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Is infarct core growth linear? Infarct volume estimation by computed tomography perfusion imaging

Cover title: Follow-up infarct volume estimation by perfusion imaging

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Objectives: Current guidelines for recanalization treatment are based on the time elapsed between symptom onset and treatment and visualization of existing penumbra in computed tomography perfusion (CTP) imaging. The time window for treatment options rely on linear growth of infarction although individual infarct growth rate may vary.

We aimed to test how accurately the estimated follow-up infarct volume (eFIV) can be approximated by using a linear growth model based on CTP baseline imaging. If eFIV did not fall within the margins of +/- 19% of the follow-up infarct volume (FIV) measured at 24 h from non-enhanced computed tomography images, the results would imply that the infarct growth is not linear.

Materials and Methods: All consecutive endovascularly treated (EVT) patients from 11/2015-9/2019 at the Helsinki University Hospital with large vessel occlusion (LVO), CTP imaging and known time of symptom onset were included. Infarct growth rate was assumed to be linear and calculated by dividing the ischemic core volume (CTP_{core}) by the time from symptom onset to baseline imaging. eFIV was calculated by multiplying the infarct growth rate with the time from baseline imaging to recanalization or in case of futile recanalization to follow-up imaging at 24 h, limited to the penumbra. Collateral flow was estimated by calculating hypoperfusion intensity ratio (HIR).

Results: Of 5234 patients, 48 had LVO, EVT, CTP imaging and known time of symptom onset. In 40/48 patients (87%), infarct growth was not linear. HIR did not differ between patients with linear and non-linear growth ($p>0.05$). As expected, in over half of the patients with successful recanalization eFIV exceeded FIV.

Conclusions: Infarct growth was not linear in most patients and thus time elapsed from symptom onset and CTP_{core} appear to be insufficient parameters for clinical decision-making in EVT candidates.

Introduction

Patients with large vessel occlusion (LVO), small core infarct and salvageable penumbra are considered suitable for endovascular treatment (EVT). [1,2,3] Computed Tomography Perfusion (CTP) and comprehensive magnetic resonance imaging are recommended as selection tools for both intravenous thrombolysis (IVT) and EVT especially in acute stroke code patients presenting with symptoms more than 6 hours from stroke onset and in wake-up stroke patients. Patient selection for IVT and EVT in the prolonged time window utilizes cut-off values for the ischemic core and perfusion lesion volumes. [1-4]

Patient selection for acute recanalization treatments relies on time from symptom onset although the pace of ischemic core growth may vary individually. [5,6,7,8] Different guidelines concerning EVT are largely based on assumption of linear growth of the infarct and time from symptom onset beside volumes of ischemic core and perfusion lesion by CTP. [1,2,3,9,10] Hakimelahi et al have previously shown a poor correlation of infarct volume to time after stroke with comprehensive magnetic resonance imaging. [10]

The temporal evolution of ischemic lesion varies between individuals and hyperacute infarction growth depends on collaterals.[7,8,10,11] A CTP based imaging biomarker (hypoperfusion intensity ratio, HIR) has been shown to reflect collateral flow and eligibility for thrombectomy.[12,13,14] Further, patients with less robust collaterals and higher HIR values by CTP have been shown to develop larger infarcts than predicted at follow-

up imaging compared with more favorable HIR profile patients.[15] Although collateral flow may have an important effect on individual variance of ischemic core growth, other factors impacting ischemic core evolution remain poorly understood. [9,14,17,17,18,19]

As there are probably multiple factors affecting infarct core growth in addition to time, we wanted to test how often measured follow-up infarct volume (FIV) differs from estimated FIV (eFIV) from CTP baseline imaging with the linear growth model in acute stroke code patients treated with EVT. We aimed to determine whether baseline infarct growth rate alone could be used to prognosticate follow-up infarct volume from non-enhanced computed tomography (NCCT images).

Materials and Methods

A single-center, retrospective analysis was performed of imaging findings of all consecutive acute stroke patients (stroke code) from 17 November 2015 to 30 September 2019 at Helsinki University Hospital (HUS) based on the Helsinki Stroke Quality Registry (HSQR). Ethical approval was not sought and informed consent was waived due to the retrospective nature of the study. This study was conducted in accordance with the Declaration of Helsinki as revised in 2013.

NCCT is the first-line imaging modality for stroke code patients in our hospital. The decision for multimodal imaging was made by the treating physician guided by our local guidelines which are in line with the current American Heart Association guidelines.[1,2] Visualization of penumbra by CTP is not usually required by the Helsinki protocol in the 0-6h time window for clinically obvious ischemic strokes.

Inclusion criteria were as follows:(1) patients presented to HUS with acute symptoms of stroke with a witnessed time of symptom onset (2) verified LVO (occlusion of a proximal anterior circulation artery occlusion; terminal internal carotid artery, proximal middle cerebral artery (MCA) [M1] or tandem occlusion (M1+terminal ICA)) on computed tomography angiography (CTA), (3) EVT of LVO, and (4) CTP imaging at baseline prior to any EVT therapy. The treating clinician decided whether to proceed to EVT based on clinical and radiological findings by applying our hospital guidelines. Recanalization was defined as modified on the Treatment in Cerebral Infarction (mTICI)) scale as successful (TICI 2b or 3) or futile (TICI 0,1,2a) and assessed by the performing interventional radiologist.[20]

Follow-up imaging of the brain at 24 h (±6 h) was available for all included patients. Demographic (sex, age) and clinical parameters (glucose,tandem occlusion), National Institute of Health Stroke Scale (NIHSS) score at baseline and modified Rankin scale (mRS) at 3 months were registered. Favorable outcome was defined as mRS scores 0-2 and unfavorable outcome as scores 3-6.

Imaging protocol

NCCT and CTP were performed on a Definition AS Siemens (Siemens, Erlangen, Germany) 128-section scanner with slice thickness of 1 mm. The following parameters were used for the CTP acquisition: slice thickness of 5mm, collimator of 32 × 1.2 mm, 70kVp and 135 mAs with total coverage of 100 mm. The plane of imaging was parallel to the floor of the anterior cranial fossa starting just above the orbits. Thirty cycles were obtained with a total scan time of 46 s. The CTP images were sent to RAPID® (iSchemaView Inc) to quantify ischemic core (CTP_{core}) and volume of perfusion lesion ($CTP_{penumbra,}$).

The CTP_{core} was defined as relative cerebral blood flow (CBF) below 30% of normal brain[21]. T_{max} threshold of 6s was used as an estimate of tissue at risk of infarction in the absence of reperfusion ($CTP_{penumbra}$)[3]. The volumes of CTP_{core} and $CTP_{penumbra}$ were measured in milliters (mL). Infarct growth rate was calculated by dividing baseline infarct core volume (CTP_{core}) by the time difference from baseline imaging to onset of symptoms.

To test the accuracy of linear growth of infarction during the observed time course, we estimated the eFIV by multiplying the baseline infarct growth rate by the time difference from successful recanalization to onset of symptoms limited to $CTP_{penumbra}$. A previous study by Campbell et all[21] has shown that relative CBF below 30% of normal with area under the curve of 0.81 is optimal for identifying infarct core using CTP compared with comprehensive magnetic resonance imaging. Based on this study, we assumed a +/- 19% accuracy to be sufficient for the eFIV assessment in comparison with FIV for linear growth of infarct. In case of futile recanalization baseline infarct growth was multiplied by the time to follow-up imaging or until eFIV reached the volume of $CTP_{penumbra}$. In case of CTP_{core} 0 mL at baseline imaging, $CTP_{penumbra,}$ was divided by the time from baseline imaging to follow-up imaging (h) to approximate infarct growth rate. We calculated time (min) until linear infarct growth would result in a lesion consuming the whole penumbra (salvageable tissue time,$CTP_{penumbra}$-CTP_{core}/baseline infarct growth) in case of successful EVT after baseline imaging. The concept of ghost infarct core, in which CBF overestimates acute infarct core compared with FIV has been suggested by previous studies especially with hyperacute imaging.[22-24] Therefore, patients were divided into early (<100 min of symptom onset) and late imaging subgroups to examine the effect of imaging time among patients with linear and nonlinear infarct growth. As hypoperfusion intensity ratio (HIR) has been shown to reflect collateral flow, HIR (Tmax10s/Tmax6s) was calculated by CTP imaging.[12-15].

The neuroradiologist (AA) was blinded to any other imaging including RAPID software. He defined the territory and side of the infarction and measured semi-automatically the FIV from the follow-up NCCT by using the volume of interest (VOI) tool (syngo.via MM-Reading) and CT Neuro – workflow implemented in syngo.via (Siemens Healthineers). Ischemic changes were identified visually and marked as regions of interest (ROIs). Those ROIs had mean Houndsfield units (HU) ranging from 25 to 31, while normal cerebral parenchyma was measured at a mean >42 HU. The "create VOI tool" was applied to include all voxels situated within the afore mentioned threshold at different slices of the same infarction. Edges were manually adjusted when necessary.

Statistics

Descriptive statistics were performed using SPSS, version 25.0 (IBM Corp., Armonk, NY, USA). Shapiro-Wilk test was used to assure normality on continuous variables. Categorical variables are presented as absolute values and percentages, continuous variables as mean ± standard deviation (STD) if normally distributed or median (interquartile intervals, IQR) if not normally distributed. Statistical significance was assessed by using Mann-Whitney U-test and Pearson X^2-test. The absolute difference between eFIV and FIV and eFIV and $CTP_{pemumbra}$ was calculated. The association of HIR with the difference between eFIV and FIV was analyzed by linear regression model. A p value less than 0.05 was defined as statistically significant.

Results

We screened 5254 consecutive acute stroke code patients (Figure 1). Of these, 209 (4%) had EVT due to LVO, 116 (56%) of whom had CTP baseline imaging available. Five patients with both CTP baseline imaging and LVO had to be excluded due to technical problems in RAPID output. One patient died after EVT and was excluded from analysis because of missing follow-up imaging data. Sixty-two patients with eligible CTP imaging and LVO were excluded as exact time of symptom onset was unknown.

The final analysis consisted of 48 LVO patients who had undergone EVT with CTP baseline imaging and had known time from symptom onset (Table 1). Of these, 25 (51%) had EVT and IVT and 23 (49%) EVT alone. In 13 patients (27%), IVT was initiated prior to baseline CTP imaging. Baseline CTP imaging and follow-up NCCT imaging in this cohort were done at HUS in all cases. The FIV was measured from follow-up NCCT at 24 h (median 23.9, IQR 22.1-25.7) after baseline imaging. Cohort characteristics and process measures are shown in Table 1. Median infarct growth rate was 11 mL/h (IQR 3-38) and median HIR 0.46 (0.15-0.60). Of 48 recanalization attempts, 42 (88%) were successful and 6 (12%) futile. Four patients (10%) with successful recanalization had baseline infarct growth rate of 0 mL/h.

Figure 2 illustrates examples of linear (A) and nonlinear (B) infarct core growth[7,9,11]. Figure 2A illustrates linear growth model in a 57-year-old male patient with M1-occlusion and successful recanalization. In this patient eFIV accurately predicted FIV and salvageable tissue time in minutes agreed with linear infarct core growth. Figure 2B illustrates nonlinear infarct growth in a 70-year-old male patient with tandem-occlusion and successful recanalization. In this patient, linear model leads to underestimation of eFIV compared with FIV and fails to show +/-19% for the accuracy of FIV (gaey area). eFIV also exceeds $CTP_{penumbra,}$

Figure 3 illustrates volumes of CTP_{core}, $CTP_{penumbra}$, eFIV, and FIV, difference between eFIV and FIV in milliliters, and HIR in all 48 patients. eFIV predicted FIV accurately in only 8 patients (17%), whereas 40 (83%) showed nonlinear growth of infarct. All eight patients (Patients 14, 26, 28, 29, 30, 32, 35, and 40) with linear infarct growth are marked with yellow in Figure 3. Patients with linear and nonlinear infarct core growth showed no significant difference in medians of salvable tissue time, onset to imaging time, onset to recanalization, or onset to follow-up imaging ($p>0.05$). No significant difference observed between baselines of NIHSS score, glucose (mmol/L), infarct growth, CTP_{core},, HIR Tmax>6 s, and eFIV and FIV volumes (mL) or in successful recanalization, T-occlusion or early vs. late imaging among patients with nonlinear infarct core growth compared with patients with linear infarct core growth ($p>0.05$). Twenty-three (58%) of 40 patients with nonlinear infarct core growth had poor outcome compared with 6 (75%) of 8 patients with linear infarct core growth ($p>0.05$).

Among 42 patients with successful recanalization, eFIV exceeded FIV in 25 (60%) (median absolute difference 25 mL, IQR 7-73). The median HIR did not differ between patients with eFIV>FIV and those with eFIV<FIV ($p>0.05$). Of all 48 EVT patients, 3 (6%) (Patients 37, 44, and 48) showed larger FIV than $CTP_{penumbra}$ and none of them had linear growth of infarct. Patients 37 and 48 had hemorrhagic transformation of infarct and edema in the MCA territory.

To evaluate the effect of possible ghost core as bias, the patients were divided into early and late imaging subgroups. Among the 22 patients with successful recanalization and early imaging, eFIV exceeded FIV in 18 patients (82%) (median absolute difference 28 mL, IQR 18-85). Among the 20 patients with successful recanalization and late imaging, eFIV exceeded FIV in 7 patients (35%) (median absolute difference 13 mL, IQR

(2-52). For all patients with successful recanalization, the absolute difference between eFIV and FIV or HIR did not differ between patients with early and late imaging ($p>0.05$).

A possible association of HIR with the difference between eFIV and FIV was analyzed by linear regression model. HIR alone was significantly associated with the difference between eFIV and FIV (B=134.4, CI 31.0-237.8, p=0.012). After adjusting the model for time from symptom onset to baseline imaging, baseline NIHSS, ischemic core volume and volume of perfusion lesion, no significant association was remained (B 62.7,CI –92.7-218.1, $p>0.05$).

Discussion

eFIV from a linearly extrapolated growth model failed to predict the follow-up infarct volume in a reliable manner. In our model, eFIV overestimated FIV in over half of the patients with successful recanalization, especially when imaged early after symptom onset. In a few patients (6% of all patients), FIV exceeded even $CTP_{penumbra}$ due to hemorrhagic transformation and edema, which can hamper FIV estimation from NCCT. No significant difference was present among patients with linear and nonlinear infarct core growth in baseline core or perfusion lesion volumes, HIR, NIHSS core, T-occlusion, outcome or onset times to imaging, recanalization, or follow-up imaging. None of the examined demographic or clinical parameters were associated with nonlinear growth of infarct core, but it is likely that the collaterals have an important role.[7,8,13-16]

145 Our study suggests that the linear model of infarct core growth is too simplistic, decisions on recanalization should therefore be based more on
146 individual status of brain perfusion rather than on time elapsed from symptom onset particularly in the early time window after stroke.[7,10]
147 Collateral flow has important role in ischemic core growth.[7,8,10-15] In our cohort, the median HIR was 0.46, suggesting that in most patients the
148 collateral flow was weak. However, a clear association of HIR with difference between eFIV and FIV was not found after adjusting for relevant
149 clinical parameters.

150 The transition from ischemic core at baseline imaging to actual infarction can be partly nonlinear especially in the hyperacute phase and difficult
151 to estimate from a snapshot of baseline ischemic growth rate, which can vary individually.[7,10,25,26] The possible nonlinear phase at the beginning
152 and the end of infarct growth can still be considered short lived, with most of the infarct growth following a linear path which is not contrary to
153 non-linear growth of infarct core.[7,8,25,26] Earlier studies have shown, that infarct growth rate and CTP imaging might be more accurate several
154 hours after stroke onset as suggested by guidelines and RAPID has been successfully used in large clinical trials in predicting FIV. [1,2,3,13,22,23] It is
155 likely that in the hyperacute stage the baseline infarct growth is faster and potentially recruited collateral flow and other factors affect the
156 perfusion more than at he later stage and thus linear extrapolation of follow-up infarct volume based on initial infarct growth rate can lead to
157 overestimation of the eFIV.[7]

158 Hyperacute infarction growth has been shown to strongly associate with leptomeningeal collateral status although to our knowledge follow-up
159 infarct estimation based on a mathematical model and CTP baseline infarct growth rate only has not been investigated previously.[8,10] A recent
160 study in the DEFUSE3 cohort showed that the volume of the estimated ischemic core combined with the volume of persistent hypoperfusion can
161 predict the infarct volume 24 h after randomization with reasonable accuracy in patients who present 6-16 hours after last seen well[14]. Further,
162 Rao et al showed that patients with 24-h infarcts larger than predicted at baseline had evidence of less favorable baseline collaterals that fail
163 within 24 h.[15] In our cohort, eFIV seemed to overestimate FIV in 60% of patients with successful recanalization especially when imaged early
164 after symptom onset as we only included patients with known symptom onset. Although we did have a higher median core volume than in the
165 DEFUSE3 cohort, there was no significant difference in baseline core volume among patients with linear and nonlinear infarct growth. Median
166 HIR of our cohort was 0.46, which is higher than the median HIR of 0.43 of patients who developed larger infarct than predicted at 24h in the
167 study by Rao et al study.[15] Further, most of our patients were imaged early after symptom onset.[14-15] It has been shown earlier that CTP might
168 overestimate acute infarct core especially in the hyperacute time window.[7,22,23,24] An overestimation of infarct core at baseline would result in a
169 larger infarct growth rate, which would also result in a larger eFIV than FIV (Figure 2B).[22] Our study showed no significant absolute difference

(eFIV and FIV) among patients with early baseline imaging and successful recanalization compared with other patients with successful recanalization nor was HIR associated with overestimation or underestimation of eFIV.

Previous studies have also shown that a 30% CBF threshold in large clinical trials might also slightly overestimate follow-up infarct volume by comprehensive magnetic resonance imaging among patients with successful recanalization compared with larger CBF thresholds.[23,27] It has been suggested that lower CBF thresholds could depict an irreversibly damaged core more accurately in the early time window. We did not have any other CBF threshold volume but failed to show a statistically significant difference between eFIV and FIV between subgroups of early vs. late imaging and nonlinear and linear infarct growth. FIV was measured from NCCT which is not as accurate as comprehensive magnetic resonance imaging. NCCT is, however, widely available and often used as the main screening tool for acute recanalization treatments. Difference between eFIV and measured FIV at 24 h may also be due to inaccuracy in FIV measurement, as follow-up infarct volumes by NCCT may in some cases underestimate FIV if imaged <24 hours of symptom onset.[7] In our study, median time from baseline to follow-up imaging was 23.9 (22.1-25.7) h. It is likely that in this time period the infarct is fully developed and is readily measured from NCCT. In addition, there was no significant difference between with patients of linear infarct growth and those with nonlinear infarct growth in onset or baseline to follow-up imaging ($p>0.05$). Finally, there was no significant difference in outcome between patients of linear and nonlinear growth. A previous study by de

183 Havenon et al showed no effect of good collaterals by CTA on outcome although this was associated with reduced core growth which is in line
184 with our results as potential factor by collateral flow in eFIV estimation.[28]

185 The major limitation of this study are its retrospective nature and the relatively small number of patients despite the large number of screened
186 acute recanalization candidates. We included only patients with known symptom onset, comprehensive baseline imaging (CTP and CTA and
187 NCCT follow-up imaging at 24 h), LVO and EVT (exact time of recanalization) to examine the linearity of infarct growth as accurately as
188 possible and to avoid any deviations that could hamper the interpretation of the data. Further, all patients were treated in one comprehensive
189 stroke center (HUS) avoiding possible protocol deviation. Despite the relatively small number of patients in the cohort, we are confident that
190 individual treatment decisions should not be based solely on calculations of remaining time for recanalization. In 13 patients (27%), IVT was
191 given prior to baseline CTP imaging which could result in partial recanalization and affect cerebral blood flow. However, all patients were
192 studied with digital subtraction angiography confirming the presence of LVO, and treated with EVT and none were recanalized prior to EVT.

193 New imaging biomarkers as surrogates for infarct growth rate are needed since tertiary stroke centers are facing increasing number of candidates
194 screened for EVT. Our results show that a linear model is not an accurate tool to predict follow-up infarct volume in EVT candidates. Although
195 we did not find a statistically significant difference in HIR between patients with linear and non-linear growth of infarct core, other studies have

shown HIR to reflect collateral flow accurately compared with CTA.[12,13,15,28-31] As collaterals likely play a major role in infarct core growth[15], the association of HIR with infarct growth should be further studied in a larger cohort with various HIR profiles.

To conclude, linear extrapolation of the CTP_{core} appeared to be an oversimplified approach to estimate FIV. We cannot recommend using his approach in clinical decision making. Infarct growth was not linear in most of the patients here, and thus, time elapsed from symptom onset alone appears insufficient for clinical decision-making in recanalization candidates.

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Conflicts of Interest

The authors have no conflicts of interest to declare in connection with this article.

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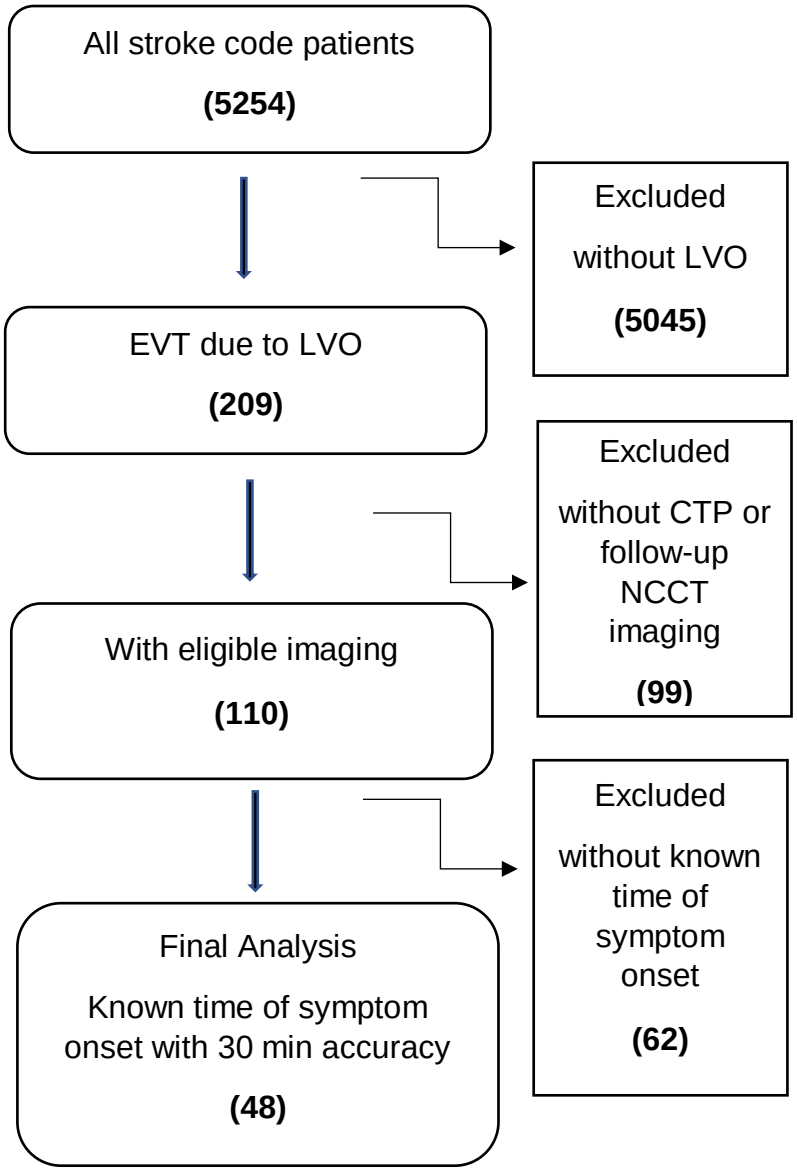

Figure 1 Flowchart of study patients. LVO; large vessel occlusion (internal carotid artery,M1-branch of middle cerebral artery,tandem-occlusion), EVT; endovascular Treatment, CTP; computed tomography perfusion imaging, NCCT; non-enhanced computed tomography

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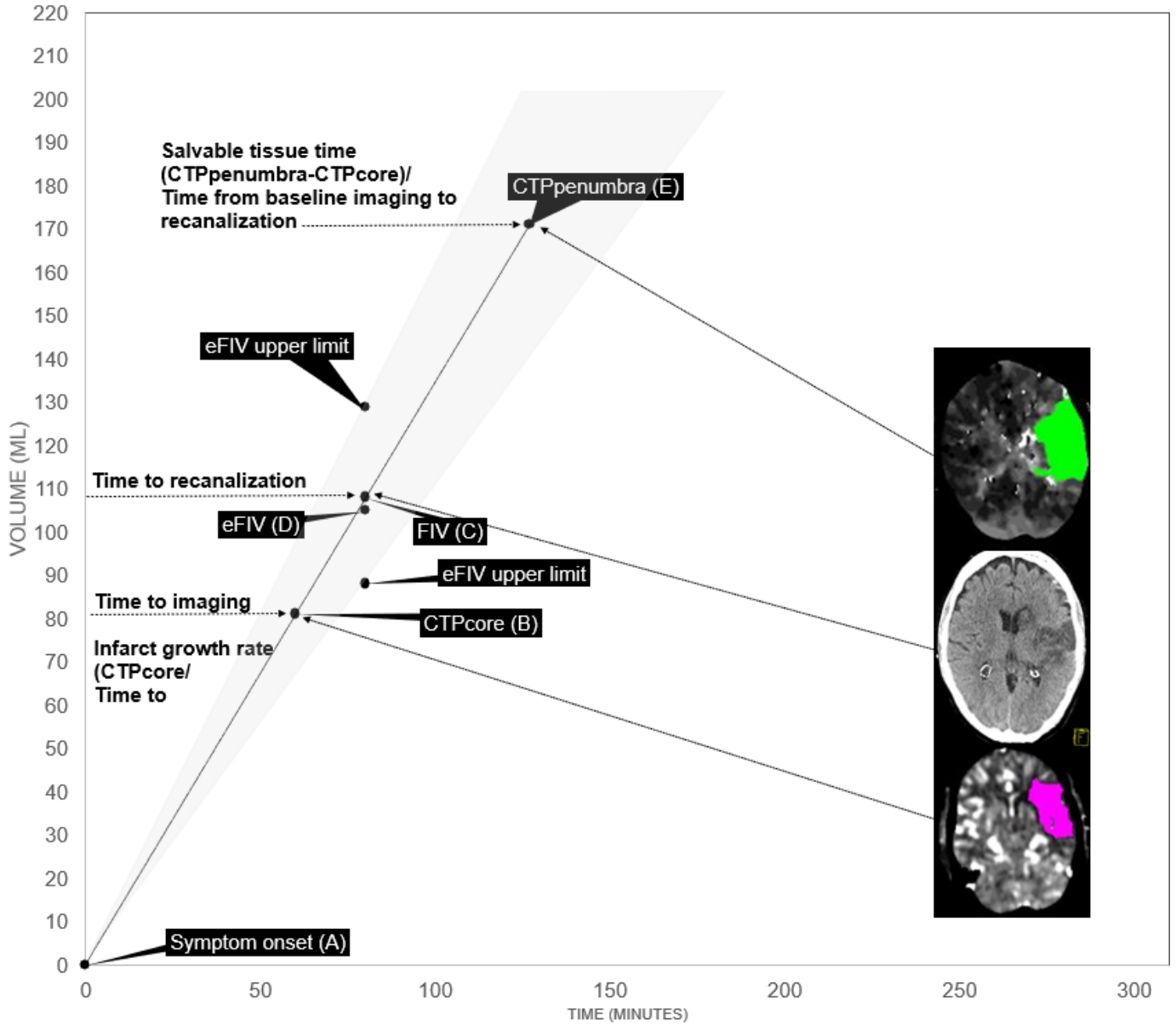
Salvable tissue time
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Time from baseline imaging to
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CTPpenumbra (E)
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Time to recanalization
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FIV (C)
eFIV upper limit
Time to imaging
CTPcore (B)
Infarct growth rate
(CTPcore/
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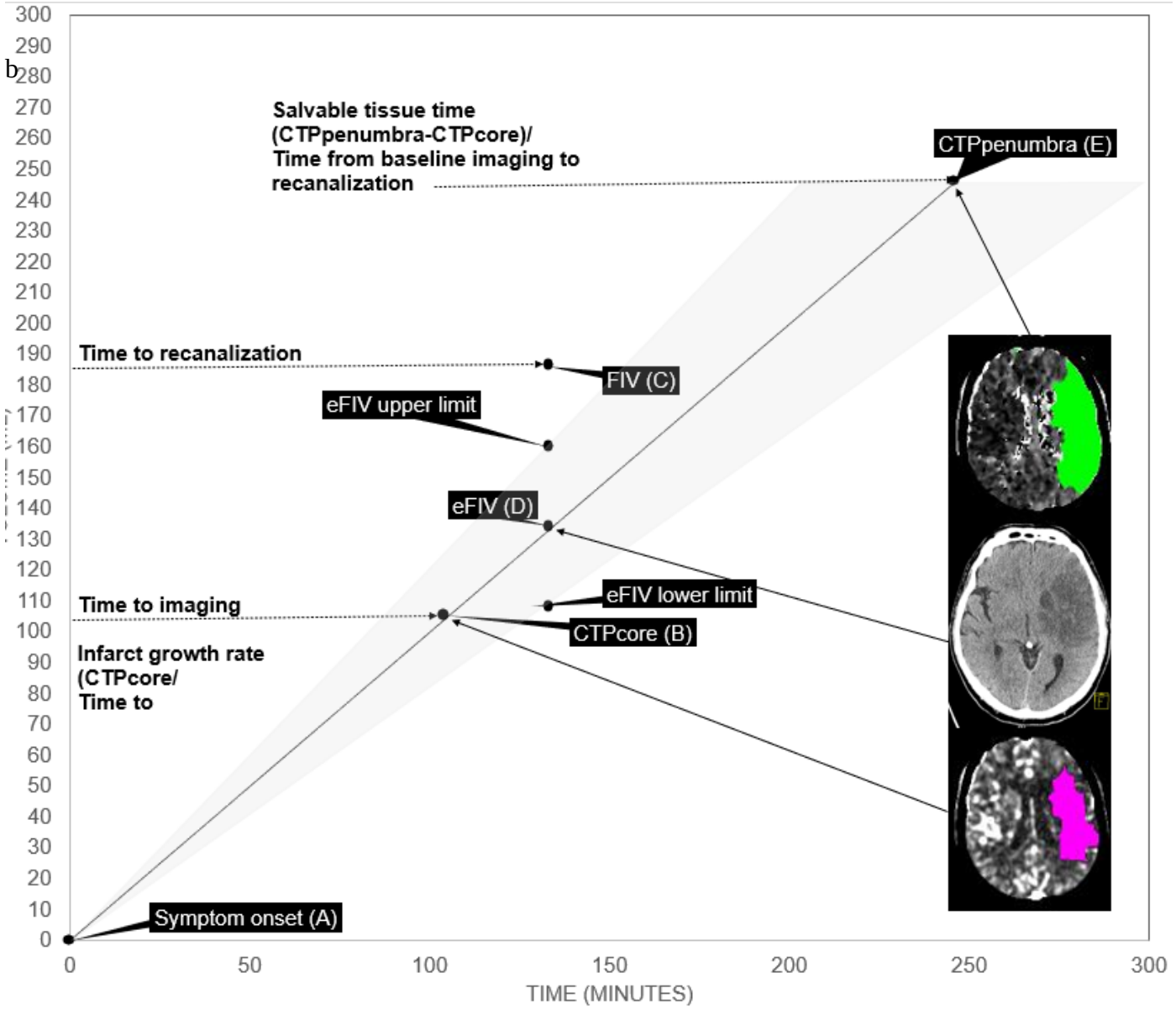
b
Salvable tissue time
(CTPpenumbra-CTPcore)/
Time from baseline imaging to
recanalization
CTPpenumbra (E)
Time to recanalization
FIV (C)
eFIV upper limit
eFIV (D)
eFIV lower limit
Time to imaging
CTPcore (B)
Infarct growth rate
(CTPcore/
Time to
Symptom onset (A)
300
290
280
270
260
250
240
230
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
0
50
100
150
200
250
300
TIME (MINUTES)

Figure 2. Examples of linear (a) and nonlinear (b) infarct core growth. Times from symptom onset (A) to imaging (B) recanalization (D) and salvageable tissue time ($CTP_{penumbra}$-CTP_{core}/baseline infarct growth, E) are shown in minutes. CTP_{core} (B), follow-up infarct volume (FIV) (C), estimated FIV (eFIV) based on baseline infarct growth rate and CTP RAPID (D) and $CTP_{penumbra}$ (E) measured in milliters.

a An example of linear growth of the infarct core in a 57-year-old male patient with M1-occlusion and successful recanalization. In case of successful recanalization and linear infarct core growth, eFIV accurately predicts FIV and salvageable tissue time in minutes until the infarction reaches the entire volume of $CTP_{penumbra}$.

b An example of nonlinear growth with underestimation of eFIV compared with FIV in a 70 year-old male patient with tandem occlusion and successful recanalization. In this nonlinear growth example, the measured infarct size from follow-up imaging (FIV) exceeds the 19% margins (gray area) of linear growth based on the linear growth model.

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Table 1 Cohort characteristics of all patients, and a comparison of patients who had a follow-up infarct volume (FIV) within and not within the margins of linear infarct core growth.

mTICI classification; modified treatment in cerebral infarction , IVT; intravenous thrombolysis, Salvageable tissue time (minutes); $CTP_{penumbra}$ ((T_{max}>6s ,volume of perfusion lesion) -CTP_{core}(cerebral blood flow (CBF) below 30% of normal brain)/baseline infarct growth), mRS; modified rankin scale, NIHSS; NIH stroke scale, CTP; computed tomography perfusion, Hypoperfusion intensity ratio (HIR); ratio of delay time >10 s/delay time >6 s volume, Successful recanalization (mTICI; modified treatment in cerebral infarction 2b or 3), EVT; endovascular treatment. eFIV; extrapolated follow-up infarction volume (infarction growth rate, mL/h x time (hours) to recanalization), Potentially saved tissue ($CTP_{penumbra}$, -FIV).

	All patients	Linear	Nonlinear	P-value
Patients	48 (100)	8 (17)	40 (83)	
Age in years, mean (SD)	67 (+/- 13)	72 ((+/- 14)	66 (+/13)	0.26†

Male	28 (58)	5 (63)	23 (58)	0.79§
Glucose in mmol/L	6.6 (6.2-8.0)	6.6 (5.9-8.3)	6.7 (6.3-7.9)	0.95†
IVT	25 (52)	6 (75)	19 (48)	0.16§
Process measures				
Onset to baseline imaging, min	101 (68-142)	138 (68-174)	97 (68-133)	0.38†
Onset to recanalization, min	210 (147-260)	209 (113-315)	210 (147-254)	0.89†
Baseline imaging to recanalization, min	102 (66-131)	73 (23-130)	104 (76-131)	0.20†
Baseline imaging under 100 min	25 (52)	5 (63)	20 (50)	0.52§
Salvageable tissue time, h	9.0 (3.1-26.2)	43.4 (2.6-57.7)	9.7 (4.5-27.4)	0.96†
Onset to follow-up imaging, h	25.8 (23.4-28.6)	1448 (1346-1552)	1556 (1427-1721)	0.10†

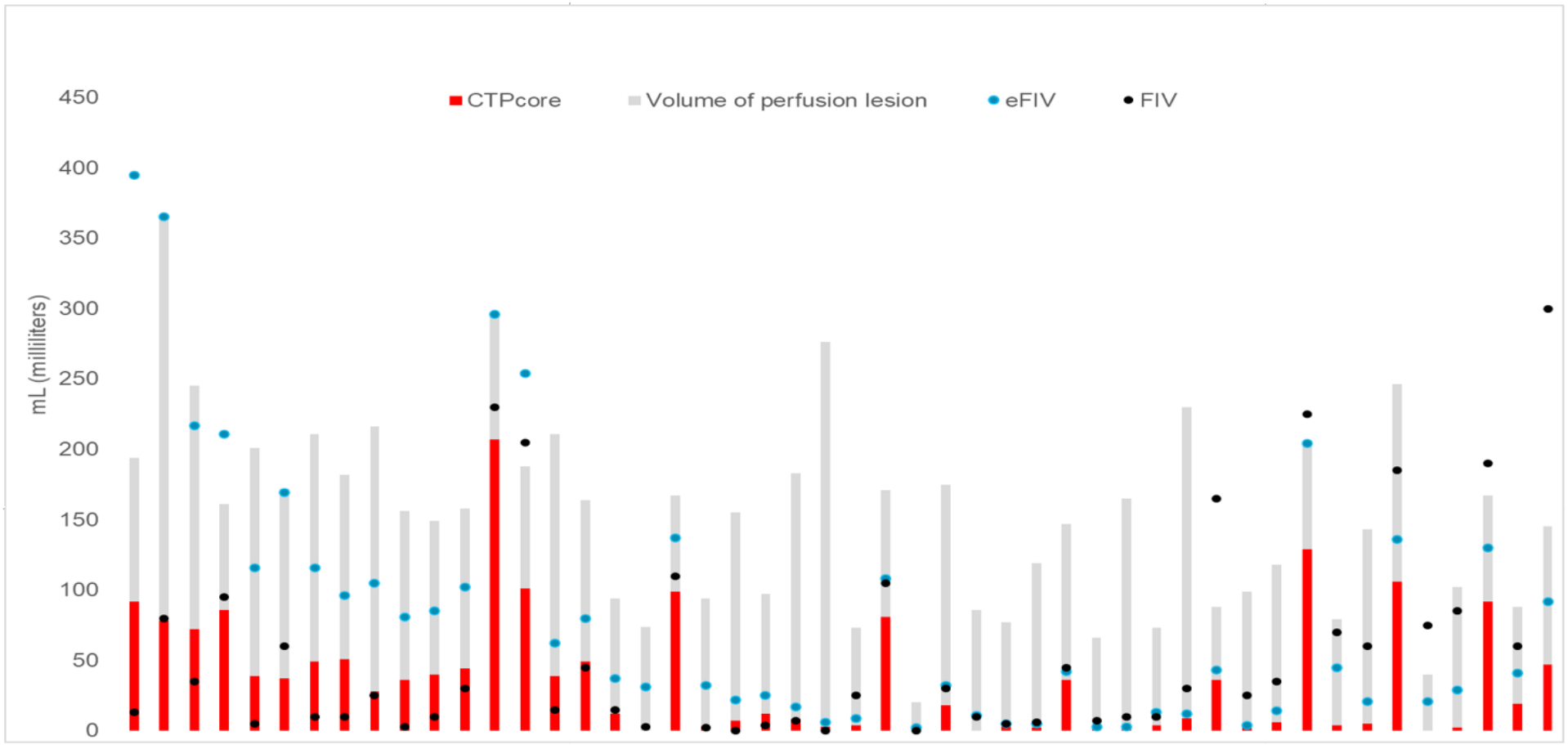
Baseline to follow-up imaging, h	23.9 (22.1-25.7)	1365 (1191-1459)	1443 (1343-1542)	0.15†
Poor outcome (mRS 3-6)	29 (60)	6 (75)	23 (58)	0.36§
Baseline NIHSS	16 (11-22)	15 (11-21)	16 (10-22)	0.90†
Baseline CTP_{core} volume*, mL	24 (4-51)	27 (2-96)	24 (4-49)	0.89†
Baseline $CTP_{penumbra}$ volume*, mL	157 (94-193)	159 (94-185)	157 (94-199)	0.96†
$CTP_{penumbra}$>15 mL*	48 (100)	8 (100)	40 (100)	-
Infarction growth rate, mL/h	11 (3-38)	9 (2-74)	11 (3-38)	0.85†
HIR	0.46 (0.15-0.60)	0.42 (0.15-0.64)	0.46 (0.15-0.59)	0.78†
Successful recanalization	42 (88)	7 (88)	35 (88)	1.00§

EVT attempts	1 (1-3)	1 (0-2)	2 (1-3)	0.20§
M1/ICA+M1	41 (85)/7 (15)	7 (88)/1 (13)	34 (85)/ 6 (15)	0.86§
eFIV, mL	42 (15-116)	37 (7-168)	44 (18-116)	0.80†
FIV, mL	28 (8-79)	38 (7-180)	25 (8-74)	0.48†
Potentially saved tissue, mL	83 (58-155)	74 (110)	88 (58-175)	0.35†

*CTP RAPID. Data are n (%) or median (interquartile range, IQR) unless otherwise stated

†Two-tailed Mann-Whitney U test

§ Pearson X^2-test



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48
BtR (h)	3.0	FR	2.1	2.4	3.0	2.7	1.4	2.0	FR	1.6	1.3	2.0	FR	1.1	1.5	1.0	2.7	1.9	0.6	1.6	2.4	1.0	1.3	1.8	1.9	0.3	0.5	2.3	1.3	1.9	3.6	0.5	1.9	1.5	1.9	0.9	1.3	1.0	1.1	FR	FR	4.2	0.5	1.6	FR	1.0	2.3	1.7
TL (h)	1.9	9.4	3.5	3.1	7.7	3.6	4.3	8.0	71	5.3	4.2	5.3	1.4	1.4	13.5	5.0	10	22	2.6	5.2	25	7.3	27	161	28	2.1	24	29	23	67	126	12	213	176	16	60	16	224	16	4	39	37	4.0	22	94	4.3	9.2	5.6
D (mL)	382	285	182	116	111	109	106	86	80	78	75	72	66	49	47	35	30	28	27	22	22	21	10	6	3	3	2	2	1	0	-1	-3	-4	-7	-16	-18	-19	-21	-21	-21	-25	-39	-49	-54	-56	-60	-122	-208
HIR	0.85	0.48	0.58	0.65	0.63	0.53	0.45	0.61	0.50	0.37	0.6	0.69	0.83	0.73	0.59	0.51	0.00	0.05	0.59	0.23	0.31	0.12	0.57	0.34	0.23	0.61	0.00	0.34	0.13	0.08	0.44	0.50	0.06	0.35	0.00	0.39	0.56	0.44	0.02	0.65	0.11	0.27	0.62	0.00	0.07	0.65	0.59	0.47

Figure 3 Volumes (mL) of estimated relative cerebral blood flow (CBF) below 30% of normal brain (CTP_{core}, red bars), volumes of perfusion lesion ($CTP_{penumbra}$, gray bars), estimated follow-up infarct volumes (eFIV, blue dots) and follow-up infarct volumes (FIV, black dots) in 24 h follow-up non-contrast computed tomography images in all 48 patients. In cases where infarct growth is linear (n=8), patients appear in yellow. Patients are organized by descending order of difference between eFIV and FIV. The eFIV is limited to $CTP_{penumbra}$ in cases 1,2,4,13,14 and 40.

BtR; baseline imaging to recanalization (h), FR; futile recanalization, TL; time left for salvageable tissue ($CTP_{penumbra}$-CTP_{core}/baseline infarct growth,h), D; difference between eFIV and FIV (mL), HIR; hypoperfusion intensity ratio

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