Single-phase CT angiography predicts ASPECTS decay and may help determine when to repeat CT before thrombectomy

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Objetives: Time is relative in large-vessel occlusion acute ischemic stroke (LVO-AIS). We aimed to evaluate the rate of inter-hospital ASPECTS decay in patients transferred from a primary (PSC) to a comprehensive stroke center (CSC); and to identify patients that should repeat computed tomography (CT) before thrombectomy. *Materials and methods:* This was a retrospective cohort study of consecutive anterior circulation LVO-AIS transferred patients. The rate of ASPECTS decay was defined as (PSC-ASPECTS − CSC-ASPECTS)/hours elapsed between scans. Single-phase CT angiography (CTA) at the PSC was used to classify the collateral score. We compared patients with futile versus useful CT scan re-evaluation. *Results:* We included 663 patients, of whom 245 (37.0%) repeated CT at a CSC. The median rate of ASPECTS decay was 0.4/h (0.0-0.9). Patients excluded from thrombectomy after a CT scan repeat (n=64) had a median ASPECTS decay rate of 1.18/h (0.83-1.61). Patients with absent collateral circulation had a median rate of 1.51(0.65-2.19). The collateral score was an independent predictor of the ASPECTS decay rate (aβ = -0.35; 95%CI -0.45 - -0.19, p<0.001). Age (aOR: 1.04 95% CI 1.02-1.07, p<0.001), NIHSS (aOR: 1.11 95% CI 1.06-1.15, p<0.001), PSC ASPECTS (aOR: 0.74 95% CI 0.60-0.91, p=0.006) and the CTA collateral score (aOR: 0.14 95% CI 0.08-0.22, p<0.001) were independent predictors of the usefulness of a CT scan repeat. *Conclusions:* The rate of ASPECTS decay can be predicted by the CTA collateral score, helping in the selection of patients that would benefit from repeating a CT assessment on arrival at the CSC.

Keywords: Ischemic stroke—Thrombectomy—Computed tomography angiography—Workflow

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Introduction

The success of endovascular treatment (EVT) in large vessel occlusion acute ischemic stroke (LVO-AIS) is time-bound.[1] Even so, each brain has a unique tissue window, making time relative in LVO-AIS.[2,3]

When patients are admitted directly to a comprehensive stroke center (CSC) capable of providing EVT, the standard pathway includes computed tomography (CT) or magnetic resonance imaging. But when patients are transferred from a primary stroke center (PSC) – a growing population[4] - where LVO-AIS is documented by simple neuroimaging, doubts arise concerning which patients should have repeat imaging at the CSC before EVT and who should be a candidate for direct transfer to angio-suite (DTAS). A trade-off between delaying reperfusion and avoiding futile or hazardous recanalization in patients with a large infarction core guides this decision. Although DTAS is safe and effective[5], there is a potential risk of overload[5] and it may be unfeasible under certain conditions.[6] A recent single-center randomized controlled trial[7] comparing DTAS and conventional workflow within 6 hours of symptom onset, including both primary admissions and secondary transferred stroke patients (in a 1:2 ratio), showed that DTAS improved functional outcome. However, the study was performed at a center with considerable previous experience with DTAS and enrolled only 176 out of 466 consecutive patients, showing how difficult this strategy may be to implement routinely.

The Alberta Stroke Program Early CT Score (ASPECTS) is the most used quantitative score to estimate the extent of early ischemic changes in anterior cerebral circulation.[8] It is unclear how and why it varies over time in transferred patients. Knowing, beforehand, the expected inter-hospital ASPECTS decay per unit of time could help optimize transfer and imaging decisions at the CSC.

Aims

Our study has two main aims: to determine the rate of inter-hospital ASPECTS decay and how it varied according to demographic, clinical, and imaging data; and to identify transferred LVO-AIS patients that might benefit from a second CT scan at the CSC.

Methods

Study design and population

We designed a retrospective cohort study at a CSC belonging to a stroke network that includes 7 referring PSCs. Consecutive transferred patients with anterior circulation LVO-AIS from 1/1/2016 to 31/12/2019 were included. The study was approved by the local ethics committee (CHUC-114-19). The data that support the findings of this study are available from the corresponding author on reasonable request.

Data collection

Clinical data collection was based on electronic medical records. All patients' PSC-admission non-contrast CT and CT angiography (CTA) scans were reviewed by two experienced neuroradiologists to determine the ASPECTS, site of occlusion and collateral score. The CT and CTA were acquired with a standardized multicenter protocol in a multi-slice scanner. Axial CT was performed with sequential sections parallel to the orbitomeatal line, from the skull base to the vertex. The CT scanning was followed immediately by CTA imaging using a helical scan technique. Acquisitions were obtained after single-bolus intravenous contrast injection of 70–90 mL of a nonionic contrast medium into an antecubital vein at 3-5 mL/s. Imaging was manually triggered by the appearance of the contrast medium in the internal carotid artery. Standard coverage included the area from the skull base to the vertex. Source images were reconstructed with slices of 1mm thickness in axial planes at 0.625mm thickness intervals. The collateral score was assessed by CTA as 0 – absent, 1- ≤ 50% of the vascular territory distal to the occluded middle cerebral artery segment, 2 – >50%, and 3- equal to or greater than the contralateral side, based on Tan's collateral grading system[9]. A score of 0-1 was considered to be poor, while 2-3 were considered to be good collaterals.

No prespecified protocol is applied regarding the decision to submit a patient to a CT scan re-evaluation before EVT. Indication for EVT is reviewed in those that repeat CT and withheld in the case of a large infarction, as depicted in Fig. 1, and/or hemorrhagic transformation. At our comprehensive stroke center, patients in whom recanalization during transfer is suspected due to clinical improvement are submitted to digital subtraction angiography without CT/CTA re-evaluation.

Outcome measures

Successful reperfusion was defined as a final modified treatment in cerebral infarction (mTICI) score ≥ 2b.[10] A good clinical outcome was defined as a 90-day modified Rankin Scale (mRS) ≤ 2 or equal to the premorbid mRS.

Rate of ASPECTS decay

The difference between PSC and CSC ASPECTS was calculated (ASPECTS decay). The time span between PSC CT and CSC CT was determined in hours (Time CT-CT). The rate of ASPECTS decay per hour was calculated by dividing ASPECTS decay / Time CT-CT.

Repeat CT analysis

We defined each patient's stroke pathway as shown in Fig. 1. The futile CT group consisted of patients transferred directly to the angio-suite with a good clinical outcome; and patients that repeated a CT scan at the CSC with an ASPECTS > 5. The useful CT group consisted of

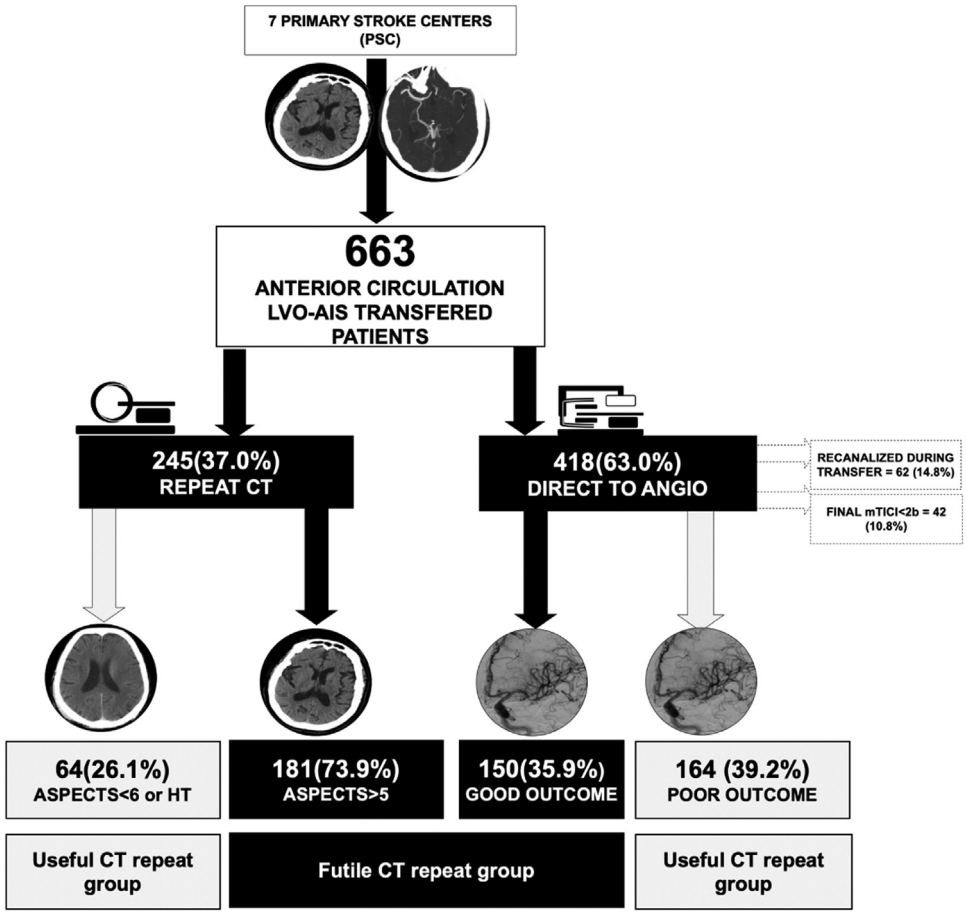

Fig. 1. *Algorithm for study inclusion. Good outcome defined as 90-day modified Rankin Scale <3 or equal to baseline; HT= Hemorrhagic transformation;*

patients re-evaluated by a CT scan at the CSC and excluded from EVT; and patients that went directly to angio-suite, were submitted to a successful EVT and had poor outcome.

Statistical analysis

Rate of ASPECTS decay

We calculated the rate of ASPECTS decay in patients that repeated CT at the CSC. Normality of the distribution of the ASPECTS decay rate (continuous variable) was evaluated through a histogram and Kolmogorov-Smirnoff tests. Differences in the rate of ASPECTS decay across categorical variables (sex, hypertension, dyslipidemia, diabetes, tobacco consumption, atrial fibrillation, oral anticoagulation, and IV alteplase) were evaluated through the Mann-Whitney U test. We calculated Spearman's correlation coefficient between continuous variables (glucose, systolic blood pressure, age, NIHSS) and the rate of ASPECTS decay. The distribution of the rate of ASPECTS decay and ordinal variables (ASPECTS at the PSC, collateral score, and location) were assessed through the Kruskal-Wallis test. Variables with $p<0.05$ entered a multivariable linear regression analysis to find independent predictors of the rate of ASPECTS decay. An adjusted binary logistic regression model estimated and compared the 90-day clinical outcome (dichotomized into good versus bad) predictive value of CSC pre-EVT ASPECTS and the rate of ASPECTS decay.

Repeat CT analysis

A comparison between the futile and useful CT group was carried out. Categorical variables (sex, hypertension, dyslipidemia, diabetes, tobacco consumption, atrial fibrillation, oral anticoagulation, IV alteplase, a previous mRS<3 and a good collateral score) were compared using an χ^2 test. The non-normally distributed continuous data (time, glucose, systolic blood pressure, age, NIHSS) were evaluated by the Mann-Whitney U test. Associations between the location of the occlusion, PSC-ASPECTS, collateral score and CT repetition were assessed by Kruskal-Wallis. A multivariable binary logistic regression analysis including variables with $p<0.05$ identified independent predictors of usefulness in CT scan re-evaluation. A receiver operating characteristic curve discriminated the optimal cut-off points of each predictor. A score based on such binary predictors was designed and its accuracy in

identifying patients that belong to useful CT scan groups was evaluated.

Results

Study population

We included 663 patients in our study. Fig. 1 shows the algorithm for study inclusion. Table 1 describes characteristics of the study population.

Rate of ASPECTS decay

The rate of early ASPECTS decay was calculated in the subgroup of patients submitted to CT scan re-evaluation before EVT (n=245, 37.0% of transferred patients). The median time of PSC CT to CSC CT was 176 minutes (140-220 min). Supplemental Table 1 presents the rate of ASPECTS decay per hour according to clinical variables. A multivariable regression model (r=0.403, r^2=0.159, p<0.001) identified the collateral score as an independent predictor of the rate of ASPECTS decay (adjusted

Table 1. *Baseline variables of all patients.*

	Variable	All patients (n=663)
	Age (mean, SD).	73.8 (12.4)
	Female sex	359 (54.2%)
	Hypertension	451 (68.0%)
	Dyslipidemia	355 (53.5%)
	Diabetes	116 (17.5%)
	Tobacco consumption	48 (7.2%)
	Atrial fibrillation	321 (48.4%)
	Oral anticoagulant	135 (20.4%)
Admission	Previous mRS<3	639 (96.4%)
	Baseline NIHSS (median, IQR)	17 (10)
	Glucose at admission (mean, SD)	129 (39)
	Systolic blood pressure at admission (mean, SD)	153 (29)
	IV alteplase	389 (58.7%)
Imaging (median, IQR)	PSC ASPECTS	10 (2)
	CTA Collateral score	2 (1)
	CSC ASPECTS (n=234)	8 (3)
	ASPECTS 24h post thrombectomy	7 (4)
	Hemorrhagic transformation	114 (17.2%)
Location	Left anterior circulation	369 (55.7%)
	Extracranial ICA	33 (5.0%)
	Intracranial ICA	153 (23.1%)
	Tandem occlusion	21 (3.7%)
	M1	467 (74.4%)
	M2	158 (23.8%)
Procedure	Total number of thrombectomies	537
	Stent retriever	105 (19.6%)
	Aspiration	275 (51.2%)
	Combination	157 (29.2%)
	Number of passes (median, IQR)	2 (2)
	Extracranial stent	13 (2.4%)
	Intracranial stent	17 (3.2%)
	Post-mTICI>=2b	465 (86.6%)
Distance median (min-max)	75km (58-190)	
Time (minutes: median, IQR)	Last-known-well (LKW) - PSC CT	93 (61)
	PSC CT-CSC CT	139 (59.8)
	LKW-CSC	293 (121)
	LKW-CSC CT	304 (128)
	LKW-puncture	355 (135)
	LKW-reperfusion	419 (161)
Outcome	90 day mRS<3 or equal to premorbid	277 (41.8%)
	Death	122 (18.4%)

CTA= computed tomography angiography; CSC= comprehensive stroke center; PSC=primary stroke center.

β = -0.354; 95%CI: -0.194, -0.447, $p<0.001$). Fig. 2 presents ASPECTS decay in each collateral score and ASPECTS decay rate modifiers. The median rate of ASPECTS decay was 1.51(0.65-2.19), 0.64(0.0-0.9), 0.31(0.0-0.8) and 0.0(0.0-0.7) in ascending order of the collateral score from 0 to 3 ($p<0.001$). Supplemental Fig. 1 shows illustrative examples.

Patients excluded from EVT after a CT scan (n=64) had a median ASPECTS decay rate of 1.18 (0.83-1.61). Only 23.6% of those had a good collateral score ($p<0.001$). In contrast, patients that repeated CT and were submitted to EVT with good outcomes (n=75) had a median early ASPECTS decay rate of 0.30 (0.00-0.62) ($p<0.001$). Of these patients, 81.7% had a good collateral score (2-3).

In patients submitted to CT scan re-evaluation at the CSC with successful reperfusion (n=151) and adjusting for age and baseline NIHSS, the rate of ASPECTS decay (aOR: 4.03 95% IC 1.12-14.53, p=0.033) was superior to pretreatment ASPECTS at the CSC (aOR: 1.40, 95% IC 0.95-2.05, p=0.086) in predicting an unfavorable outcome at 90 days. A similar adjusted binary logistic analysis, but including all recanalized patients (n=465), showed superiority of the collateral score (aOR: 4.01 95% IC 2.634 - 6.101, $p<0.001$) over time to reperfusion (aOR: 1.00 95% IC 0.999 - 1.000, p= 0.077) in outcome prediction. A shift analysis of the 90- day mRS according to time to reperfusion and the collateral score is presented in Fig. 3.

Repeat CT analysis

A comparison between useful versus futile CT scan patients is presented in supplemental Table 2 as well as a descriptive analysis of patients recanalized during transfer. The futile CT group had a lower age [73.4 (11.0) vs. 77.0 (SD=11.0), $p<0.001$], lower baseline NIHSS [14 (9-18) vs. 19(15-23), $p<0.001$] and higher ASPECTS at the PSC [10 (9-10) vs. 9 (8-10), $p<0.001$)], as well as a higher prevalence of good collateral scores (73.2% vs. 30.3%, $p<0.001$). We found stroke time metrics not to differ between groups. A multivariable regression analysis identified age (aOR: 1.04 95% CI 1.02-1.07, $p<0.001$), NIHSS (aOR: 1.11 95% CI 1.06-1.15, $p<0.001$), ASPECTS at the PSC (aOR: 0.74 95% CI 0.60-0.91, p=0.006) and the collateral score (aOR: 0.14 95% CI 0.08-0.22, $p<0.001$) to be independent predictors of usefulness in CT scan re-evaluation (Table 2). We identified the optimal cut-offs of each variable and designed a 0-5 score presented in supplemental Fig. 2 (NIHSS ≥18 − 1 point, poor collaterals - 2 points, ASPECTS at the PSC ≤8 − 1 point and age ≥ 70 − 1 point), which had an area under the curve of 0.82 (95% CI 0.78- 0.86, $p<0.001$). A score of ≥ 3 had 70.3% sensitivity and 81.3% specificity in identifying patients whose re-evaluation by CT changes eligibility for EVT.

Discussion

In transferred LVO-AIS patients there is a median inter-hospital ASPECTS decay of 0.40 per hour, which is

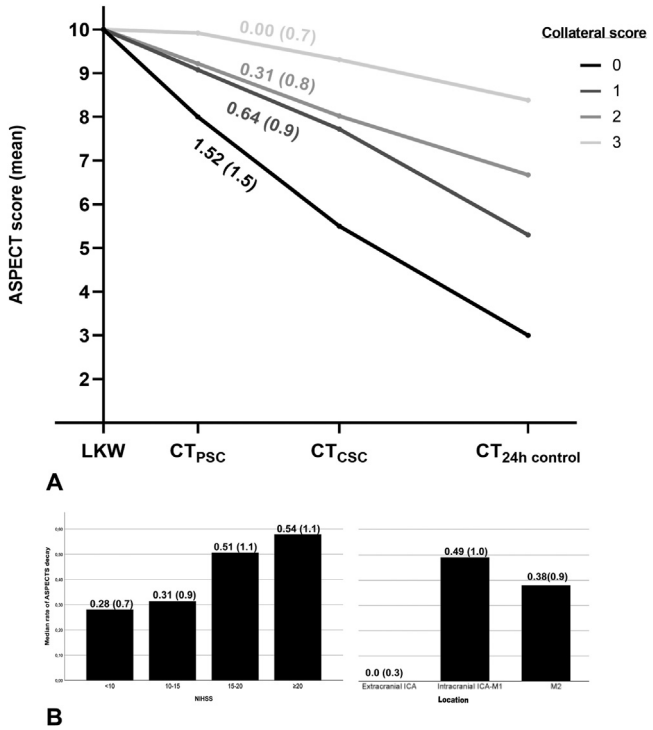

Fig. 2. *Rate of ASPECTS decay per hour according to collateral score, NIHSS (A) and location of the occlusion (B).Values presented as median (interquartile range). LKW= last known well.*

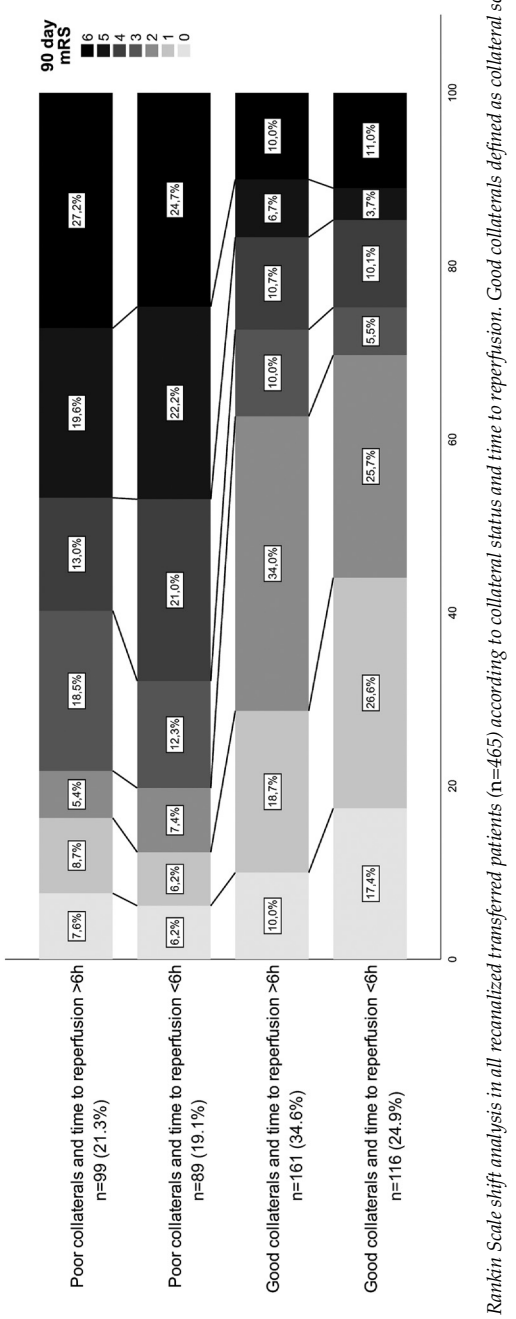

Fig. 3. *90-day modified Rankin Scale shift analysis in all recanalized transferred patients (n=465) according to collateral status and time to reperfusion. Good collaterals defined as collateral score> 1 according to Tan.*

considerably higher in the subgroup of patients excluded from EVT (1.18/h), and this rate is heavily influenced by collateral status. An age ≥ 70, NIHSS≥18, ASPECTS at the PSC ≤8, and in particular a poor CTA collateral score, variables easily assessed at most PSCs, predict the usefulness of a second CT scan evaluation in these patients.

The rate of ASPECTS decay has been studied before in smaller sample sizes.[11,12] Reddy et al. [11] found a median rate of 0.7 (0.3-1.3) in all patients, 1.8 (1.3-2.4) in fast, and 0.5 (0.0-0.9) in slow progressors. Sun et al. [12] analyzed the rate of decay according to the outcome, concluding that patients with good outcomes had a mean (SD) of 0.14 (0.23) ASPECTS decline per hour, while patients with poor outcomes had a decline of 0.49 (0.39). None of the studies, however, differentiated the rate according to clinical, demographic, or imaging variables. Differences among published rates of ASPECTS decay may be explained by different sample sizes and, in particular, different criteria used in performing a second CT scan at the CSC. The study by Sun et al. included patients transferred between 2010 and 2013, and the vast majority (78%) had a repeat CT scan, explaining why there is a shift towards a lower rate of ASPECTS decay.

In a recent study of transferred LVO patients, imaging was repeated in 30% of patients, and in only 8% of those with clinical deterioration did it change EVT eligibility. [13] In our cohort, 37.0% had a repeat neuroimage (n=245) and in 26.1% of those (n=64) EVT was withheld. This difference may be explained by our considerably longer transfer times.

In a CT perfusion study, internal carotid artery (ICA) occlusion was more frequent in fast progressors, and middle cerebral artery M1 or M2 in slow progressors[14]. On the contrary, a different CT/CTA study[11] found no differences in clot location in fast and slow progressors. Our study comes as a tie-breaker, showing that there are significantly different profiles of ASPECTS decay per hour according to clot location, being higher in proximal M1 occlusions and lower in extracranial ICA clots.

We did not find transfer time to be relevant in deciding for or against a CT re-evaluation at the CSC before EVT. Previous studies have shown that transfer time does not have a significant impact on inter-hospital infarct progression.[5,11,15,16] Requeña et al hypothesize that the fastest progressing patients are generally excluded from transfer to a CSC due to a low PSC-ASPECTS, thus removing from the analysis the subgroup of patients in whom time has the strongest impact.[17]

Baseline NIHSS has been shown to be associated with CT and diffusion-weighted imaging ASPECTS deterioration,[11,17–19] and poorer outcomes in transferred patients.[11] Mokim et al found that 13 out of 42 patients (31%) transferred from an outside hospital presented with an ASPECTS < 6 on repeat CT, and a higher NIHSS was the only clinical factor associated with ASPECTS deterioration[18]. They did not analyze ASPECTS decay per unit of

Table 2. *Independent predictors of useful CT repeat at the comprehensive stroke center.*

Variable	aOR (95% CI)	*p*	Optimal cut-off point
CTA Collateral score	0.14 (0.08-0.22)	<0.001	<2
PSC ASPECTS	0.74 (0.60-0.91)	0.006	≤8
Age	1.04 (1.02-1.07)	0.001	≥ 70
NIHSS	1.11 (1.06-1.15)	<0.001	≥18

CTA= computed tomography angiography; PSC = primary stroke center.

transfer time. We found that a higher baseline NIHSS predicted the benefit of a repeat CT scan at the CSC, which corroborates those previous findings. Moreover, we also found a correlation between the NIHSS and the rate of ASPECTS decay. A recent CT perfusion study[14] dichotomized fast versus slow progressors according to the outcome and found the former group to have a higher median NIHSS. Our study brings novelty as it adopts a different, non-dichotomized and outcome-independent approach to a surrogate of the early infarct growth rate, which is the rate of ASPECTS decay that does not require perfusion imaging.

An independent effect of aging on fast collateral failure and rapid infarct progression is yet to be proven[3]. Age has been shown to be similar between fast and slow progressors.[11,14] We have found that age does not modify the rate of ASPECTS decay but rather predicts which patients may benefit from CT scan re-evaluation at the CSC since elderly patients are more prone to futile EVT.[20]

As in a previous study,[12] the rate of ASPECTS decay was superior to the pre-EVT CSC-ASPECTS in predicting unfavorable outcomes among patients successfully submitted to EVT. This is particularly relevant in patients with unclear ASPECTS eligibility criteria. The timespan of the decay may help in the decision. Patients with a low ASPECTS a long time from stroke onset (low decay) may fare better than patients with a low ASPECTS a short time from onset (high decay).

A study of a smaller 94-patient cohort of untreated AIS patients has reported that infarct growth is less dependent on time and more on collateral flow.[21] Another study with 91 patients[22] has demonstrated that CTA collateral status impacts diffusion-weighted imaging infarct core volume more than time in patients presenting within 6 hours of stroke onset. In this study, the evolution of the infarct was not evaluated as patients were only submitted to one magnetic resonance imaging scan. With our study, we were able to show that not only infarct growth but also outcome appears to be better predicted by collateral status than time to reperfusion in treated LVO-AIS patients.

The limitations of our study should be noted. We used ASPECTS as a surrogate for infarct volume quantification, and its decay as a surrogate for expansion. Each ASPECTS region is dichotomized into a 0-1 classification that neglects the continuous evolution of brain tissue density across the ischemic insult.[23] In addition, inter-rater variability in ASPECTS grading is always a possible limitation. However, we chose to use ASPECTS grading, as it remains the mainstay in all acute stroke guidelines for the identification of candidates for EVT.[24] We used single-phase CTA imaging at the PSC for collateral scoring, which is simple and useful for transfer decisions but may not be as accurate as multiphase CTA, which adds temporal resolution by acquiring information at three different time-points.[25] Single-phase CTA may underestimate pial arterial filling and the collateral status of the patient due to the variability in the timing of acquisition and contrast arrival.[26] Early imaging acquisition may underrate the collateral status, while late image acquisition may overlook the primary occlusion. However, there is no consensus regarding the ideal imaging method to rate the collateral score, and single-phase CTA appears to be the most widely used technique.[27] Our definition of good and poor outcome was based on a dichotomization of mRS (0-2 versus 3-6) but we acknowledge that it may be an oversimplification of an ordinal scale. However, the majority of stroke trials has still used a dichotomous analysis.[28] Repeating CT delays reperfusion which theoretically may lower the odds of a favorable outcome. However, a recent meta-analysis[29] found no significant differences in the rates of functional independence between direct transfer to angio-suite compared with conventional imaging approach in transfer patients. Explanation is grounded in the fact that infarct growth is higher in the very early time window,[30] declining afterwards, making time less valuable and allowing decision-making to take longer after the very early window. In the repeat CT analysis, DTAS patients that had poor outcomes (n=164) were included in the useful CT group. Since 100 (60.98%) of those had poor collaterals it is fair to assume that most were fast progressors and would have been excluded from EVT with a CT reassessment at the CSC. Likewise, we assumed that patients that went direct to angio-suite and had good outcome would not have been excluded from EVT if they were submitted to a CT scan re-evaluation. The score developed to identify patients whose re-evaluation by CT changes eligibility for EVT lacks internal and external validation, which limits its generalizability. Limitations apart, this study derives its strength from the simple and easily reproducible methods, particularly in terms of

imaging, making it valuable in optimizing workflow in many stroke networks.

Conclusion

Patients with a higher NIHSS, intracranial ICA-M1 occlusions and poor collaterals have higher rates of inter-hospital ASPECTS decay, which can be independently predicted by a CTA collateral score. Age, NIHSS, ASPECTS and especially the CTA collateral score, all variables that can be collected at the PSC, may help to select patients that would benefit from a CT scan reassessment at the CSC.

Authors´contribution

João André Sousa MD - Drafting of the manuscript, concept, design, data collection and critical revision of manuscript for intellectual content; Ana Rita Machado MD- Drafting of the manuscript, data collection, and critical revision of manuscript for intellectual content; Luís Rito-Cruz MD - Drafting of the manuscript, data collection, and critical revision of manuscript for intellectual content; Joana Paiva-Simões MD - Data collection, and critical revision of manuscript for intellectual content; Leonor Santos-Martins MD- Data collection, and critical revision of manuscript for intellectual content; Sara Bernardo-Castro MSc - Analysis, and critical revision of manuscript for intellectual content; Ana Inês Martins MD - Data collection, and critical revision of manuscript for intellectual content; Ana Brás MD - Data collection, and critical revision of manuscript for intellectual content; Luciano Almendra MD - Data collection, and critical revision of manuscript for intellectual content; Carla Cecília MD – Data collection, and critical revision of manuscript for intellectual content; Cristina Machado MD – Data collection, and critical revision of manuscript for intellectual content; Bruno Rodrigues MD - Data collection, and critical revision of manuscript for intellectual content; Orlando Galego MD - Data collection, and critical revision of manuscript for intellectual content; César Nunes MD - Data collection, and critical revision of manuscript for intellectual content; Ricardo Veiga MD - Data collection, and critical revision of manuscript for intellectual content; Gustavo Santo MD - Data collection, and critical revision of manuscript for intellectual content; Fernando Silva MD - Data collection, and critical revision of manuscript for intellectual content; Egidio Machado MD - Concept, data collection and critical revision of manuscript for intellectual content; João Sargento-Freitas MD PhD - Concept, design, data collection and critical revision of manuscript for intellectual content

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Availability of data and material

Data supporting the findings of this study will be available upon reasonable request to the corresponding author;

Ethics approval

This study was approved by Centro Hospitalar e Universitário de Coimbra Ethics Committee (CHUC-114-19);

Consent to participate

All patients were informed of anonymized data collection for clinical studies and were free to withdraw consent to participate;

Consent for publication

All patients were informed of anonymized data publication in a journal article and were free to withdraw consent for publication;

Declaration of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2022.106815.

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