Original Article

Early and late infarct growth rate in ischemic stroke patients after successful endovascular treatment in early time window: correlation of imaging and clinical factors with clinical outcome

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Background: The prospective study assessed infarct growth rate (IGR) in acute ischemic stroke (AIS) with large vessel occlusion (LVO) after recanalization in early time window. Early IGR (EIGR) and late IGR (LIGR) were correlated with imaging and clinical data; we searched for outcome predictors.

Methods: We included 71 consecutive patients. Subjects underwent computed tomography perfusion (CTP) for ischemic core volume assessment at 99.0 minutes (median) from stroke onset, recanalization was performed at 78.0 minutes (median) from CTP. Final infarct volume (FIV) was measured on 24±2 hours imaging follow-up. EIGR was calculated as the core volume/time between stroke onset and CTP; LIGR was calculated as FIV/time between CTP and imaging follow-up. Twenty-two subjects were assessed as poor outcome, 49 as good outcome. Group differences were tested by Mann-Whitney test and χ^2 test. Bayesian logistic regression models were used to predict clinical outcome, Pearson correlations for the log-transformed predictors.

Results: Subjects with poor outcome were older, median age 78.0 [interquartile range (IQR): 71.8, 83.8] versus 68.0 (IQR: 57.0, 73.0) years; 95% confidence interval (CI): 6.00 to 16.00; P<0.001. Their stroke severity scale was higher, median 19.0 (IQR: 16.0, 20.0) versus 15.5 (IQR: 10.8, 18.0); 95% CI: 1.00 to 6.00; P<0.001. They had higher EIGR, median 23.9 (IQR: 6.4, 104.0) versus 6.7 (IQR: 1.7, 13.0) mL/h; 95% CI: 3.26 to 53.68; P=0.002; and larger core, median 52.5 (IQR: 13.1, 148.5) versus 10.0 (IQR: 1.4, 20.0) mL; 95% CI: 11.00 to 81.00; P<0.001. In subjects with poor outcome, infarct growth continued after thrombectomy with LIGR 2.0 (IQR: 1.2, 9.7) versus 0.3 (IQR: 0.0, 0.7) mL/h; 95% CI: 1.10 to 6.10; P<0.001; resulting in larger FIV, median 186.5 (IQR: 49.3, 280.8) versus 18.5 (IQR: 8.0, 34.0) mL; 95% CI: 55.30 to 214.00; P<0.001. Strong correlations among predictors were found e.g., core and EIGR (r=0.942),

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LIGR and FIV (r=0.779), core and FIV (r=0.761). Clinical outcome was best predicted using data from later measurements as FIV and LIGR.

Conclusions: Data from later measurements were more predictive, there was no major benefit to use growth over volume data.

Keywords: Computed tomography perfusion (CTP); core; infarction; progressors

Submitted Feb 07, 2023. Accepted for publication Jun 30, 2023. Published online Aug 03, 2023.
doi: 10.21037/qims-23-153
View this article at: https://dx.doi.org/10.21037/qims-23-153

Introduction

Despite massive scientific effort in the diagnosis of acute ischemic stroke (AIS) with large vessel occlusion (LVO) in the anterior circulation and its treatment, time factors and size of the ischemic core remain the main factors that influence clinical outcome (1). In 2006, Saver quantified the number of neurons, synapses, and myelinated fibers lost as a function of time in AIS, and concluded that each minute of AIS leads to the loss of 1.9 million neurons, 14 billion synapses, and 12 km of myelinated fibers (2). Fortunately, it is now known that the above-mentioned scenario is not valid in all cases. The statement "time is brain" is still undisputedly valid; however, it is clear that the processes evolve more slowly in some subjects, and that they may be successfully treated endovascularly in the late time window (3,4).

It is recommended to consider ischemic core volume, estimated on magnetic resonance imaging (MRI) or computed tomography (CT) perfusion (CTP), in the decision-making process for endovascular treatment (EVT) in the late time window or in cases when time of AIS onset or last known well (LKW) is not known. Conversely, in the early time window, the use of CTP is not recommended (5). Opponents of CTP in the early time window generally cite possible overestimation of the acute ischemic core and risk of excluding some patients from casual EVT (6,7). Considering our research in stroke and the application of CTP in acute ischemia (8-10), we believe that carefully-used CTP could bring important information even in the early time window.

In the present study, we focused on infarct growth rate (IGR) in the early time window after LKW and evaluated how infarct growth is affected by urgent recanalization. We evaluated how IGR correlated with other imaging, demographic and clinical variables and factors. We searched for predictors of clinical outcome between factors such as early infarct growth rate (EIGR), ischemic core, late infarct growth rate (LIGR), final infarct volume (FIV), collateral status and the Alberta stroke program early CT score (ASPECTS). We hypothesized that LIGR is the strongest predictor of clinical outcome. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-23-153/rc).

Methods

Study design and patient selection

This prospective, single-center study was initiated in January 2020 and terminated in September 2022. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics committee of the Faculty Hospital Kralovske Vinohrady (No. EK-VP/57/0/2021) and informed consent was taken from all individual participants. The study cohort were selected from consecutive patients with AIS due to LVO in the anterior circulation [occlusion of the M1 or M2 segments of the medial cerebral artery (MCA) or occlusion of the internal carotid artery (ICA)] who were treated by EVT in early time window, up 8 hours after LKW. Further inclusion criteria were as follows:

- Known stroke onset time;
- Successful EVT scored as TICI 3-2b (11);
- Initial technically-compliant CTP study available;
- MRI follow-up, or dual-energy CT follow-up in case of MRI contraindication, 24±2 hours after EVT;
- Three months clinical follow-up available;
- Patient agreement with enrolment in the study provided with signed, informed consent.

Exclusion criteria were as follows:

- Lack of complete initial diagnostic imaging stroke

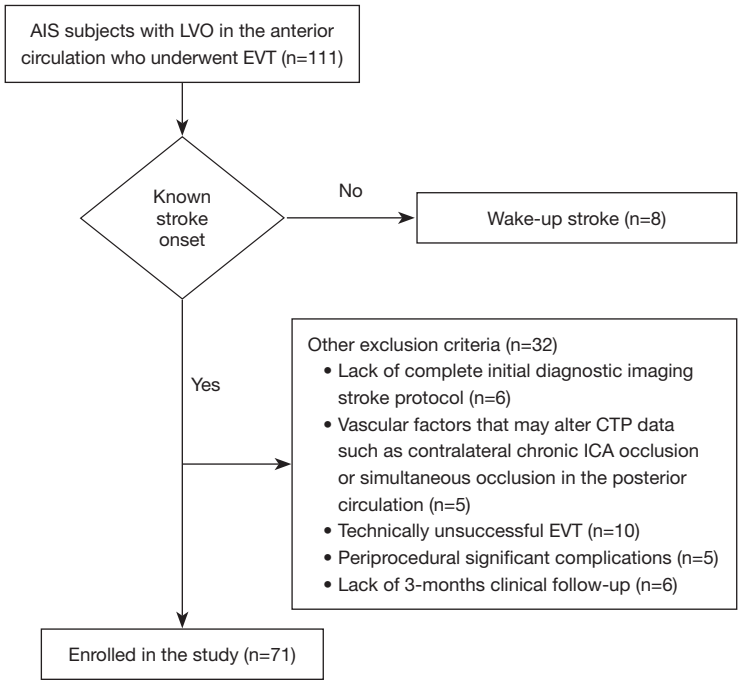

Figure 1 Patient selection flow-chart. AIS, acute ischemic stroke; LVO, large vessel occlusion; EVT, endovascular treatment; CTP, computed tomography perfusion; ICA, internal carotid artery.

protocol at our institution (mostly subjects that were referred only for EVT from other institutions);

- ❖ Vascular factors that may alter CTP data such as contralateral chronic ICA occlusion or simultaneous occlusion in the posterior circulation (both ipsilateral or contralateral);
- ❖ Technically unsuccessful EVT scored as TICI 0, 1, 2a (11);
- ❖ Periprocedural complications of EVT such as clinically-significant haemorrhage, vessel rupture, new vessel occlusion due to significant periprocedural embolization or dissection;
- ❖ Lack of imaging follow-up 24±2 hours after EVT for any reason;
- ❖ Lack of clinical follow-up 3-month after successful treatment (patients that died for any reason at any time up to 3 months after EVT were assessed as poor outcome and were not excluded from the study).

For more details, see also *Figure 1*.

The following additional data were recorded: the National Institute of Health Stroke Scale (NIHSS) for assessing the severity of AIS at the time of diagnosis and at the time of discharge from the neurology ward, all temporal data in relation to AIS and its management, and all clinically-relevant data.

Study outcome

Clinical outcome was assessed using the 3 months modified Rankin Scale (mRS). Good clinical outcome was considered as functional independence (mRS =0–2). Clinical outcome in all subjects was assessed by one neurologist (DL). According to the results of clinical outcome assessment, subjects were divided into 2 subgroups: a subgroup with favorable clinical outcome (mRS =0–2) and a subgroup with poor clinical outcome (mRS >2). All clinical, demographic, temporal and imaging data of the subgroups were further analyzed and subgroups were compared with each other.

Initial diagnostic stroke CT protocol and CTP post-processing

All subjects underwent an initial CT examination using a multidetector dual source Somatom Drive scanner (Siemens Healthineers, Erlangen, Germany). The standard CT stroke protocol consisted of the following:

- ❖ Non-enhanced CT (NECT) covering the brain from the skull base to the vertex (tube voltage

120 kVp, tube current 273 mAs, rotation time 1 s, primary reconstruction slice thickness/increment: 3/3 mm, field of view (FOV) 250 mm, soft tissue reconstruction filter, multiplanar reconstruction/increment: 3/3 mm slice thickness);

- CT angiography (CTA) covering the precerebral arteries from the aortic arch and cerebral arteries to the vertex (tube voltage 120 kVp, tube current 84 mAs, rotation time 0.28 s, primary reconstruction slice thickness/increment: 0.75/0.5 mm, FOV 250 mm, soft tissue reconstruction filter, multiplanar reconstruction/increment: 3/3 mm slice thickness, maximum intensity projection 3D reconstruction slice thickness/increment: 10/2 mm) after intravenous (IV) administration of 50 mL iodinated contrast agent with a concentration of 400 mg/mL. Iodinated contrast agent was applied by a power injector with a flow of 5 mL/s followed by saline flush.
- CTP covering the entire supratentorial brain (100 mm in the z-axis; tube voltage 70 kVp, tube current 200 mAs, rotation time 0.28 s, primary reconstruction slice thickness/increment: 1.5/1 mm, FOV 200 mm, soft tissue reconstruction filter) was performed during IV administration of 50 mL iodinated contrast agent with a concentration of 400 mg/mL, administered by a power injector with a flow of 5 mL/s followed by saline flush.

In the acute scenario, CTP data were not used for EVT decision making process, thus patients were diagnosed in the early time window. CTP data were processed on a dedicated syngo.via workstation using the Neuro Perfusion suite, version VB30A. The ischemic core was defined as an area with cerebral blood flow <20% in comparison to the contralateral, non-affected hemisphere. The penumbra was defined as an area with a time to maximum of >6 s. These settings were selected according to our previous work where we tested the accuracy of different syngo.via CT Neuro Perfusion suite settings (Siemens Healthineers, Erlangen, Germany) in the estimation of the acute ischemic core (10), as they showed the smallest percentage of core overestimation. According to secondary analysis of our previous results (10), we concluded that most overestimated cases showed only minimal core overestimation, up to 5 mL, in comparison with FIV (we consider it as acceptable measurement error and, in those cases, we calculated ischemic core = FIV). In the remaining overestimated cases, we found occlusion in the posterior circulation, which could affect the calculation results. We therefore excluded all vascular factors that could affect CTP results in the present study, and only included cases with solitary MCA and/or ICA occlusion.

ASPECTS was assessed on NECT. For scientific purposes, ASPECTS was visually and blindly re-evaluated by 2 neuroradiologists with 25 (HM) and 4 years' experience (KK) in random order; those data were used for evaluation (12). However, in the acute scenario, ASPECTS was evaluated differently, primarily using artificial intelligence software or was evaluated visually by non-neuroradiologists. Data from the acute scenario were not used in the present study; however, patients were selected for EVT according to those data.

The pattern of collaterals was assessed visually in random order by the same 2 neuroradiologists, who were blinded to clinical and radiological outcomes. Maximum intensity projection 3D reconstructions of CTA data were used for evaluation. Collateral patterns were assessed according to the method proposed by Regenhardt *et al.* as symmetric, malignant and other (13). For easier statistical evaluation, symmetric collaterals were scored as 1, malignant as 3, and other patterns as 2.

Imaging follow-up and FIV evaluation

Imaging follow-up was performed median 23.4 hours after successful EVT. The majority of subjects underwent MRI (51 subjects). All MRI scans were performed at 1.5 T scanners (Signa HDx 1.5 T, GE Healthcare, Milwaukee, USA; Magnetom Sola, Siemens Healthineers, Erlangen, Germany). The imaging protocol consisted of the following non-enhanced axial sequences: T2 fluid-attenuated inversion recovery (FLAIR), T2 susceptibility-weighted imaging (SWI), diffusion-weighted imaging [DWI; b-value 0 and 1,000; corresponding apparent diffusion coefficient (ADC) map], 3D time of flight (TOF) angiography. The final infarct on MRI was considered as a hyperintense area on both T2 FLAIR and DWI images with corresponding ADC hypointense area. The 3D TOF native angiography sequence with maximum intensity projection 3D reconstruction was used for confirmation of recanalization stability. T2 SWI was used for hemorrhage exclusion.

Patients with contraindications to MRI (primarily pacemakers or cardioverters) or patients unable to undergo MRI due to overall poor health were examined on a dual source CT scanner (20 patients) (Somatom Drive, Siemens Healthineers, Erlangen, Germany) using the following dual-energy settings: tube A 80 kV, tube B 140 kV with a tin filter. Three sets of CT brain images were reconstructed:

standard 120 kV images, virtual native CT images and iodine map images. Virtual native CT images were used for FIV assessment; a visible hypodense area was assessed as the final infarct.

FIV was segmented manually on both MRI and virtual native CT images, all measurements were performed with dedicated syngo.via volumetric measurement software (Siemens Healthineers, Erlangen, Germany) using DWI or virtual native CT images with 5 mm slice thickness. All manual segmentations and measurements were performed by two neuroradiologists (HM, KK), who were blinded to the CTP results.

IGR calculation

Both EIGR and LIGR were calculated from known and measurable data as follows: EIGR = ischemic core volume on CTP/time from LKW to CTP; LIGR = FIV/time from CTP to imaging follow-up.

Statistics

All statistical tests and evaluations were performed by an experienced statistician (JL). We report descriptive statistics (medians and interquartile ranges) for the whole sample and then split by clinical outcome (good and poor outcome subgroups). Differences between outcome subgroups were evaluated by Mann-Whitney test for continuous variables and χ^2 test for proportions (with no continuity correction and P values simulated using the Monte Carlo method for χ^2 tests). P values below 0.05 were considered statistically significant. We did not correct P values for multiple comparisons as we considered the subgroup comparison as exploratory. All tests were two-sided.

To test which available data provided the best prediction with respect to clinical outcome (mRS >2 versus mRS ≤2), we first selected potential predictors (ASPECTS, status of collaterals, CTP, FIV, EIGR and LIGR). Their values were log-transformed to account for skewed distribution (CTP, FIV, EIGR and LIGR) and z-transformed, to allow the use of parametric tests. We used Bayesian logistic regression models to predict clinical outcome. The models were calculated with the brms R package using non-informative priors (14). All evaluated models included a single predictor (from the potential set of ASPECTS, status of collaterals, CTP, FIV, EIGR or LIGR). We compared the models using leave-one-out cross-validation reporting the difference in expected log pointwise predictive density (ELPD difference) relative to the top-performing model and its standard error (SE). Additionally, we report Pearson correlations for the log-transformed predictors.

Results

Patient selection data

Seventy-one consecutive subjects median age 70.0 [interquartile range (IQR): 59.5, 76.5] years were included in the study; 29 of them females; 36 subjects suffered from left-sided occlusion. Three months after EVT, 49 (69%) patients were evaluated as good clinical outcome (mRS ≤2), the remaining 22 (31%) subjects were evaluated as poor clinical outcome (mRS >2). Complete patient selection data are summarized in *Table 1*. Subgroups with good and poor clinical outcomes significantly differed in age and NIHSS assessment at admission. The median age of patients in the subgroup with good clinical outcome was 68.0 (IQR: 57.0, 73.0) years, while the median age in the subgroup with poor clinical outcome was 10 years higher, median 78.0 (IQR: 71.8, 83.8) years; 95% confidence interval (CI): 6.00 to 16.00; P<0.001. NIHSS in all subjects was evaluated as median 16.0 (IQR: 12.0, 19.3); however, NIHSS in patients with poor outcome was assessed as 19.0 (IQR: 16.0, 20.0) and in patients with good clinical outcome NIHSS was 15.5 (IQR: 10.8, 18.0); 95% CI: 1.00 to 6.00; P<0.001. The proportion of patients receiving bridging thrombolysis was higher in the subgroup with good clinical outcome (67.4% versus 40.9%; χ^2=4.39, P=0.042). No statistically significant differences were observed in temporal parameters or comorbidities. All subjects underwent initial CT very early after LKW, median 99.0 (IQR: 76.5, 142.0) minutes and immediately underwent EVT, and achieved recanalization after initial CT within median 78.0 (IQR: 62.5, 97.5) minutes.

CT, magnetic resonance and IGR data and correlations

We found statistically significant differences between both subgroups in ASPECTS, collateral patterns, ischemic core on CTP, FIV on MRI/CT follow-up, EIGR and LIGR. For a summary see *Table 2*. The subgroup with poor clinical outcome had significantly worse ASPECTS on initial NECT median 6.0 (IQR: 4.0, 8.0) versus 8.0 (IQR: 7.0, 9.0) in the subgroup with good clinical outcome; 95% CI: −3.00 to −1.00; P<0.001. The distribution of collateral patterns differed in both groups with worse collaterals' status in the poor clinical outcome group (χ^2=10.80; P=0.004). In the

Table 1 Patient selection data and data related to stroke management

Variables	Whole group (n=71)	Good clinical outcome (n=49)	Poor clinical outcome (n=22)	P value/95% CI/χ^2
Age (years), median (IQR)	70.0 (59.5, 76.5)	68.0 (57.0, 73.0)	78.0 (71.8, 83.8)	<0.001/6.00 to 16.00/NA
Sex (M/F)	42/29	28/21	14/8	0.794/NA/0.26
Occlusion (% of subjects)				
M1 MCA	56.3	63.3	40.9	0.120/NA/3.08
M2 MCA	16.9	14.3	22.7	0.497/NA/0.77
ICA + MCA	19.7	14.3	31.8	0.115/NA/2.80
ICA	7	8.1	4.5	0.581/NA/0.63
Side of occlusion (%)				
Left/right	50.7/49.3	46.9/53.1	59.1/40.9	0.443/NA/0.90
NIHSS score, median (IQR)	16.0 (12.0, 19.3)	15.5 (10.8, 18.0)	19.0 (16.0, 20.0)	<0.001/1.00 to 6.00/NA
Time: LKW-CT (minutes), median (IQR)	99.0 (76.5, 142.0)	92.0 (69.0, 145.0)	107.0 (85.0, 138.3)	0.437/−17.00 to 33.00/NA
Time: CT-recanalization (minutes), median (IQR)	78.0 (62.5, 97.5)	75.0 (61.0, 91.0)	87.0 (71.3, 104.5)	0.071/−2.00 to 28.00/NA
Time: initial CT-MRI/CT follow up (hours), median (IQR)	23.4 (20.3, 24.9)	23.3 (20.3, 24.8)	23.9 (21.1, 25.4)	0.597/−1.55 to 2.23/NA
Bridging IV thrombolysis (% of subjects)	59.2	67.4	40.9	0.042/NA/4.39
Atrial fibrillation (% of subjects)	54.9	42.9	63.6	0.128/NA/2.62
Ventricular tachyarrhythmias (% of subjects)	5.6	5.6	0.0	0.315/NA/1.73
Significant valvular heart disease (% of subjects)	18.3	16.3	22.7	0.500/NA/0.70
Acute or chronic heart failure (% of subjects)	19.7	16.3	27.3	0.321/NA/1.64
Pacemaker/ICD (% of subjects)	11.3	10.2	13.6	0.682/NA/0.32
Hypertension (% of subjects)	81.7	83.7	77.3	0.741/NA/0.42
History of myocardial infarction (% of subjects)	14.1	14.3	13.6	>0.999/NA/0.13
History of previous ischemic stroke (% of subjects)	11.3	10.2	13.6	0.682/NA/0.32
Diabetes (% of subjects)	12.7	12.2	13.6	>0.999/NA/0.03

CI, confidence interval; IQR, interquartile range; NA, non-assessed; M, male; F, female; MCA, medial cerebral artery; ICA, internal carotid artery; NIHSS, National Institute of Health Stroke Scale; LKW, last known well; CT, computed tomography; MRI, magnetic resonance imaging; IV, intravenous; ICD, implantable cardioverter-defibrillator.

subgroup with good outcome, collaterals were evaluated more often as symmetric (34.7% versus 18.4% malignant), as opposed to the subgroup with poor outcome (9.1% symmetric versus 54.5% malignant). The ischemic core volumes on CTP were significantly larger in subjects with poor outcome, median volume was 52.5 (IQR: 13.1, 148.5) versus 10.0 (IQR: 1.4, 20.0) mL in the subgroup with good clinical outcome; 95% CI: 11.00 to 81.00; P<0.001. These data corresponded with significant differences in FIV; in subjects with poor outcome the median FIV was 186.5 (IQR: 49.3, 280.8) versus 18.5 (IQR: 8.0, 34.0) mL in the subgroup with good clinical outcome; 95% CI: 55.30 to 214.00; P<0.001. Median EIGR was 6.7 (IQR: 1.7, 13.0) mL/h in subjects with good outcome. After recanalization, infarct growth nearly stopped; LIGR was calculated as median 0.3 (IQR: 0.0, 0.7) mL/h. In subjects with poor clinical outcome, median EIGR was 23.9 (IQR: 6.4, 104.0) mL/h and after successful recanalization growth continued with median LIGR 2.0 (IQR: 1.2, 9.7) mL/h. Differences between both subgroups in EIGR and LIGR were assessed as statistically significant; in case of EIGR 95% CI was 3.26 to 53.68, P=0.002; in LIGR 95% CI was 1.10 to 6.10, P<0.001. Both groups

Table 2 CT, MRI and IGR data

Variables	Whole group (n=71)	Good clinical outcome (n=49)	Poor clinical outcome (n=22)	P value/95% CI/χ^2
ASPECTS, median (IQR)	8.0 (6.0, 9.0)	8.0 (7.0, 9.0)	6.0 (4.0, 8.0)	<0.001/−3.00 to −1.00/NA
†Collaterals (n/% of subjects)				
Symmetric (3 points)	19/26.8	17/34.7	2/9.1	0.004/NA/10.80
Other (2 points)	31/43.7	23/46.9	8/36.4	
Malignant (1 point)	21/29.6	9/18.4	12/54.5	
CTP core (mL), median (IQR)	16.0 (4.2, 41.0)	10.0 (1.4, 20.0)	52.5 (13.1, 148.5)	<0.001/11.00 to 81.00/NA
EIGR (mL/h), median (IQR)	8.5 (2.0, 17.5)	6.7 (1.7, 13.0)	23.9 (6.4, 104.0)	0.002/3.26 to 53.68/NA
††n/% of fast progressors with EIGR >10 mL	31/43.7	17/34.7	14/63.6	0.023/NA/5.17
FIV on MRI/CT follow-up (mL), median (IQR)	29.0 (10.8, 83.5)	18.5 (8.0, 34.0)	186.5 (49.3, 280.8)	<0.001/55.30 to 214.00/NA
LIGR (mL/h), median (IQR)	0.5 (0.1, 1.8)	0.3 (0.0, 0.7)	2.0 (1.2, 9.7)	<0.001/1.10 to 6.10/NA

†, assessment according to Regenhardt *et al.* 2022 (13); ††, assessment according to Sarraj *et al.* 2021 (15). CT, computed tomography; MRI, magnetic resonance imaging; IGR, infract growth rate; CI, confidence interval; ASPECTS, Alberta stroke program early CT score; IQR, interquartile range; NA, non-assessed; CTP, computed tomography perfusion; EIGR, early infarct growth rate; FIV, final infarct volume; LIGR, late infract growth rate.

significantly differed in number of fast progressors with EIGR >10 mL/h, the good outcome group included 17 fast progressors while the poor outcome group included 14 fast progressors (χ^2=5.17; P=0.023). For illustration, see also *Figure 2*.

We found many strong correlations between predictors (see *Figure 3*). Clinical outcome was best predicted by LIGR, closely followed by FIV (ELPD diff =−3.0, SE =1.6). Core on CTP, EIGR and ASPECTS showed similar performance (core on CTP: ELPD diff =−7.4, SE =2.2; EIGR diff =−8.4, SE =2.4; ASPECTS: ELPD diff =−8.4, SE =2.2). Collateral status showed the weakest performance in our dataset (ELPD diff =−10.1, SE =3.0). In general, our analysis showed that data from later measurements are more predictive (FIV, LIGR) and there is no major benefit to using growth over volume data (LIGR, EIGR versus FIV, core on CTP), or vice versa.

Discussion

In a recent study, we assessed IGR and evaluated how IGR affects and correlates with other variables and factors in subjects with AIS with LVO in the anterior circulation diagnosed and recanalized in the early time window. In our subjects, median time since LKW to initial CT scan was 99.0 minutes and median time from CTP to full vessel recanalization was 78.0 minutes. Despite the positive stroke management temporal data and successful urgent EVT, 31% of subjects did not achieve functional independence at the 3 months clinical follow-up. In the present study, we analyzed available clinical, CT and MRI data, calculated both EIGR and LIGR and correlated them with clinical outcome. Subgroups of subjects with good and poor clinical outcome significantly differed in age, NIHSS, ASPECTS, pattern of collaterals, ischemic core volume on CTP, EIGR, FIV and LIGR. We searched for predictors of clinical outcome and found many large correlations between the predictors. However, clinical outcome was best predicted by LIGR and FIV, while collateral status showed the weakest performance.

The primary focus of our study was both EIGR and LIGR. We found significantly faster EIGR in the group with poor outcome in comparison with subjects with functional independence after EVT (median 23.9 versus 6.7 mL/h). Ischemic core volume also differed between the subgroups, with median 52.5 mL in subjects with poor outcome versus 10.0 mL in functionally independent patients. A strong, positive correlation was detected between EIGR and ischemic core volume. Recently the concept of fast and slow progressors was introduced (16). Sarraj *et al.* secondary analyzed subjects from SELECT study (15,17). They divided subjects according to EIGR into slow (EIGR under 10 mL/h) and fast (EIGR above 10 mL/h) progressors and found that EIGR independently

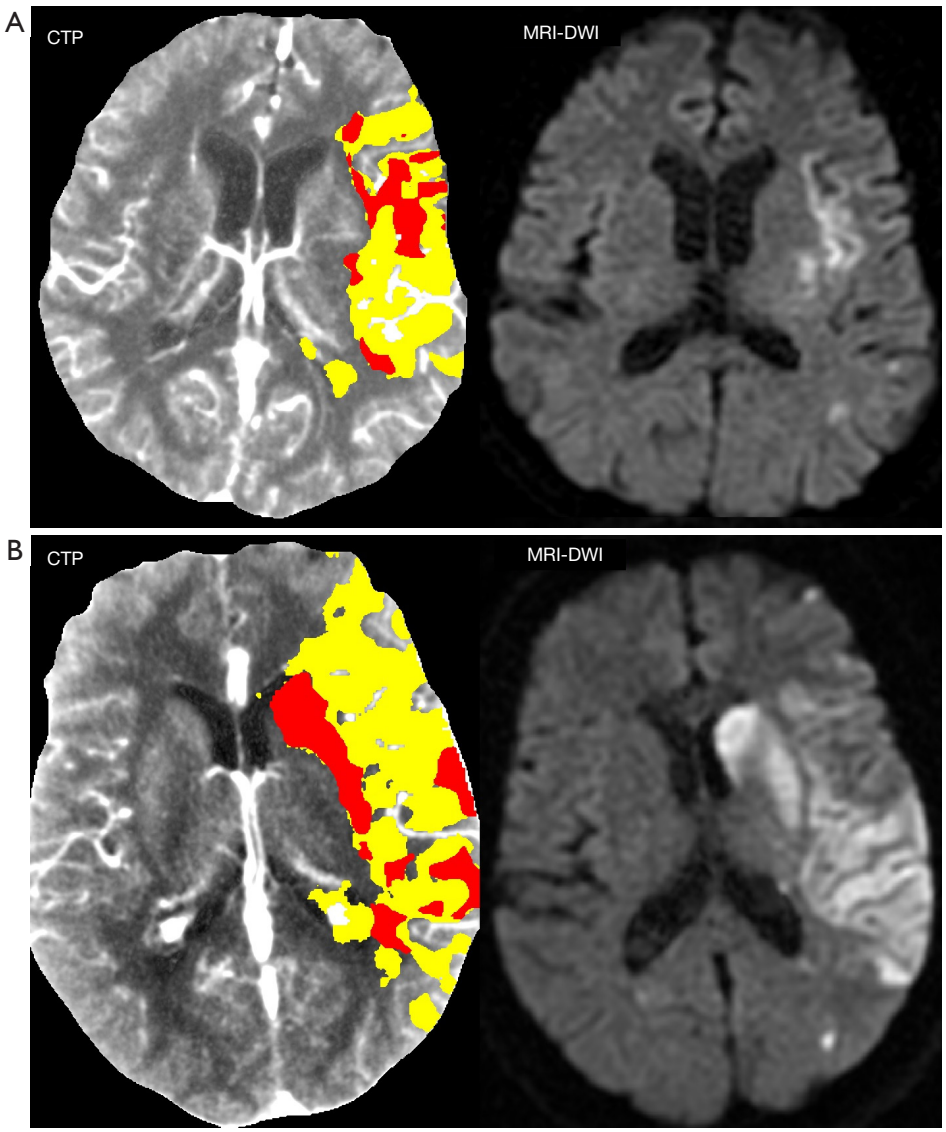

Figure 2 CTP (illustration cases). Two cases are demonstrated. The upper line (A) demonstrates the case when CTP precisely predicts FIV, which is shown on MRI follow-up (DWI) 24 hours after EVT. The lower line (B) demonstrates the case of the fast progressor. Red color on CTP depicts the ischemic core, yellow color depicts the penumbra, potentially salvageable brain tissue. CTP, computed tomography perfusion; MRI, magnetic resonance imaging; DWI, diffusion weighted images; FIV, final infarct volume; EVT, endovascular treatment.

correlated with functional independence after EVT. According to their calculation, each 5 mL/h EIGR increase led to a 14% decrease in the probability of functional independence after EVT. Additionally, better collaterals were strongly associated with slow progression of ischemic core volume (15). Following EVT, fast progressors achieved worse outcome in both the early and late time windows (15). In our study, 64% of subjects with poor outcome could be considered as fast progressors, versus 35% in the functionally independent group. In the study by Sarraj *et al.* (15), fast progressors had higher median NIHSS (19 points) in comparison to slow progressors (15 points). We found similar results, as NIHSS was 3.5 points higher in the group with poor outcome than in patients with 3 months functional independence (19.0 versus 15.5). These findings were expected, and NIHSS surely reflects the extent of the ischemic core (18). Puhr-Westerheide *et al.* analyzed clinical and imaging parameters associated

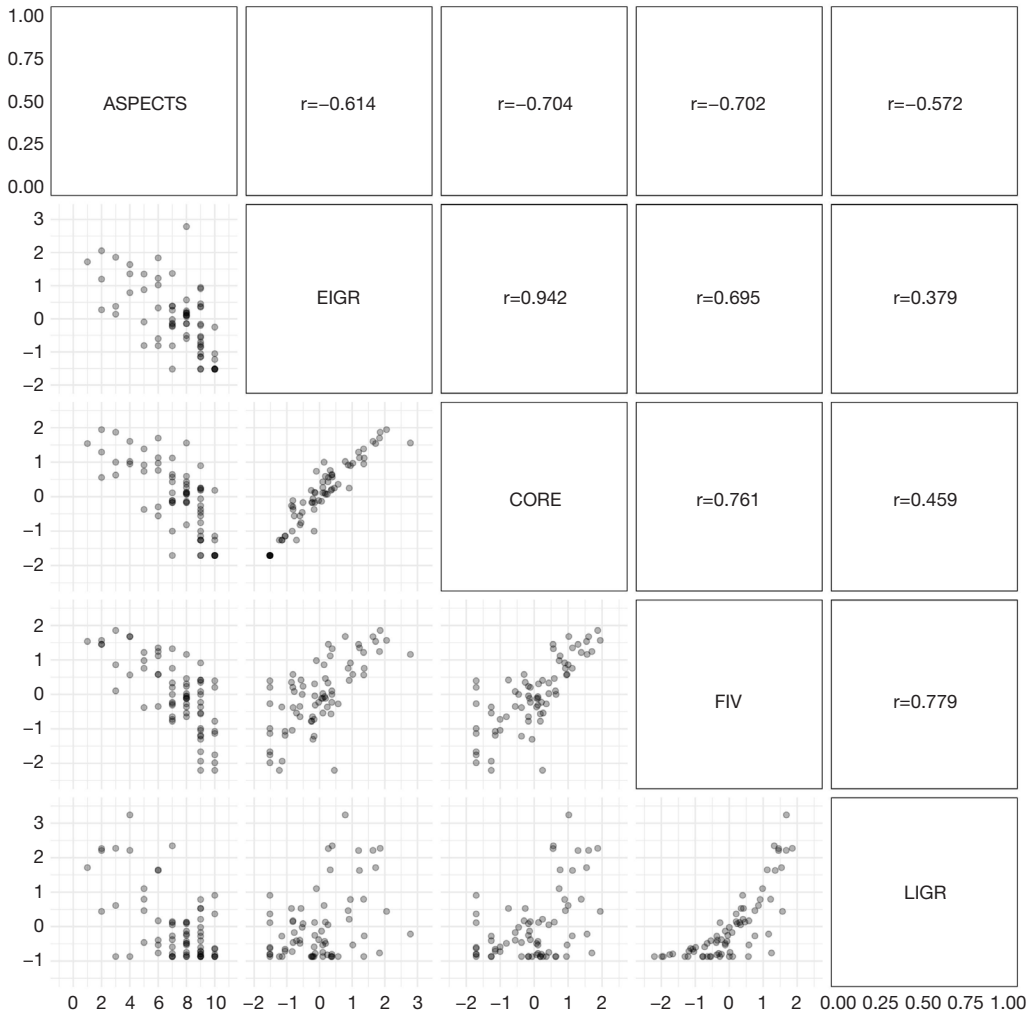

Figure 3 Inter-correlations between predictors. The Pearson correlation coefficients between predictors are depicted above the diagonal, the corresponding scatterplots below the diagonal. The reported P values are not corrected for multiple testing. ASPECTS, Alberta stroke program early CT score; EIGR, early infarct growth rate; CORE, ischemic core volume on computed tomography perfusion; FIV, final infarct volume; LIGR, late infract growth rate.

with hyperacute infarct growth in 178 subjects with 137 minutes median time between LKW and CTP. According to their study, hyperacute IGR was assessed at 16.2 mL/h (19). Similar to Sarraj *et al.*, they found strong correlation between infarct growth and collateral status (16,19). Our results are in concordance with results of the above-mentioned studies as our subjects that achieved functional independence had significantly better collateral patterns than subjects with poor outcome. However, we found that the status of collaterals showed the weakest performance with respect to outcome prediction. Our results could be affected by simplicity of collaterals' status assessment as well as by limited accuracy of single-phase CTA. We also found correlation between ASPECTS and ischemic core volume on CTP, FIV and EIGR. However, we also found significant differences in age between both groups; patients with good outcome were 10 years younger (median 68.0 years). This could affect clinical outcome, as age is known to be a strong predictor of better clinical outcome (18). Studies have reported the target cutoff FIV that predicts good clinical outcome in patients under 70 years of age is approximately 50 mL, and above 80 years of age is only 15 mL (20,21). In the present study, FIV and LIGR were

assessed as the strongest predictors of clinical outcome. Subjects that achieved functional independence had a median FIV of 18.5 mL, as opposed to patients with poor outcome where median FIV was 186.5 mL. However, at the time of AIS onset, FIV is an unknown factor. Patients with good outcome in the present study likely benefited from IV thrombolysis; however, we found only weak statistical significance. Despite comorbidities, we surprisingly did not find any statistical differences between both groups.

We calculated LIGR from known temporal factors, time of CTP, time of imaging follow-up and FIV on follow-up. We did not extrapolate EIGR to the time of recanalization; however, we hypothesize that infarct growth continued at a similar pace up to recanalization. Our data shows that recanalization nearly or completely arrested infarct growth in subjects that achieved functional independence; median LIGR was calculated as 0.3 mL/h included the time between CTP to recanalization. From our data it is clear that infarct growth in subjects with poor outcome continued to the time of imaging follow-up; LIGR was calculated as median 2.0 mL/h. LIGR was the strongest predictor of clinical outcome. FIV nearly linearly correlated with ischemic core volume on CTP as well as with ASPECTS. Olive-Gadea *et al.*, also found correlation between ASPECTS and FIV, as well as cerebral blood volume on CTP and ASPECTS (22).

LIGR significantly correlated with FIV. Continued growth of infarct after successful EVT has been described previously (23). This phenomenon has been explained by several conditions such as ischemic reperfusion injury, overestimation of FIV due to edema, progression of infarction due to delays or failure to achieve complete reperfusion, or vascular re-occlusion after EVT (23). However, in the present study, in majority of subjects reperfusion was achieved quickly and stability was proven on follow-up MRI by TOF 3D angiography.

Both subgroups divided by clinical outcome significantly differed in ASPECTS (8 points versus 6 points in the group of poor outcome). ASPECTS as a semiquantitative simplified score, is a critical tool used for estimating acute stroke burden on NECT and is associated with good clinical outcome after EVT (18). Although ASPECTS cannot be considered for the same as a stroke volume, we found that ASPECTS negatively correlated with infarct core volume on CTP, with FIV and both EIGR and LIGR. Some previous studies are not completely in agreement with our results, for instance Haussen *et al.* found great variability between ASPECTS and cerebral blood volume on CTP (24). In a study by Nannoni *et al.*, only moderate correlation between ASPECTS and ischemic core volume on CTP was reported; they found stronger correlation in subjects with LVO and in patients in the late time window (25). Nannoni *et al.*, similar to our study, reported association of higher ASPECTS and good collateral patterns (25). We however must emphasize that ASPECTS evaluation has some pitfalls, namely poor interrater and even intrarater agreement (26), which may be partially solved by the use of automated software. However, the critical limitation of ASPECTS is that ASPECTS is not a linear scale, the same scale may be different in terms of tissue volume and functional eloquence (27).

Our study has several important limitations. It is a single center, observational, non-randomized study. Selection bias may be relevant, as subjects with clinically-significant hemorrhagic complications after EVT were excluded due to inability to measure FIV. With respect to measurement methods and calculations, FIV was measured on dual energy NECT (as opposed to MRI) in a minority of subjects; we admit that CTP is not the gold standard method for measurement of the ischemic core (17). With the exception of RAPID software (iSchemaView Inc, Menlo Park, CA, USA), several vendors have developed postprocessing software for CTP, e.g., syngo.via CT Neuro Perfusion (Siemens Healthineers, Erlangen, Germany), Olea (Olea Medical, La Ciotat, France), and IntelliSpace Portal CT Brain Perfusion (Royal Philips Healthcare, Best, The Netherlands). There is mounting evidence that the use of software from various vendors may be problematic due to significant discrepancies in results with the same postprocessing settings (28-31). Furthermore, we used postprocessing settings for the ischemic core calculation that were tested in a previous study, and determined as the most reliable (10). However, there were cases that slightly overestimated core volume on initial CTP up to 5 mL. In those cases, we calculated FIV as equal to core volume, thus we considered that approach as acceptable error in measurement. LIGR calculation is also not precise as we calculated this value from the time between CTP and second day follow-up imaging; however, EVT that patients underwent (median 78.0 minutes from CTP) must have significantly affected IGR. In short, we do not know how large the ischemic core was at the moment of reperfusion. However, from our data it is clear that in subjects that achieved functional independence after EVT, infarct growth was nearly or completely arrested, as opposed to in patients with poor outcome where infarct growth clearly continued with undeniable speed. Finally, we admit that our results

may be affected by the relatively small study group.

Conclusions

Despite the fact that all included subjects underwent EVT in the early time window, 31% of subjects did not achieve functional independence. In those subjects with a median EIGR of 24 mL/h, infarct growth continued following EVT. In contrast, infarct growth was arrested following EVT in subjects with EIGR of roughly 7 mL/h. Fast progressing subjects significantly differed in the age, NIHSS, ASPECTS, the pattern of collaterals, ischemic core volume on CTP, EIGR, FIV and LIGR. Large correlations between the above-mentioned predictors were found. However, our study showed that data from later measurements as FIV and LIGR were more predictive and there was no major benefit to using growth over volume data (LIGR, EIGR versus FIV, core on CTP).

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-23-153/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-153/coif). HM serves as an unpaid editorial board member of *Quantitative Imaging in Medicine and Surgery*. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics committee of the Faculty Hospital Kralovske Vinohrady (No. EK-VP/57/0/2021) and informed consent was taken from all individual participants.

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Cite this article as: Malikova H, Kremenova K, Lukavsky J, Holesta M, Lauer D, Koznar B, Weichet J. Early and late infarct growth rate in ischemic stroke patients after successful endovascular treatment in early time window: correlation of imaging and clinical factors with clinical outcome. Quant Imaging Med Surg 2023;13(9):5770-5782. doi: 10.21037/qims-23-153

