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The Capillary Index Score in Thrombectomy: Results from the Prospective, Multicenter CIS Study

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Abstract

Background— The Capillary Index Score (CIS) is an angiographic biomarker of initial infarction volume in patients presented with anterior circulation ischemic stroke. In retrospective studies it correlated with post-thrombectomy infarction growth and clinical outcome. We report the results of a prospective, multi-center assessment of these correlations.

Methods— Five centers enrolled 61 consecutive patients. Digital cerebral angiograms were evaluated for CIS (0-3) and mTICI score revascularization. CIS values 0, 1 were considered poor (pCIS), whereas 2, 3 were considered favorable (fCIS). A decrease in ASPECTS ≥ 3 on post-treatment CT-Scan was defined as CT-infarction growth. Clinical outcome at 90 days was defined as good, fair, and non-futile (mRS score of 0-2, 0-3 and 0-4) respectively. Multivariable logistic regression was used to relate the CIS to outcome measures, for the entire cohort and good revascularization group (mTICI 2b, 3).

Results— The rate and time of successful revascularization were similar for fCIS and pCIS groups. fCIS was more than 5 times likely to have good clinical outcome than pCIS (50% vs. 9%). In the whole cohort CIS correlated with CT-infarction growth (p=0.017), mRS 0-3 and 0-4 (p=0.03, p=0.024, respectively). In the good revascularization group CIS correlated with CT-Infarction growth (p=0.042), mRS 0-2, 0-3 and 0-4 (p = 0.04, 0.049, and 0.025, respectively). pCIS correlated with futile outcome (mRS 5,6) with or without revascularization (62% and 73% p=0.025 and 0.024, respectively).

Conclusion— CIS strongly correlated with CT-infarction growth and clinical outcome prospectively. Its potential use for decision making and prognosis is promising.

BACKGROUND

The recent publication of 3 randomized clinical trials showing efficacy of thrombectomy in patients with large core infarction, showing benefits of thrombectomy in patients presenting with ASPECTS 3-10 and/or patients with or without a mismatch on perfusion imaging, casts doubt on the merits of the current established selection criteria for thrombectomy.[1-3] This raises an important question: should we offer thrombectomy to every patient presenting within 24 hours with large vessel occlusion (LVO) and clinically significant stroke (NIHSS≥ 6) ?

The aim of thrombectomy is to save life with meaningful recovery. The definition of meaningful recovery is elastic, but it is reasonable to consider mRS = 5 or 6 as qualitatively futile thrombectomy. The published clinical trials demonstrated a high percentage (30-50%) of patients with mRS 5 and 6.[1-8]

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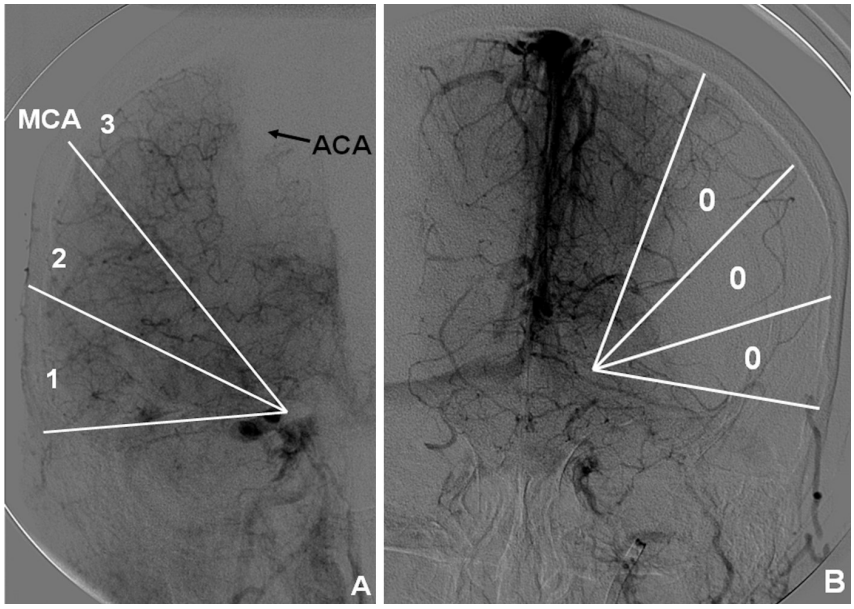

FIGURE 1: Calculating the CIS from DCA.

A reliable marker to identify patients with very high chance of achieving mRS 5, 6 following successful thrombectomy is needed.

AIMS

The capillary index score (CIS) is an angiographic classification system designed to grade the proportion of nonviable cerebral tissue in the middle cerebral artery territory prior to thrombectomy, i.e., initial infarction volume (IIV). It is based on the following two concepts: (1) The presence of capillary blush represents viable tissue, ischemic or not, while (2) the absence of a capillary blush at angiography corresponds to non-viable tissue. Two previous papers corroborated the above concepts.[9,10] The CIS was described previously (Fig 1).[11] CIS = 0 or 1 was considered poor (pCIS) and scores of 2 or 3 were considered favorable (fCIS).

Multiple retrospective publications have demonstrated the correlation between the CIS, CT-infarction growth, and clinical outcome.[10-17] This prospective study was performed to test this correlation prospectively.

METHOD

This prospective, multi-center study (The Capillary Index Score Trial, NCT02618031) included seventy subjects enrolled from six centers, with the study approved by the Institutional Review Board for each center, and informed consent obtained from each family. Of the seventy subjects enrolled, nine were withdrawn early upon reviewing the study form: Two had insufficient imaging to calculate the CIS (only the one carotid was injected), one with occlusion site that did not match the inclusion criteria (M3), and six had an incomplete consent process, leaving sixty-one subjects from 5 centers constitute the study cohort. Study protocol is provided in the supplement.

The pre-study power analysis using contingency tables was based on previously published paprers.[10-13] The analysis indicated 58 subjects were required to achieve a power of 0.9 and p-value of 0.05 for a population with fCIS in 60% of subjects and a percentage of good outcomes (mRS 0 to 2) 5 times larger for the fCIS group than the pCIS group.

A core lab, located at a separate institution from the treatment sites, evaluated diagnostic imaging at the end of the trial in a blinded fashion. The core lab characterized the CIS, and modified TICI score. Modified TICI scores of 0, 1, and 2A were considered poor revascularization, while scores of 2B and 3 were considered good. The two core lab members independently evaluated the images and came to consensus adjudication for all measures that were not in initial agreement. The pre and 24 hours post treatment non-contrast CT scans (NCCT) were evaluated by a blinded member of the safety committee separate from treatment sites and from the core lab and ascribed the pre-treatment and 24 hours post-treatment ASPECTS.

CT-infarction growth was defined as an ASPECTS decrease of at least 3 points between the pre- and 24 hours on post-thrombectomy CT, considered to represent infarct growth in approximately one-third of the MCA territory, so clinically significant. During final verification of the data, we found 4 mislabeled DCAs. These four patients' DCAs were correctly labeled and mixed with eight other DCAs chosen arbitrarily. We asked the core lab to re-score the CIS in these twelve cases, blinded to the cause of reassessment and to their previous scoring. The added 8 cases had the same initial CIS score, the new score was used for analysis. mRS score of 0-2 was considered good clinical outcome, 0-3 fair, and 0-4 as non-futile and mRS 5,6 as qualitatively futile.

The study sponsor did not edit the data or manuscript prior to submission.

STATISTICAL ANALYSIS

For the whole cohort, contingency tables, t-tests, and Mann-Whitney U tests were used to compare demographic information, medical condition, and time to treatment between the fCIS and pCIS groups. Analysis of contingency tables was based on Chi square tests with Yates correction or Fisher exact tests, as appropriate based on the expected frequencies within the tables. Continuous data was evaluated for normality with Shapiro-Wilk tests to determine whether t-tests or Mann-Whitney U tests were used. Statistical significance was set at $p < 0.05$.

TABLE 1: Characteristics of the subjects for poor CIS (n = 11) and favorable CIS (n = 47). Average values are presented with standard deviations.

	pCIS (0, 1)	fCIS (2, 3)	p-value
Age (years)	72±14	70±16	0.79
Sex (male/female)	5/6	14/33	0.48
Diabetes (yes/no)	3/8	7/40	0.38
Arrhythmia (yes/no)	5/6	20/27	1.0
Anticoagulants (yes/no)	5/5	20/17	1.0
Systolic blood pressure (mm Hg)	155±31	148±32	0.53
Diastolic blood pressure (mm Hg)	82±20	80±19	0.68
NIHSS score	20±5	17±5	0.055
Time ictus to revascularization (min)	337±101	310±96	0.41
Time from groin puncture to revascularization (min)	85±60	77±43	0.39
Time to angiography suite (min)	233±125	207±81	0.59
Pre-treatment ASPECTS	7.2±1.9	9.1±1.1	<0.001
Successful revascularization (yes/no)	8/3	38/9	0.83

pCIS: poor Capillary Index Score

fCIS: favorable Capillary Index Score

TABLE 2: Proportions of infarction growth and clinical outcome for favorable and poor CIS along with level of significance from contingency analyses.

	pCIS (0, 1)	fCIS (2, 3)	p-value	All Subjects
All Subjects				
Δ ASPECTS ≥ 3/total	8/11 (0.73)	14/44 (0.32)	0.02	22/55 (0.40)
mRS 0-2/total	1/11 (0.09)	23/46 (0.50)	0.02	24/57 (0.42)
mRS 0-3/total	2/11 (0.18)	28/46 (0.61)	0.02	30/57 (0.53)
mRS 0-4/total	3/11 (0.27)	32/46 (0.70)	0.02	35/57 (0.61)
Good Revascularization Only (mTICI 2B, 3)				
Δ ASPECTS ≥ 3/total	5/8 (0.68)	10/37 (0.27)	0.09	15/45 (0.33)
mRS 0-2/total	1/8 (0.13)	20/37 (0.54)	0.051	21/45 (0.47)
mRS 0-3/total	2/8 (0.25)	25/37 (0.68)	0.04	27/45 (0.6)
mRS 0-4/total	3/8 (0.38)	28/37 (0.76)	0.049	31/45 (0.69)

pCIS: poor Capillary Index Score

fCIS: favorable Capillary Index Score

PH: parenchymal hematoma 1 or 2

HI: Hemorrhagic infarction 1 or 2

mTICI: modified treatment in cerebral infarction

Successful revascularization (yes/no)

mRS 0-2: good clinical outcome

mRS 0-3: fair clinical outcome

mRS 0-4: non futile clinical outcome

TABLE 3: Binomial logistic regression results for relating independent variables to infarction growth.

	p-value	OR	95% confidence interval for OR	
All Subjects				
Δ ASPECTS < 3 vs. ≥ 3				
CIS (fCIS vs. pCIS)	0.017	7.4	1.4	37.7
puncture to end (min)	0.018	0.982	0.968	0.997
Good Revascularization Only (mTICI 2B, 3)				
Δ ASPECTS < 3 vs. ≥ 3				
CIS (fCIS vs. pCIS)	0.042	6.3	1.1	37.2
puncture to end (min)	0.045	0.98	0.97	1.00

OR: odds ratio, pCIS: poor Capillary Index Score, fCIS: favorable Capillary Index Score mTICI: modified treatment in cerebral infarction

TABLE 4: Binomial logistic regression results for relating independent variables to clinical outcomes.

	p-value	OR	95% confidence interval for OR	
All Subjects				
mRS 0-2 vs. 3-6				
NIHSS (unit values)	0.031	0.86	0.75	0.99
CIS (fCIS vs. pCIS)	0.069	7.6	0.9	67.1
mRS 0-3 vs. 4-6				
diabetes (no vs. yes)	0.005	30.1	2.7	330.3
CIS (fCIS vs. pCIS)	0.03	8.7	1.2	61.3
modified TICI (2B,3 vs. 0-2A)	0.04	5.9	1.1	31.8
arrhythmia (no vs. yes)	0.03	4.8	1.2	20.2
mRS 0-4 vs. 5-6				
diabetes (no vs. yes)	0.015	10.9	1.6	75.4
CIS (fCIS vs. pCIS)	0.024	8.3	1.3	52.3
modified TICI (2B,3 vs. 0-2A)	0.059	5.1	0.94	27.7
arrhythmia (no vs. yes)	0.007	8.3	1.8	38.2
Good Revascularization Only (mTICI 2B, 3)				
mRS 0-2 vs. 3-6				
age (years)	0.03	0.95	0.91	0.995
CIS (fCIS vs. pCIS)	0.04	10.9	1.1	111.2
mRS 0-3 vs. 4-6				
diabetes (no vs. yes)	0.03	13.7	1.4	136.3
CIS (fCIS vs. pCIS)	0.049	9.2	1.01	84.0
age (years)	0.06	0.94	0.89	1.00
mRS 0-4 vs. 5-6				
CIS (fCIS vs. pCIS)	0.025	10.3	1.3	79.0
age (years)	0.012	0.92	0.85	0.98

OR: odds ratio, pCIS: poor Capillary Index Score, fCIS: favorable Capillary Index Score mTICI: modified treatment in cerebral infarction

Dichotomized CIS was compared to a dichotomized measure of growth of infarction (ASPECTS) and clinical outcome (mRS). Binary logistic regression (SPSS Statistics, IBM, Armonk, New York) was also utilized for correlation of all parameters of demographics, medical condition, and time to treatment versus infarction growth, and the three categories of clinical outcome. Logistic regression was performed in a stepwise manner, with $p < 0.10$ treated as the cut-off for inclusion in the final regression. Goodness of fit was evaluated with Hosmer-Lemeshow tests, with no tests considered a poor fit based on $p < 0.05$. The analysis was performed on the whole cohort, and on only patients who achieved good revascularization (mTICI2b, 3).

RESULTS

Of the sixty-one subjects, the core lab was unable to ascribe the CIS for three subjects due to motion artifact, leaving fifty-eight subjects forming the study cohort. Of the 58 subjects with a CIS available, 57 had a mRS score at 90 days and 55 had pre and post treatment CT ASPECTS available.

For the 58 subjects, 47 (81%) had a fCIS and 11 (19%) had a pCIS. The only significant differences noted between the two groups was the pre-treatment ASPECTS, which was greater for the fCIS group ($p < 0.001$, Table 1). Good revascularization (mTICI2b,3) was achieved in 46/58 patients (79%) and good clinical outcome (mRS 0-2) was 42% (50% in the fCIS and 9% in pCIS group, $p = 0.02$). Futile outcome (mRS 5,6) was 39% (30% in the fCIS and 73% in pCIS group, $p = 0.02$) (Table 2).

Concerning CT-infarction growth, the multivariable logistic regression for the whole group correlated with CIS ($p = 0.017$) and time from groin puncture to end of the procedure ($p = 0.018$). The same parameters were significantly correlated with infarction growth for the good revascularization group ($p= 0.042$ and 0.045, respectively) (Table 3).

Concerning clinical outcome, multivariable logistic regression for the whole group, showed a significant relationship between good outcome (mRS 0-2) and NIHSS ($p=0.031$). CIS was not significantly correlated with good outcome ($p=0.069$). CIS correlated with fair mRS 0-3 ($p=0.03$) and non-futile clinical outcome mRS 0-4 ($p=0.024$). In the good revascularization group, mRS 0-2 was correlated with CIS and age only ($p=0.04$ and 0.03, respectively). Fair outcome correlated with CIS and diabetes ($p=0.049$ and 0.03, respectively). Non-futile outcome correlated with CIS and age ($p=0.025$ and 0.012, respectively). pCIS correlated with futile outcome (mRS 5, 6) with or without revascularization (62% and 73%, $p=0.025$ and 0.024, respectively) (Table 4, FIG 2).

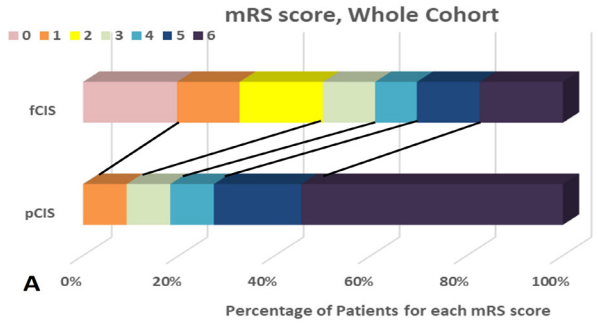

FIGURE 2A: Whole cohort. clinical outcome shift analysis.

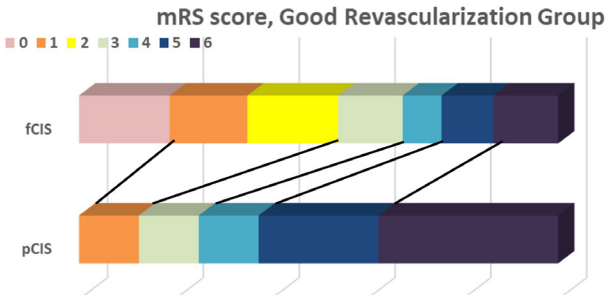

FIGURE 2B: mTICI, 2b, 3 cohort. clinical outcome shift analysis

DISCUSSION

The results indicate patients with fCIS do clinically better than pCIS, showing the projected 5-fold increase in the likelihood of good clinical outcome of mRS 0-2 (50% vs. 9%). In multivariate analysis, the correlation between the CIS and good clinical outcome (mRS 0-2) was not present in the whole group (p=0.069) but present in the good revascularization group. This highlights the importance of revascularization in patients with fCIS and validates the first assumption behind the CIS: the presence of a capillary blush=normal or ischemic tissue that still needs revascularization. The significant correlation between the CIS and CT-infarction growth, both in the whole and good revascularization groups (p=0.017 and p=0.042, respectively) indicates that successful revascularization did not alter the fate of the tissue devoid of a capillary blush. This supports the second concept behind the CIS: the absence of capillary blush represents infarcted tissue. The CIS was a strong predictor of non-futile clinical outcome (mRS 0-4) with or without successful revascularization (p=0.025 and 0.024, respectively). pCIS patients had high percentage of mRS 5,6 with or without good revascularization (62% and 73% respectively).

CIS and ASPECTS and initial infarction volume (IIV)

Only one significant baseline difference between the fCIS and pCIS groups was identified: a lower ASPECTS for the pCIS group (p<0.001). The CIS and ASPECTS are both thought to be related to the initial infarction volume (IIV). ASPECTS was not, however, significantly correlated with infarction growth or clinical outcome, which could indicate that the CIS reflects IIV more accurately than ASPECTS.

The pathophysiology behind the CIS is straightforward. If contrast material does not reach the capillary bed, blood flow also would not. Cerebral tissue can only survive severe ischemia (absence of blood flow) for a few minutes. Hence the assessment of IIV using the CIS should be relatively accurate.

ASPECTS relies on the presence of CT-Scan signs reflecting a local increase in water. The original publication describing ASPECTS incorporated 3 signs (sulcal effacement, loss of the gray-white differentiation and frank hypodensity).[18] Later publications eliminated sulcal effacement.[19] It is not clear, however, if frank hypodensity and loss of grey-white matter differentiation share a common pathophysiology. Frank hypodensity reflects infarcted tissue where the local increase of water is due to disruption of the blood-brain-barrier (BBB), which takes some time to be CT visible.[20-24] The source of local excess water behind the loss of grey-white differentiation, which is significantly less than the frank hypodensity, is less clear and may be partially or completely due to a different pathophysiology.[25,26] Mounting evidence points to the cerebrospinal fluid (CSF) as an important source of this early excess water.[26-29] CSF penetrates the brain parenchyma around peri-arterial channels. Aquaporin-4 (Aqp4), a passive transmembrane water channel, disperses water into the interstitial space. CSF is then cleared through the peri-venous channels, aided by arterial pulsation. CSF enters brain tissue minutes following the onset of ischemia along peri-arterial channels due to spreading depolarization, aided by vasoconstriction which enlarges the perivascular space and the absence of arterial pulsation delay clearance.[26,30-32] So early signs of increased local water, i.e., subtle grey/white matter dedifferentiation, could merely reflect signs of arterial occlusion and not necessarily cell death or ischemia. This potential lack of conformity of the pathophysiology behind the two ASPECTS signs and the time delay for frank hypodensity to develop may explain why ASPECTS did not correlate with CT-infarction growth or clinical outcome in our study and the overall poor correlation between pre thrombectomy ASPECTS and the final infarction volume following successful thrombectomy in priors studies.[33] Although ASPECTS remains a valuable first-line noninvasive imaging tool for patient selection, the CIS provides useful intraprocedural data as to the viability of tissue which shows equivocal signs of irreversible injury.

CIS, and quantification of the IIV

The MCA territory volume in humans is approximately 300 cc. The CIS divides the MCA territory into 3 equal sections on anteroposterior angiography views, so we approximate that every 1-point drop in the CIS scale corresponds to a loss of up to 100 cc of brain tissue. Hence, we approximate that a CIS score of 0 or 1 corresponds to almost two-thirds

or more of the MCA territory lacking capillary blush, i.e., infarcted. While CIS of 2 represents up to 1/3 of the MCA territory to be already infarcted, i.e., maximum 100cc of IIV. A CIS score of 3 corresponds to very small IIV. This approximation has limitations, as the CIS is calculated from the frontal view (2D images) without an anterior posterior dimension, while volume measurements require a 3D representation. Although this approximation still needs to be validated, we believe it is pragmatic and logical. Following internal carotid artery (ICA) or MCA occlusion blood flows through pial collaterals into the MCA territory, in a specific pathway through the pial collaterals, of the anterior cerebral artery (ACA) and the posterior cerebral artery (PCA), if present. The ACA pial collaterals fill the MCA territory simultaneously in the anterior-posterior dimension which progresses gradually from superior to inferior. On the frontal view this opacification appears first at the upper portion of the expected MCA territory, next at the ACA territory, and then progresses gradually inferiorly until it reaches the Sylvian fissure. Since the progression of the flow in this vertical dimension is simultaneous the absence of lateral evaluation is of limited impact. The PCA pial collateral flow to the MCA territory from posterior to anterior and progresses simultaneously in the horizontal dimension (lateral-medial). Since we evaluate the CIS on the frontal view any extra blush in the horizontal dimension will be visible independently of how far anteriorly it reaches, so the CIS may overestimate the area of capillary blush, not underestimate it. The fact that CIS consistently correlated with CT-infarction growth and clinical outcome in this prospective and multiple prior retrospective studies supports that these approximations are pragmatic and valid.[10-17]

Limitations, Visual CIS (vCIS) and the Electronic CIS (eCIS)

One potential drawback of the CIS is the time required to inject one or two non-symptomatic vascular territories to identify all potential collaterals. In this study, time from groin puncture to the first time placing the stent within the clot (after injecting other vessels) was available for 30 of the 58 patients, with a median time of 34.5 minutes (one site/one operator). This time is merely a few minutes longer than what is reported in the literature, where no injection of other vessels was obtained (28-30 minutes).[5,6] Furthermore, the 42% good clinical outcome for the current study is comparable to the literature indicating that additional time for injection of other potential collaterals did not have a clinically meaningful negative effect on outcomes.[4,8]

Another limitation of the current method to calculate the CIS is relying on visual inspection of the territory of the MCA: visual CIS (vCIS) and reporting it on a categorical scale (score: 0-4. fCIS vs. pCIS) which limit accuracy and reproducibility. Two prior studies tested the vCIS inter-rater agreement test and showed a very good to excellent agreement between readers. One study reported an average $\kappa = 0.73$, while the other study reported a range ($0.66 \leq \kappa \leq 0.97$ with an average of 0.73).[14,15] Despite this we believe a more granular reporting, electronic CIS (eCIS) using a continuous scale 0-100% based on machine learning of large database should give a more precise and reproducible measurement which should further enhance applicability and utility.

Current clinical applications of the CIS

After the publication of multiple large core trials showing clinical improvement following thrombectomy in patients with large ischemic core, one can argue why bother to obtain the CIS? As we have shown in this study, the presence of capillary blush in the ischemic territory corresponds to either normal or ischemic but viable cerebral tissue. For fCIS patients, these data suggest there is still a possibility for clinical improvement and may justify additional thrombectomy passes, whereas additional attempts in pCIS likely have significantly lower benefit to risk ratio. Another benefit is to assess the potential safety of using dual antiplatelet therapy (DAPT) during thrombectomy in patients needing common carotid bifurcation stenting. Although these need to be verified with a large randomized clinical trial we suspect that patients with pCIS will have higher rates of hemorrhagic transformation if loaded with DAPT, while it will be safer in patients with smaller core of nonviable tissue (fCIS).

The study showed a clear correlation between pCIS and qualitatively futile clinical outcome (mRS 5, 6) with or without successful revascularization, 62% vs. 73%, respectively. This information concerning the expected final infarction volume (FIV) based on pre-thrombectomy CIS i.e., IIV and post thrombectomy mTICI score can be very useful in counseling the patient's family immediately after thrombectomy to set realistic expectations and to communicate with the intensivist which may help setting a reasonable blood pressure parameter and other post-thrombectomy medical management criteria, tailored specifically to the patient.

The fact that we had only 11 patients with pCIS and 3 of them had mRS 0-4 makes vCIS unsuitable as an exclusion criterion for thrombectomy. A more granular and accurate method (eCIS) may identify a threshold beyond which thrombectomy could be futile.

Study limitations

Based on data from previous publications, the sample size was powered using a contingency table, and needed 58 patients with the assumption that 40% of patients would exhibit pCIS.[10-13] The percentage pCIS in this study was 19%. The lower-than-expected percentage of subjects with pCIS may be related to differences in the selection criteria compared to previous trials, or merely be random. This however rendered the sample size somewhat small. The lower percentage of pCIS influenced the results in an unknown way, but if anything, it may have weakened the CIS effect on the different outcome measures, not strengthened it, since most poor clinical outcomes would be found in the pCIS group. Reliance on post-operative NCCT ASPECTS to assess infarction growth may have decreased the precision of the study. Excluding nine study patients from analysis may have introduced a bias to the study in unknown way.

Regardless of these limitations, the results showed a strong correlation between the CIS CT-infarction growth and different clinical outcome measures, especially for patients who achieved good revascularization.

CONCLUSION

The results of this prospective multicentered study validate the ability of the CIS to estimate initial infarction volume, and hence guide intra-procedural decision-making, post-operative care, and clinical prognostication in patients with anterior circulation large-vessel ischemic stroke.

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DECLARATIONS

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Data can be available upon request.

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