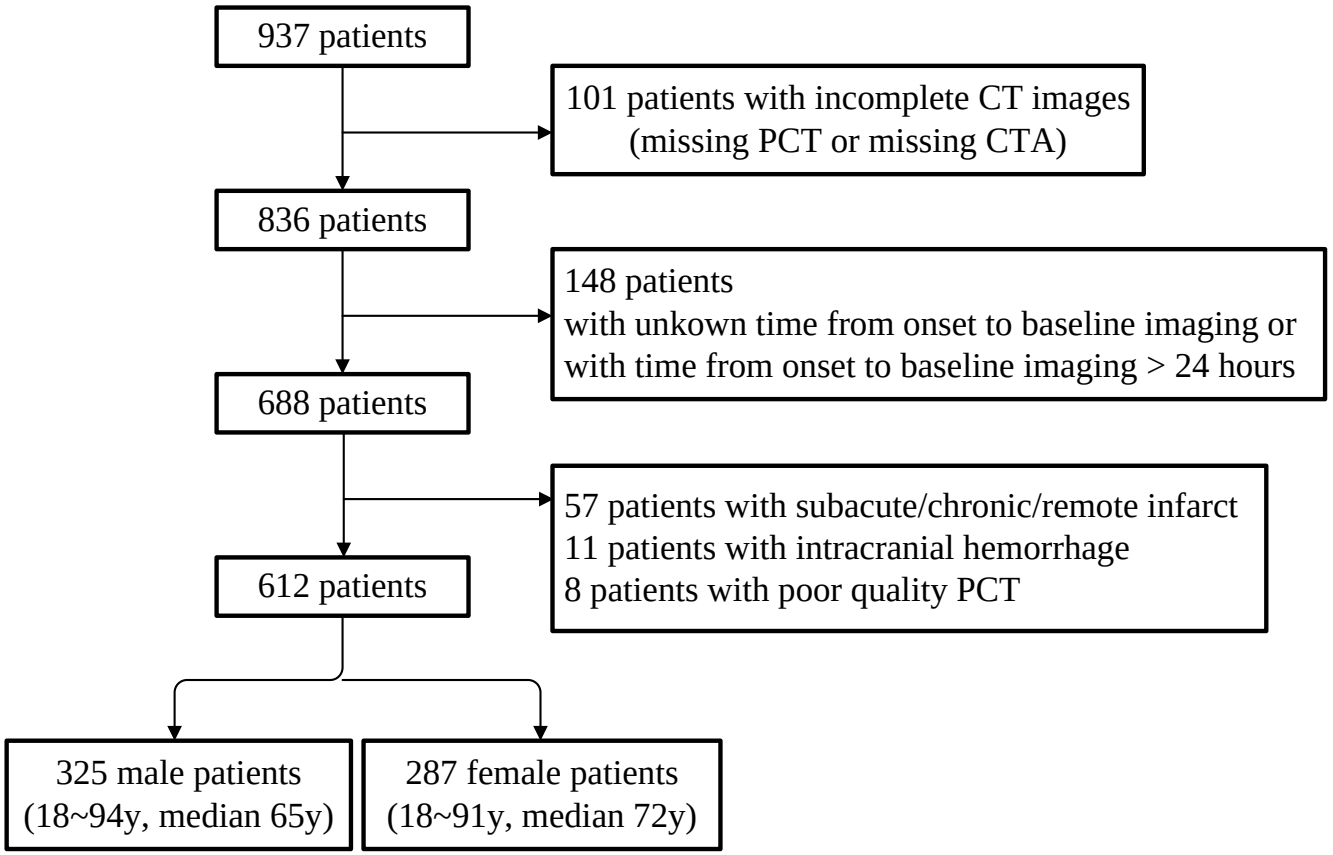

Figure I. Enrollment decision tree for our study.

Online Table

Table I. Imaging selection criteria for recent positive acute stroke clinical trials

	Occluded vessels	Infarct core	Penumbra	Collaterals
MR CLEAN	ICA, M1, M2, A1, A2	–	–	–
EXTEND-IA	ICA, M1, M2	RAPID perfusion infarct <70mL (relCBF<30% threshold)	Penumbra mismatch: RAPID perfusion ischemic core mismatch ratio>1.2, absolute mismatch >10mL (Tmax>6sec threshold)	–
ESCAPE	ICA, M1 or functional M1 occlusion (both/all M2 occlusion)	ASPECTS Score 6-10	–	Adequate collateral circulation ≥50% ischemic territory pial circulation beyond occlusion on CTA (preferably multiphase CTA)
SWIFT PRIME	ICA, M1	ASPECTS score 6-10 on NCT or DWI, RAPID perfusion infarct <50mL (relCBF<30% threshold)	Target Mismatch: RAPID perfusion penumbra/infarct ratio>1.8, penumbra absolute volume>15mL (Tmax>6 sec threshold) - Tmax>10s lesion≤100mL	–
REVASCAT	ICA or M1	ASPECTS score >6 on NCCT, ASPECTS score >5 on DWI (NCCT ASPECTS >8 for age 80-85)	Not required (Clinical/core mismatch [NIHSS >5])	–
THERAPY	ICA, M1 or M2 -Hyperdense clot length ≥8 mm	Acute ischemic changes on NCCT less than		

	-Absence of tandem extracranial steno-occlusive disease requiring treatment prior to thrombectomy	1/3 of MCA territory	_	_

Table II. Prevalence of imaging biomarkers related to core in different time windows.

Time Window	Prevalence	NCCT ASPECT (≥7)	PCT infarct <50mL	PCT infarct <70mL	PCT infarct <100ml	Malignant profile
0-3h (n = 313)	Prevalence	77.0%	57.8%	68.4%	84.0%	16.0%
	95% CI	71.9-81.5%	52.1-63.4%	62.9-73.5%	79.5-87.9%	12.1-20.5%
3-4.5h (n = 98)	Prevalence	60.2%	61.2%	71.4%	84.7%	15.3%
	95% CI	49.8-70.0%	50.8-70.9%	61.4-80.1%	76.0-91.2%	8.8-24.0%
4.5-6h (n = 46)	Prevalence	63.0%	78.3%	82.6%	84.8%	15.2%
	95% CI	47.5-76.8%	63.6-89.1%	68.6-92.2%	71.1-93.7%	6.3-28.9%
6-8h (n = 42)	Prevalence	64.3%	66.7%	69.0%	76.2%	23.8%
	95% CI	48.0-78.4%	50.5-80.4%	52.9-82.4%	60.5-87.9%	12.1-39.5%
8-12h (n = 49)	Prevalence	67.3%	59.2%	67.3%	83.7%	16.3%
	95% CI	52.5-80.1%	44.2-73.0%	52.5-80.1%	70.3-92.7%	7.3-29.7%
12-18h (n = 44)	Prevalence	72.7%	77.3%	84.1%	86.4%	13.6%
	95% CI	57.2-85.0%	62.2-88.5%	69.9-93.4%	72.6-94.8%	5.2-27.4%
18-24h (n = 20)	Prevalence	80.0%	90.0%	90.0%	90.0%	10.0%
	95% CI	56.3-94.3%	68.3-98.8%	68.3-98.8%	68.3-98.8%	1.2-31.7%

Table III. Prevalence of imaging biomarkers related to penumbra in different time windows.

Time Window	Prevalence	Target Mismatch	PCT penumbra mismatch >20%	PCT penumbra mismatch >50%	PCT penumbra mismatch >100%	CTA collaterals (≥ 2)
0-3h (n = 313)	Prevalence	73.8%	95.2%	81.8%	66.1%	56.5%
	95% CI	68.6-78.6%	92.2-97.3%	77.1-85.9%	60.6-71.4%	50.9-62.1%
3-4.5h (n = 98)	Prevalence	74.5%	92.9%	84.7%	68.4%	57.1%
	95% CI	64.7-82.8%	85.8-97.1%	76.0-91.2%	58.2-77.4%	46.7-67.1%
4.5-6h (n = 46)	Prevalence	80.4%	97.8%	84.8%	67.4%	65.2%
	95% CI	66.1-90.6%	88.5-99.9%	71.1-93.7%	52.0-80.5%	49.8-78.6%
6-8h (n = 42)	Prevalence	66.7%	85.7%	76.2%	59.5%	66.7%
	95% CI	50.5-80.4%	71.5-94.6%	60.5-87.9%	43.3-74.4%	50.5-80.4%
8-12h (n = 49)	Prevalence	71.4%	91.8%	79.6%	67.3%	65.3%
	95% CI	56.7-83.4%	80.4-97.7%	65.7-89.8%	52.5-80.1%	50.4-78.3%
12-18h (n = 44)	Prevalence	72.7%	93.2%	79.5%	65.9%	59.1%
	95% CI	57.2-85.0%	81.3-98.6%	64.7-90.2%	50.1-79.5%	43.2-73.7%
18-24h (n = 20)	Prevalence	100.0%	100.0%	100.0%	95.0%	65.0%
	95% CI	83.2-100.0%	83.2-100.0%	83.2-100.0%	75.1-99.9%	40.8-84.6%

Table IV. Prevalence of imaging biomarkers related to arterial occlusion in different time windows.

Time Window	Prevalence	NCCT dense artery sign	Visible clot on CTA	ICA	M1	M2	M1+M2	ICA+M1 (+M2)
0-3h (n = 313)	Prevalence	45.7%	85.9%	2.9%	10.9%	16.3%	30.0%	21.7%
	95% CI	40.1-51.4%	81.6-89.6%	1.3-5.4%	7.6-14.8%	12.4-20.9%	25.0-35.4%	17.3-26.7%
3-4.5h (n = 98)	Prevalence	34.7%	72.4%	2.0%	8.2%	6.1%	23.5%	21.4%
	95% CI	25.4-45.0%	62.5-81.0%	0.2-7.2%	3.6-15.5%	2.3-12.9%	15.5-33.1%	13.8-30.9%
4.5-6h (n = 46)	Prevalence	47.8%	80.4%	6.5%	10.9%	10.9%	26.1%	21.7%
	95% CI	32.9-63.1%	66.1-90.6%	1.4-17.9%	3.6-23.6%	3.6-23.6%	14.3-41.1%	10.9-36.4%
6-8h (n = 42)	Prevalence	40.5%	73.8%	2.4%	11.9%	2.4%	19.0%	23.8%
	95% CI	25.6-56.7%	58.0-86.1%	0.1-12.6%	4.0-25.6%	0.1-12.6%	8.6-34.1%	12.1-39.5%
8-12h (n = 49)	Prevalence	36.7%	83.7%	6.1%	12.2%	22.4%	16.3%	16.3%
	95% CI	23.4-51.7%	70.3-92.7%	1.3-16.9%	4.6-24.8%	11.8-36.6%	7.3-29.7%	7.3-29.7%
12-18h (n = 44)	Prevalence	31.8%	75.0%	6.8%	6.8%	18.2%	11.4%	22.7%
	95% CI	18.6-47.6%	59.7-86.8%	1.4-18.7%	1.4-18.7%	8.2-32.7%	3.8-24.6%	11.5-37.8%
18-24h (n = 20)	Prevalence	20%	55.0%	5.0%	5.0%	20.0%	15.0%	5.0%
	95% CI	5.7-43.7%	31.5-76.9%	0.1-24.9%	0.1-24.9%	5.7-43.7%	3.2-37.9%	0.1-24.9%