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Comparison of automated infarct core volume measures between non-contrast computed tomography and perfusion imaging in acute stroke code patients evaluated for potential endovascular treatment

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ABSTRACT

Introduction: Patients with small core infarction and salvageable penumbra are likely to benefit from endovascular treatment (EVT). As computed tomography perfusion imaging (CTP) is not always available 24/7 for patient selection, many patients are transferred to stroke centers for CTP. We compared automatically measured infarct core volume ($NCCT_{core}$) from the non-contrast computed tomography (NCCT) with ischemic core volume (CTP_{core}) from CTP and the outcome of EVT to clarify if $NCCT_{core}$ measurement alone is sufficient to identify patients that benefit from transfer to stroke centers for EVT.

Patients and methods: We included all consecutive stroke-code patients imaged with both NCCT and CTP at Helsinki University Hospital during 9/2016–01/2018. $NCCT_{core}$ and CTP_{core} volumes were automatically calculated from the acute NCCT images. Follow-up infarct volume (FIV) was measured from 24 h follow-up NCCT to evaluate efficacy of EVT. To study whether $NCCT_{core}$ could be used to identify patients eligible to EVT, we subgrouped patients based on $NCCT_{core}$ volumes (>50 mL and ≥ 70 mL).

Results: Out of 1743 patients, baseline $NCCT_{core}$, CTP_{core} and follow-up NCCT was available for 288 patients. Median time from symptom onset to baseline imaging was 74 min (IQR 52–118), and time to follow-up imaging 24.15 h (22.25–26.33). Baseline $NCCT_{core}$ was 20 mL (10–42), CTP_{core} 4 mL (0–16), and FIV 5 mL (1–49). Out of 288 patients, 23 had $NCCT_{core}$ ≥ 70 mL and 26 had CTP_{core} ≥ 70 mL. $NCCT_{core}$ and CTP_{core} performed similarly well in predicting large FIV (≥70 ml).

Conclusion: $NCCT_{core}$ is a promising tool to identify patients that are not eligible to EVT due to large ischemic cores at baseline imaging.

1. Introduction

Acute ischemic stroke is usually caused by an embolic or thromboembolic occlusion of a cerebral artery, which results in reduced cerebral blood flow (CBF) in the brain. This leads to brain ischemia, which can be divided into two distinct components, 1. the irreversibly damaged "core" infarction and 2. the ischemic, but viable surrounding tissue called penumbra [1–3]. Mechanical endovascular treatment (EVT) of large vessel occlusion (LVO) has been proven effective treatment in acute stroke care and the time-window for EVT has increased up to 24 h [4–11]. Recent large clinical trials have used perfusion imaging as selection tool for EVT inclusion and patients most likely to benefit from EVT are those with a relatively small volume of ischemic core (infarct core), LVO and salvageable brain tissue (volume of perfusion lesion, mismatch volume) measured by T_{max} threshold of 6 s (>15 ml (mL) [12]. Based on previous studies, $T_{max} > 6$ s is considered a reasonable estimate

Abbreviations: EVT, Endovascular Treatment; CTP, Computed Tomography Perfusion imaging; NCCT, Non-Contrast Computed Tomography; FIV, Follow-Up Infarct Volume,; MCA, Middle Cerebral Artery; LVO, Large Vessel Occlusion; ASPECTS, Alberta Stroke Program Early CT Score; EIC, Early Ischemic Changes; IVT, Intravenous Thrombolysis; mTICI, Modified Treatment in Cerebral Infarction.

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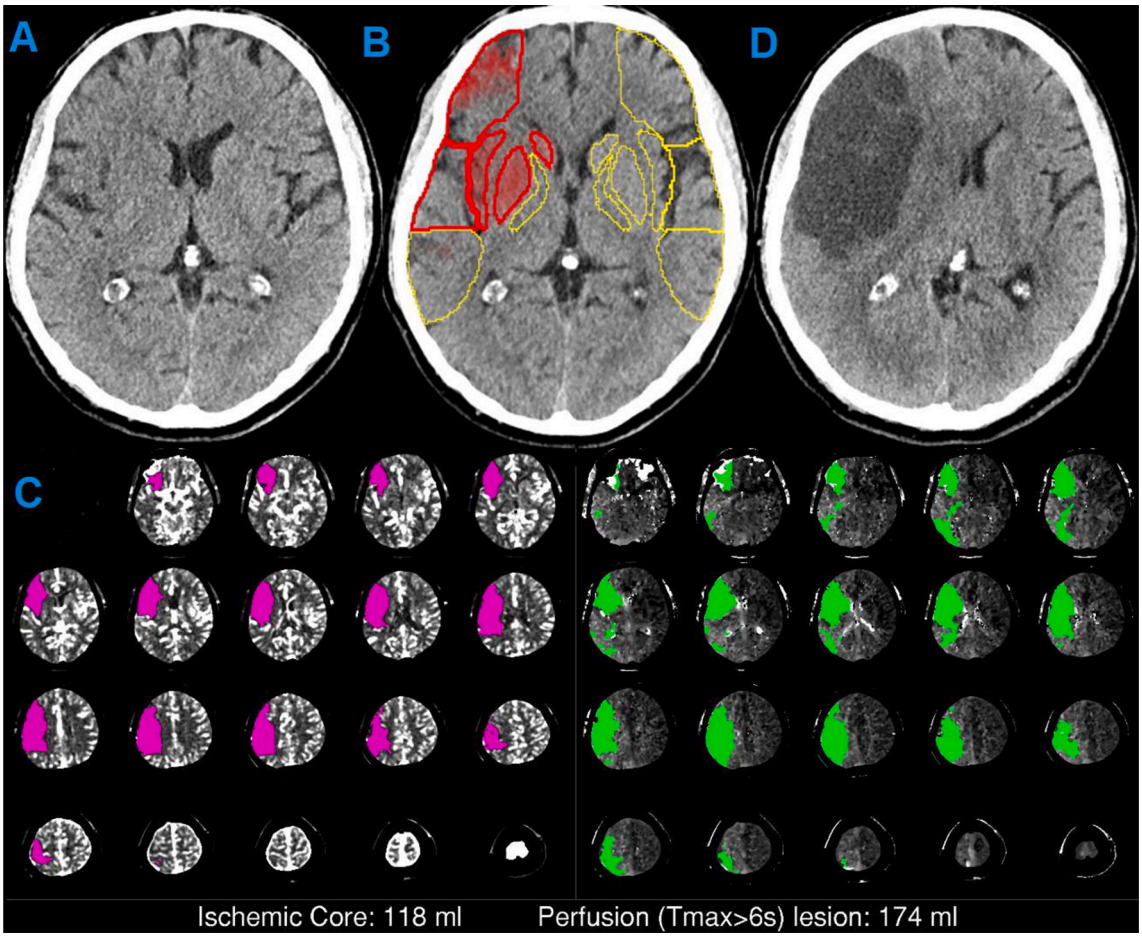


Fig. 1. Illustrates baseline non-contrast computed tomography (NCCT) (A), volumetric measure of early ischemic changes detected on NCCT in milliliters (mL) (B), estimated relative cerebral blood flow (CBF) below 30% of normal brain (LEFT) and tissue at risk of infarction in the absence of reperfusion ($T_{max} > 6$ s, RIGHT) in baseline computed tomography perfusion imaging in mL (C) and follow-up infarction volume in 24 h follow-up NCCT image (D) in a 64-year-old patient with ischemia in MCA (middle cerebral artery) territory.

of tissue at risk of infarction in the absence of reperfusion and the size of penumbra is considered as one of the prognostic biomarkers [4–7,11,12].

RAPID automated imaging analysis has been proven effective concerning computed tomography perfusion imaging (CTP) in predicting the final infarct volume as well as tissue at risk in large clinical trials although other commercial CTP software are also on market [4,11,12].

As infarct core growth is individual, CTP is often useful in the evaluation of most acute stroke code patients screened for potential EVT. The American Heart Association guidelines (AHA) recommend to follow the study inclusion and exclusion criteria of the recent EVT trials when considering EVT in patients in the 6 to 24 h time window [4,11]. This makes proper identification of suitable patients impossible in hospitals without availability of CTP or comprehensive magnetic resonance imaging leading to many futile secondary transports to comprehensive stroke centers or withholding potentially beneficial treatments of patients, depending on the local policies. An experimental feature of the machine learning based e-ASPECTS software (Brainomix Ltd.) can provide a volumetric measure of early ischemic changes (EIC) detected on non-contrast computed tomography (NCCT) images ($NCCT_{core}$). $NCCT_{core}$ might be useful in patient selection if ischemic core measurement by CTP (CTP_{core}) is not available.

Aims and hypothesis.

The aim of the study is to retrospectively compare $NCCT_{core}$ and CTP_{core} in selection of acute recanalization treatment patients (EVT) among stroke code patients to clarify whether $NCCT_{core}$ measurement alone is sufficient to identify patients with large infarct core (>50 mL and $\geq$ 70 mL) and thus do not benefit from recanalization treatment attempts.

2. Methods

We performed a single-center, retrospective analysis of imaging findings of all consecutive acute stroke patients (Stroke Code) at Helsinki University Hospital (HUS) based on the Helsinki stroke quality registry (HSQR). Ethical approval was not sought for the present study and informed consent was waived due to the retrospective nature of the study. This study was completed in accordance with the Helsinki Declaration as revised in 2013. NCCT is the first-line imaging modality for stroke code patients in our hospital. All patients evaluated for potential intravenous thrombolysis (IVT) or EVT for acute ischemic stroke were considered as stroke code patients and treatment decisions were made based on clinical symptoms and imaging findings at HUS. Multimodal imaging, usually CTP (RAPID® software, iSchemaView Inc., Golden Park, CA, USA) and computed tomography angiography (CTA) were done according to the decision of the treating neurologist based our local guideline which are in line with the current AHA guidelines [4,11]. No visualization of penumbra by CTP is required by Helsinki protocol in the 0-6 h time window for clinically obvious ischemic strokes. The NCCT is used to rule out contraindications (brain

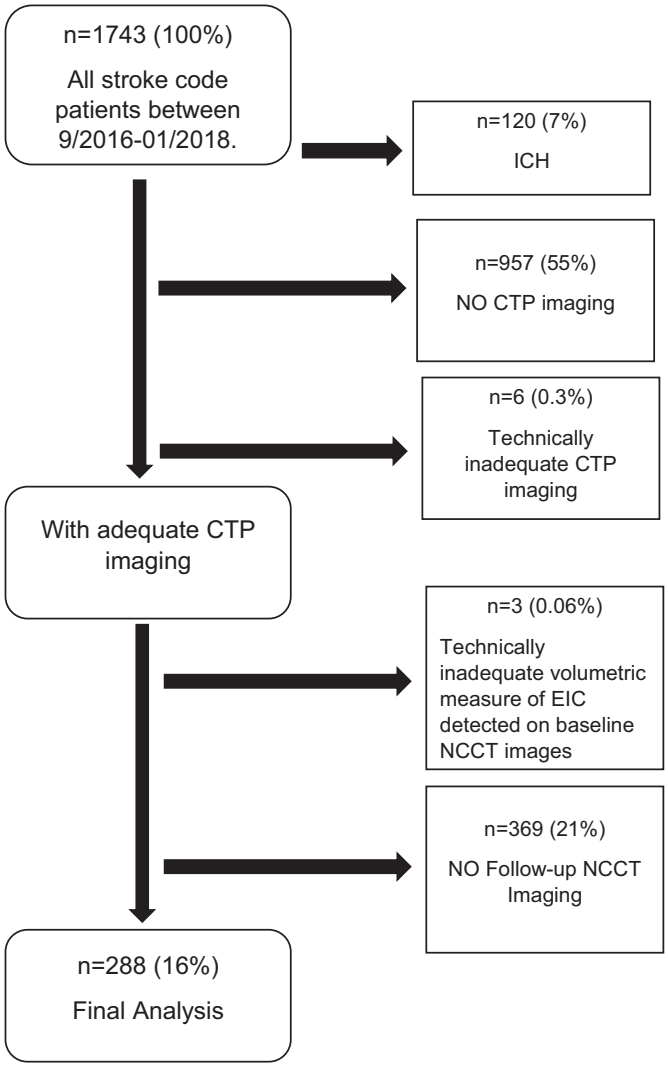


Fig. 2. Flowchart of the patients in the study. ICH; Intracerebral Hemorrhage, CTP; Computed Tomography Perfusion, EIC, Early Ischemic Changes, NCCT; Non-Contrast Computed Tomography.

hemorrhagia and extensive vascular degeneration) and CTA is taken after initiation of thrombolysis to evaluate whether EVT is indicated.

A follow-up NCCT imaging of the brain at 24 h (±6 h) was performed for all patients who underwent IVT or EVT. Clinical parameters (sex, age, glucose, INR, blood pressure), National Institute of Health Stroke Scale (NIHSS) score at baseline and 24 h and modified Rankin scale (mRS) at 3 months were registered. Symptomatic intracerebral hemorrhage (sICH) was assessed according to European Co-operative Acute Stroke Study-II (ECASS 2) criteria [13]. Recanalization was defined with modified Treatment in Cerebral Infarction (mTICI)) scale as successful (score 2b or 3) or futile (score 0, 1, or 2a) by the performing interventional radiologist [14]. Favorable outcome was defined as 0–2 on modified Rankin scale (mRS).

2.1. 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 5 mm, 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

Table 1
Cohort Characteristics of 288 acute stroke code patients imaged with non-contrast computed tomography (NCCT), computed tomography perfusion (CTP) and follow-up NCCT at 24 h

Characteristics		Participants
Age in years, mean (SD)		71 (±11)
Male		162 (56)
IVT/EVT/IVT + EVT		118 (41)/40 (14)/49 (17)
No recanalization treatment		81 (28)
Wake-up stroke		66 (23)
Time to imaging, min		74 (52–118)
Time from baseline to follow-up imaging, h		24.15 (22.25–26.33)
CTP < 6 h of symptom onset		198 (69)
mRS for patients with recanalization treatment	3–6	92 (44)
Successful recanalization in EVT patients		63 (71)
sICH[a]	IVT	5 (3)
	IVT + EVT	2 (4)
CTP_{core} > 50 mL[b]		36 (13)
CTP_{core} > 70 mL[b]		26 (9)
CTP_{core} volume[b] in mL		4 (0–16)
CTP T_{max} > 6 s volume[b] in mL		64 (5–14)
T_{max} > 6 s > 15 mL[b]		192 (67)
Baseline NIHSS score[c]		8 (4–15)
Baseline ASPECTS[c]		10 (8–10)
Baseline NCCTcore[c] in mL		20 (10–42)
FIV, mL		5 (1–49)
ACA or PCA ischemia only		33 (11)

IVT;Intravenous Thrombolysis,EVT;Endovascular Treatment, mRS;modified Rankin Scale, Successful recanalization mTICI;modified Thrombolysis in Cerebral Infarction 2b or 3, sICH; Symptomatic Intracranial Hemorrhage, NIHSS;NIH Stroke Scale, ASPECTS;Alberta Stroke Program Early CT Score, FIV; Follow-up Infarct Volume, ACA;Anterior Cerebral Artery, PCA; Posterior Cerebral Artery.

[a] According to the ECASS2 criteria.

[b] CTP RAPID.

[c] e-ASPECTS, e-ASPECTS volume feature. Data are *n* (%) or median (interquartile range, IQR) unless otherwise stated.

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) in order to quantify ischemic core and volume of perfusion lesion.

The CTP_{core} was defined as relative cerebral blood flow (CBF) below 30% of normal brain [15]. T_{max} threshold of 6 s was used as estimate of tissue at risk of infarction in the absence of reperfusion [12]. The volume of saved tissue was calculated as the difference of the volume with a T_{max} exceeding 6 s and the follow-up infarct volume (FIV) ($CTP_{Tmax>6s}$-FIV). The volume of lost tissue was calculated as the difference of the FIV and the CTP_{core} (FIV- CTP_{core}).

Alberta stroke program early CT score (ASPECTS) [16,17] score was automatically determined by using e-ASPECTS software [18,19]. e-ASPECTS volume feature ($NCCT_{core}$) was used to quantify ischemic core from the baseline NCCT in mL.

Briefly, e-ASPECTS is based on a machine learning algorithm and was developed to detect signs of EIC on NCCT. In e-ASPECTS volume feature (NCCTcore, Brainomix Ltd.) patient-specific segmentation of the ASPECTS regions is computed, and the output score and result images are generated by classifying each region according to the evidence of ischemia contained within the probability map. $NCCT_{core}$ is the volume of this probability map and comprise the sum of the voxels in which EIC have been identified which is converted in to a volumetric value in mL. Fig. 1 illustrates baseline NCCT, $NCCT_{core}$ and CTP_{core} at baseline and FIV on follow-up NCCT in the same patient.

The neuroradiologist (AA) was blinded to any other imaging including e-ASPECTS and RAPID software. He defined the territory and side of infarction and measured semi-automatically the FIV from the

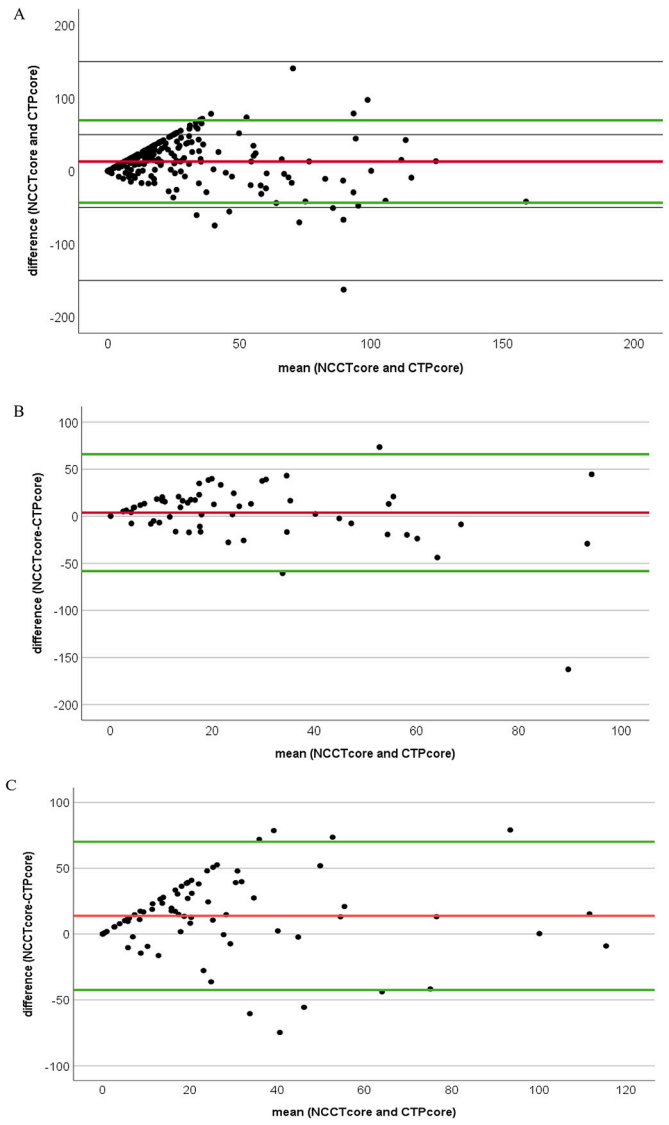


Fig. 3. Bland–Altman plot of the difference between $NCCT_{core}$ and CTP_{core} volumes among (A) all 255 patients without anterior cerebral artery (ACA) or posterior cerebral artery (PCA) ischemia only on follow-up imaging, (B) patients with successful recanalization (modified Treatment in Cerebral Infarction 2b or 3, $n = 61$) and (C) patients imaged >6 h of symptom onset ($n = 79$).

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 region of interest (ROI). Those ROIs had mean Houndsfield units (HU) ranging from 25 to 31, while normal cerebral parenchyma was measured at mean > 42 HU. The "create VOI tool" was then applied to include all voxels situated within the before mentioned threshold at different slices of the same infarction. Edges were manually adjusted when necessary.

2.2. 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 (SD) if normally distributed or median (interquartile intervals, IQR) if not normally distributed. Medians between two groups (subgroups of successful recanalization, imaging>6 h of symptom onset,

Table 2
Cohort Characteristics of 52 ($NCCT_{core}$ > 50 mL) and 23 ($NCCT_{core}$ ≥ 70 ml) acute stroke code patients imaged with non-contrast computed tomography (NCCT), computed tomography perfusion (CTP) and follow-up NCCT at 24 h.

	>50 mL *N* = 52	≥70 mL N = 23
IVT/EVT/IVT + EVT	26 (50)/16 (31)/ 11 (21)	9 (39) /7 (30)/4 (17)
No treatment	21 (40)	11 (47)
Wake-up stroke	12 (23)	6 (26)
Time to imaging, min	108 (61–185)	120 (54–206)
Time from baseline to follow-up imaging, h	24.58 (22.94–27.16)	25.25 (22.6.33)
Imaging >6 h of symptom onset	20 (38)	11 (48)
mRS 3–6 for patients with recanalization treatment	6 (12)	2 (17)
Successful recanalization in EVT patients	8 (50)	3 (43)
sICH[a]	0 (0)	0 (0)
CTP_{core}[b], mL	45 (2–91)	92 (24–108)
T_{max} > 6 s > 15 mL	46 (86)	20 (87)
$NCCT_{core}$[c],mL	64 (56–83)	81 (76–132)
FIV, mL	55 (15–208)	175 (60–255)
MCA ischemia on follow-up imaging	52 (100)	23 (0)
Volume of tissue saved in mL, mean (SD)	33 (±96)	-3 (±102)
Volume of tissue lost in mL, mean (SD)	66 (±81)	96 (±91)
ASPECTS[c]	6 (4–8)	5 (3–7)

IVT;Intravenous Thrombolysis, EVT;Endovascular Treatment, mRS;modified Rankin Scale, TICI;Thrombolysis in Cerebral Infarction, sICH;Symptomatic Intracranial Hemorrhage, FIV; Follow-up Infarct Volume MCA;Middle Cerebral Artery, Volume of tissue saved ($CTP_{Tmax6s\text{-}lesion}$-FIV) and tissue lost (FIV-CTP_{core}).

[a] According to the ECASS2 criteria.

[b] CTP RAPID.

[c] e-ASPECTS, e-ASPECTS volume feature. Data are n (%) or median (interquartile range, IQR) unless otherwise stated.

$NCCT_{core}$ > 50 and ≥ 70 mLvolumes) versus all patients without signs of ACA or PCA ischemia only on follow-up imaging were analyzed using the Wilcoxon Signed Rank test or Mann–Whitney *U* test. Bland–Altman plots were used to illustrate the distribution of the difference in volumetric measurements (mL) between $NCCT_{core}$ and CTP_{core}. The Bland-Altman plots enable visual assessment of the bias (mean difference in values obtained between the paired measurements), data scatter, and the relationship between magnitude of difference and size of measurement. The horizontal lines above and below the bias line represent 95% limits of agreement and are defined with limits of agreement = bias ± 1.96 standard deviation.

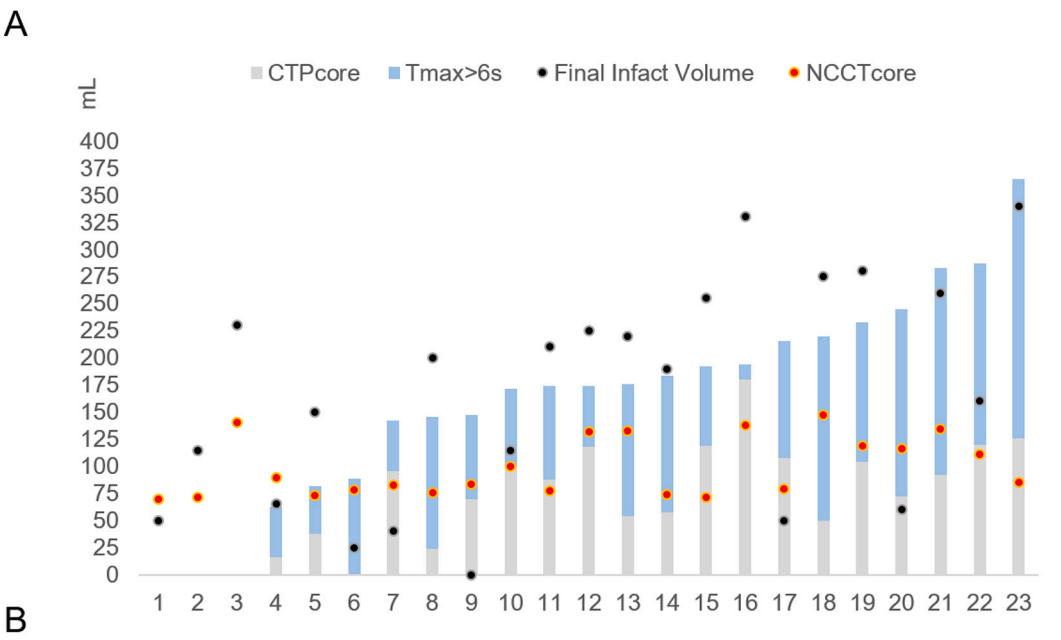
Receiver operating characteristics (ROC) curves were generated for both $NCCT_{core}$ and CTP_{core} to analyze sensitivity and specificity of $NCCT_{core}$ and CTP_{core} for dichotomized FIV >50 mL FIV ≥70 mL respectively. The standard error of ROC-curves were analyzed by the method of Hanley and McNeil. The statistical analysis plan specified a *p* value less than 0.05 as statistically significant.

3. Results

3.1. Patients

We enrolled 1743 consecutive acute stroke code patients to the study (Fig. 2). Of those, 508 (29%) received IVT, EVT or both. 295 (17%) received IVT only, 97 (6%) received EVT only, and 116 (7%) both IVT and EVT. 1235 (71%) stroke code patients were not eligible for recanalization therapy (EVT or IVT) and 120 (7%) of all patients were diagnosed with ICH.

660 out of the 1743 patients were imaged with CTP. Follow-up NCCT images were available for all patients that received IVT and/or EVT, and



Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
IVT	0	0	0	1	0	0	1	1	0	0	1	1	0	1	1	0	1	0	0	0	0	0	1
EVT	0	0	0	1	1	0	0	0	0	0	0	0	0	1	0	0	1	0	1	1	0	0	1
Tissue saved	-	-	-	-	-	+	+	-	+	+	-	-	-	-	-	-	+	-	-	+	+	+	+

Fig. 4. A and B Illustrates baseline volumetric measure of early ischemic changes detected on non-contrast computed tomography images ($NCCT_{core}$, orange dot) and estimated relative cerebral blood flow (CBF) below 30% of normal brain (colored in grey bar) volumes, follow-up infarction volume (black dot) in 24 h follow-up NCCT and tissue at risk of infarction in the absence of reperfusion (penumbra, $T_{max} > 6$ s, mL, colored in light blue bar) of all patients with $NCCT_{core} \geq 70$ mL ($n = 23$) in milliliters (mL).
Volume of tissue saved (mL) in individual patients with or without acute recanalization treatment (IVT; Intravenous thrombolysis, EVT;Endovascular treatment) marked as + >0 mL and – if <0 mL). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

in addition, for 80 patients that were imaged with CTP but who did not receive any recanalization therapy. Altogether CTP, NCCT images at baseline, and follow-up NCCT images were available for 297 patients. 9 patients had to be excluded due to technical problems in RAPID output or $NCCT_{core}$ image analysis.

Final cohort of 288 patients consisted of 118 (41%) patients treated with IVT only, 40 (14%) with EVT only, 49 (17%) with both IVT and EVT and 81 (28%) patients with no acute recanalization treatment (IVT or EVT). Medians for time from symptom onset to baseline imaging and baseline to follow-up imaging were 74 min (IQR 52–118), and 24.15 h (IQR 22.25–26.33) respectively. 198 (69% patients) were imaged <6 h of symptom onset, for more clinical characteristics see Table 1. Median ASPECTS of the patients was 10 (IQR 8–10; supplementary appendix).

As e-ASPECTS software detects signs of early ischemic damage in NCCT only in the middle cerebral artery (MCA) territory, we excluded the patients with ischemia only in the vascular territory of anterior or posterior cerebral artery (ACA, PCA) on follow-up imaging ($n = 33$, 11%).

CTP_{core} of the remaining 255 patients was smaller than the $NCCT_{core}$ (3 mL; IQR 0–20 vs. 24 mL; IQR 10–44); the median FIV was 5 mL (IQR 0–60). The median difference between $NCCT_{core}$ and CTP_{core} was 12 mL (IQR 1–26, $p < 0.001$) and between $NCCT_{core}$ and FIV 6 mL (IQR −28-21, $p > 0.05$).

We analyzed the difference between $NCCT_{core}$ and CTP_{core} further to evaluate the effect of successful recanalization and the effect of imaging time on results. 61 out of 255 (24%) patients had successful recanalization. In them, the median difference between $NCCT_{core}$ and CTP_{core} was 9 mL (IQR-8-18), and between $NCCT_{core}$ and FIV 6 mL (IQR −32-25). The difference between $NCCT_{core}$ and FIV was significantly smaller ($p < 0.005$) in patients with successful recanalization than in other patients.

79 out 255 patients (31%) were imaged >6 h of symptom onset. The median difference between $NCCT_{core}$ and CTP_{core} was 13 mL (IQR 0.2–31) and between $NCCT_{core}$ and FIV 0.4 mL (IQR –39-23). $NCCT_{core}$, did not significantly differ between the patients imaged >6 h of symptom onset and other patients.

Bland–Altman plots (Fig. 3) illustrate the difference between $NCCT_{core}$ and CTP_{core} in (A) all 255 patients, (B) patients with successful recanalization and (C) patients imaged >6 h of symptom onset.

3.2. $NCCT_{core}$ and identification of EVT candidates

To study whether $NCCT_{core}$ values could be used in identification of EVT candidates without access to perfusion imaging, the patients were subgrouped based on $NCCT_{core}$ volumes (Table 2) using the same cut-off volumes (>50 mL and ≥ 70 mL) that were used for exclusion in the recent large EVT trials [4,11]. Success of recanalization therapy was evaluated as volume of tissue saved in patients with acute recanalization treatment.

$NCCT_{core}$ volume was >50 mL in 52 (18%) and $CTP_{core} > 50$ mL in 36 (13%) of the patients. $NCCT_{core}$ volume was ≥70 mL in 23 (8%) and $CTP_{core} \geq 70$ mL in 26 (9%) of the patients. All patients (100%) with both $NCCT_{core} > 50$ mL and $NCCT_{core}$ volume was ≥70 mL had MCA ischemia on follow-up imaging. 20 (38%) patients with $NCCT_{core} > 50$ mL and 11 (46%) with $NCCT_{core} \geq 70$ mL were imaged >6 h of symptom onset.

Fig. 4A illustrates baseline $NCCT_{core}$, and CTP_{core} volumes, FIV in 24 h follow-up NCCT and volume of perfusion lesion ($T_{max} > 6$ s,

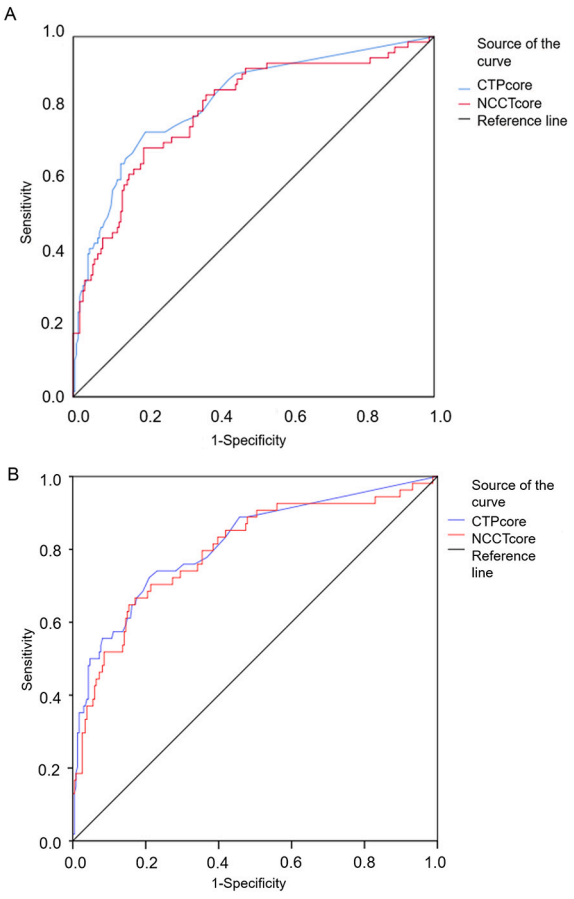


Fig. 5. Receiver operating characteristics (ROC) curves were generated for both volumetric measure of early ischemic changes detected on non-contrast computed tomography images ($NCCT_{core}$) and estimated relative cerebral blood flow (CBF) below 30% of normal brain (CTP_{core}) to analyze sensitivity and specificity of the dichotomized follow-up infarction volume in 24 h follow-up NCCT for both >50 mL and ≥ 70 mL volumes. Both $NCCT_{core}$ and CTP_{core} performed similarly well in predicting follow-up infarction volume > 50 mL (A, ((AUC 0.79, SE 0.035, $p < 0.001$, CI 0.72–0.86 and AUC 0.82, SE 0.032, $p < 0.001$, CI 0.76–0.88) and ≥ 70 mL (B, (AUC 0.79, SE 0.039, $p < 0.001$, CI 0.72–0.87 and AUC 0.81, SE 0.037, $p < 0.001$, CI 0.74–0.89) in follow-up non-contrast computed tomography.

penumbra) of all patients that had $NCCT_{core} \geq 70$ mL ($n = 23$).

As Fig. 4A illustrates, from the 23 patients with $NCCT_{core} \geq 70$ mL, 13 (57%) patients had also $CTP_{core} \geq 70$ mL. Despite the large ischemic core (>70 ml) in NCCT, IVT, EVT or both were given to 12 patients; only 4 of them benefitted from the treatment (tissue saved in cases 7, 17, 20 and 23, Fig. 4B) of which 3 (cases 17,20,23) were treated with EVT. In other 13 patients who had $CTP_{core} > 70$ mL $NCCT_{core}$ was below 70 mL.

Out of the 52 patients with $NCCT_{core} > 50$ mL, 23 (44%) had also $CTP_{core} > 50$ mL. Despite $NCCT_{core} > 50$ mL, IVT, EVT or both were given to 31 (60%) patients. Of them, 17 (55%) patients had $CTP_{core} \leq 50$ with tissue saved in 10 (59%) patients. EVT therapy alone or with IVT resulted in successful recanalization in 50% of patients with $NCCT_{core} > 50$ mL and in 43% in patients with $NCCT_{core} \geq 70$ mL (cases 4,7 and 20). More detailed information of patients with $NCCT_{core} \geq 70$ mL and acute recanalization treatment and patients with $CTP_{core} \geq 70$ mL are provided in supplemental material.

The $NCCT_{core}$ showed sensitivity of 77%, specificity of 89% and positive predictive value of 44% against the established FIV > 50 mL criterion. The $NCCT_{core}$ showed sensitivity of 45%, specificity of 96% and positive predictive value of 57% against the established FIV ≥70 mL criterion.

The performance of $NCCT_{core}$ and CTP_{core} in predicting a FIV of >50 mL and ≥ 70 ml was analyzed in ROC-curves (Fig. 5A and B) among all 288 patients.

$NCCT_{core}$ and CTP_{core} performed similarly well in predicting both FIV > 50 mL (AUC 0.80, SE 0.033, $p < 0.001$, CI 0.73–0.86 and AUC 0.82, SE 0.031, $p < 0.001$, CI 0.76–0.88)) and FIV ≥ 70 mL (AUC 0.80, SE 0.037, $p < 0.001$, CI 0.73–0.87 and AUC 0.82, SE 0.035, $p < 0.001$, CI 0.73–0.87). There was no significant difference between AUCs of $NCCT_{core}$ and CTP_{core} in both FIV > 50 mL (difference –0.02, SE 0.06, $p = 0.73$) and FIV ≥ 70 mL (difference − 0.02, SE 0.08, $p = 0.79$).

4. Discussion

Our aim was to study $NCCT_{core}$ as selection tool for EVT without knowledge of CTP or CTA data. The present study shows that exclusion criterion of $NCCT_{core} \geq 70$ mL at baseline exhibited sensitivity of only 45% against the FIV ≥70 mL criterion although good negative predictive value. 3 patients with $NCCT_{core} \geq 70$ mL seemed to have benefitted from EVT, despite a $CTP_{core} > 70$ mL and thus did not fulfill the guideline recommendations [4,11]. There was no significant difference between $NCCT_{core}$ and CTP_{core} volumes among patients imaged >6 h of symptom onset compared to other patients even though the median difference was smaller compared with other patients (9 mL vs. 12 mL, $p > 0.05$). An NCCT based identification of patients that will not benefit from revascularization treatments could save resources at smaller stroke centers by avoiding the transfers of patients with suspected LVO to comprehensive stroke centers. NCCT is usually readily available in every emergency room treating stroke patients.

ROC-curve analysis showed that both $NCCT_{core}$ and CTP_{core} had similar performance in predicting FIV. CTP_{core} has been successfully shown to predict final infarction volume on follow-up imaging at 24 h in patients with successful recanalization and $T_{max} > 6$ s has performed well in predicting subsequent infarct volume in patients who did not achieve reperfusion in prior studies [5,12,20].. The $NCCT_{core}$ and CTP_{core} are measured with different algorithms, which could have effect on baseline variation. The $NCCT_{core}$ volume as quantified using volumetric measure by e-ASPECTS software seems to overestimate the ischemic core volume in comparison with CTP_{core}. As 33 (11%) patients had ischemia only in the vascular territory of ACA or PCA on follow-up imaging, only 4 patients had baseline $NCCT_{core}$ of 0 mL even though e-ASPECTS software detects signs of early ischemic damage only in ASPECTS regions.

To our knowledge, $NCCT_{core}$ has not been studied as a screening tool of candidates for endovascular treatment. It was shown in recent study of Nagel et al. that e-ASPECTS-derived automatically derived acute ischemic volumes ($NCCT_{core}$) from NCCT correlated strongly with comprehensive magnetic resonance imaging volumes as well as CTP ischemic "core" volumes although this was studied in a small cohort ($n = 41$) and. [21] A recent study showed comparable agreement between $NCCT_{core}$ and CTP_{core} against FIV in a large, prospectively collected cohort of fully reperfused EVT patients [22]. Our study results are in line with previous studies as patients with successful recanalization had smaller median difference between $NCCT_{core}$ and FIV ($p = 0.002$) compared with other patients [21,22]. The strength of our study is that we studied $NCCT_{core}$ as screening tool among stroke code patients, not in EVT patients only. All patients were also imaged with CTP RAPID compared to study of Nagel et al. (Olea Sphere®)) which has been used successfully in large clinical trials.

However, our study has several limitations. Due to the retrospective nature of the study, one must bear in mind, that all treatment decisions were based on baseline NCCT, CTA and CTP without knowledge of the calculated $NCCT_{core}$. CTP_{core} might overestimate ischemic core especially if imaging is performed <180 min of symptom or with fast successful recanalization and the median time to imaging was 74 min in our study [23]. Considering the role as selection tool for EVT, the volumetric measure of EIC by e-ASPECTS is limited to MCA-territory, however all patients (100%) with $NCCT_{core} > 50$ mL and $NCCT_{core} \geq 70$ mL had

ischemia in MCA-territory in our cohort. If $NCCT_{core}$ had been used as selection tool for EVT instead of $CTP_{core,}$ a discrepancy of eligibility for EVT would have occurred in 43% patients. However, in 10 patients EVT was attempted despite of $CTP_{core} > 70$ mL, resulting in a smaller FIV than anticipated by the perfusion lesion in 6 cases. This suggests that CTP_{core} is not an optimal selection tool either. Surprisingly, the median $NCCT_{core}$ volume was larger than CTP_{core} and FIV which may due to sensitivity of the algorithm to for example vasogenic edema in the early phase of infarction [24]. The FIV was measured by only one neuroradiologist, however he was blinded to any other imaging or outcome data. As NCCT was used as imaging modality of follow-up imaging at 24 h after the baseline imaging, underestimation of FIV might have occurred.

Both $NCCT_{core}$ and CTP RAPID should be used as decision support tools and clinical decision making is in the key role identification possible discrepancies between core estimates and clinical symptoms.

5. Conclusions

New NCCT based imaging biomarkers would be beneficial in clinical decision making especially with drip-and ship patients and when there is no straight access to CTP or comprehensive magnetic resonance imaging. $NCCT_{core} \geq 70$ mL at baseline should be further investigated as an exclusion tool for recanalization therapies, especially in EVT patients in the 6 to 24 h time window.

Data access statement

Data openly available in a public repository that issues datasets with DOIs.

Authors contributors

OPS and SC were involved in conceptualization, OPS, SC and AEA were involved in data curation, formal analysis, investigation and methodology. SC was involved in supervision. OPS was involved in visualization.OPS, SC., AEA, NF, MT, NM-M were responsible for writing-original draft and review and editing.

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Declaration of Competing Interest

The Author(s) declare(s) that there is no conflict of interest. The author(s) declare no relationship to Brainomix Ltd. or iSchemaView Inc. concerning RAPID or e-ASPECTS software.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2021.117483.

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