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ORIGINAL ARTICLE

Accuracy and Reliability of Multiphase CTA Perfusion for Identifying Ischemic Core

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Abstract

Purpose Acute stroke treatment requires simple, quick and accurate detection of early ischemic changes to facilitate treatment decisions guided by published selection criteria. The aim of this study was to determine the accuracy and reliability of multiphase computed tomography angiography (mCTA) perfusion hypoattenuation for detecting early severe ischemia.

Methods Non-contrast CT (NCCT), mCTA for regional leptomeningeal score (mCTA-rLMC), and mCTA perfusion lesion visibility (mCTA-arterial and mCTA-venous) were assessed blinded to clinical information in patients treated with endovascular therapy (EVT). The extent of early ischemia defined by regions of hypoattenuation was evaluated by the Alberta Stroke Program Early CT Score (ASPECTS). The ASPECTS scores were dichotomized based on the American Heart Association (AHA) guidelines for EVT selection, ASPECTS ≥6 vs. <6. The diagnostic accuracy was calculated by comparison to 24-h magnetic resonance imaging (MRI) or CT ASPECTS. Inter-observer reliability of NCCT and mCTA ASPECTS was evaluated. Machine learning models were used to predict the clinical follow-up outcome, e.g. National Institutes of Health Stroke scale (NIHSS) and modified Rankin scale (mRS) from baseline imaging data and patient information.

Results A total of 89 acute stroke patients (68 ± 15 years of age) were analyzed (33 TICI-0, 56 TICI-2b or 3). Median baseline NIHSS was 17. The mCTA-venous had a large effect on accurately identifying early ischemia when dichotomized for ASPECTS ≥6 vs <6 (likelihood ratio [LR+] > 10 vs. [LR–] < 0.29) compared to the moderate effect of NCCT ([LR+] = 6.7; [LR–] = 0.56) and mCTA-rLMC [(LR+ = 8.0; (LR–) = 0.83)]. The inter-observer reliability in mCTA-venous was almost perfect for all ASPECTS regions except the internal capsule. The machine learning support factor regression model identified mCTA-venous as the most important imaging covariate for predicting 24-h NIHSS and 90-day mRS.

Conclusion The assessment of mCTA-venous permits a more accurate detection of early ischemia than NCCT and mCTA-rLMC score and is predictive of clinical outcome. We would recommend the inclusion of mCTA perfusion lesion in future endovascular trials aiming at extending current AHA guidelines for EVT in stroke patients with low ASPECTS.

Keywords Ischemic stroke · Endovascular therapy · MCTA · Perfusion · Collaterals

Introduction

Endovascular therapy (EVT) often leads to impressive results for improving stroke outcome and mortality [1–3]. The emphasis on fast treatment decisions for acute ischemic stroke patients requires simple, quick and accurate neuroimaging of patients for detection of early ischemic changes. The EVT treatment selection, and decisions regarding the transfer of acute stroke patients, requires accurate identification of the extent of early ischemic change. Computed tomography (CT) is the most commonly used and practical technology for assessing acute stroke pa-

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tients. The American Heart Association (AHA) has made recommendations to consider acute stroke patients for EVT with a minimum Alberta Stroke Program Early CT Score (ASPECTS) of ≥6, recognizing that there is limited data for benefit of EVT with lower ASPECTS [4]; however, the subtle ischemic changes on non-contrast CT (NCCT) in acute stroke have undeniably influenced the moderate sensitivity and reliability of this investigation even among experts [5, 6].

The CT angiography (CTA) has been used to select patients for EVT in randomized control trials as it can determine the site of the intracranial occlusion and reliably identify regional leptomeningeal collateral (rLMC) circulation compromise [7, 8]. Single phase CTA has been used in the past to identify a perfusion lesion but suffers from acquisition timing insufficiencies [9, 10]. Multi-phase CTA (mCTA) has the potential for improved detection of perfusion lesion by acquiring data at multiple time points after the arrival of contrast [11]. It could offer greater generalizability in community-based primary stroke centers for accurate detection of ischemia compared to other resource intensive modalities, such as CT perfusion and magnetic resonance imaging (MRI).

In this study, it was hypothesize that perfusion lesions detected on multi-phase CTA can better predict follow-up infarction and clinical outcomes when compared to NCCT and mCTA-rLMC (pial collateral scoring), regardless of successful reperfusion, and with better reliability compared to NCCT. Therefore, we endeavored to score the ASPECTS regions for each CT modality (NCCT, mCTA lesion perfusion, mCTA-arterial, mCTA-venous and mCTA-rLMC), and to determine the accuracy of each modality by comparing them to the gold standard follow-up MRI or NCCT. Assuming that mCTA perfusion lesion can better predict early ischemic change compared to NCCT and mCTA-rLMC, it can be determined whether AHA guidelines for EVT treatment are appropriate in predicting radiological outcome [12].

Materials and Methods

Patients

Patients were included in the study if they presented within 12 h from last seen normal. Inclusion criteria for this study were as follows: 1) age >18 years; 2) complete anterior circulation occlusion on admission CTA; 3) reperfusion, assessed on conventional angiography at the end of the endovascular treatment, modified thrombolysis in cerebral infarction (mTICI; [4]) of TICI-0 (no reperfusion), or TICI-2b or 3 (good reperfusion) within 90 min of admission CT and 4) had 24-h follow-up imaging on MR diffusion weighted imaging (DWI) or NCCT. The TICI scoring was performed blind by an expert radiologist (MG) from all other clinical and imaging analyses. Clinical characteristics and demographics, medical history, and work-flow timing (last seen normal, imaging times, recanalization) were collected prospectively. Inclusion criteria was applied retrospectively. All imaging data were anonymized and reading of scans was performed blinded to all demographic and outcome data. Each imaging modality was read independently. The local ethics boards approved the study.

Image Acquisition Protocols

Baseline NCCT and multiphase head/neck CTA were acquired at admission using a standardized protocol [11]. Follow-up DWI and NCCT scans were acquired at 24 h for final infarct ASPECTS. Standard non-helical NCCT was performed on a multi-slice CT scanner (GE Healthcare, Chicago, Illinois, United States or Siemens, Munich Germany) using 120 kV, 170 mAs with 5-mm slice thickness and continuous axial slices parallel to the orbitomeatal line from the skull base to vertex. The NCCT was followed by mCTA with a helical scan technique. Acquisitions were obtained after single bolus intravenous injection of 90–120 ml non-ionic contrast media into an antecubital vein at 3–5 ml/s. Imaging was auto-triggered by the appearance of contrast medium in the ascending aorta. Standard coverage included area from the arch to the vertex. Source images were reconstructed at 1.25, 2.5, or 4.0 mm thickness in axial planes at half-thickness intervals. These were used to create time-resolved cerebral angiograms of the cerebral vasculature.

Follow-up DWI was performed using a spin-echo echo planar imaging (SE-EPI) sequence. Acquisition details were: repetition time (TR) = 9000 ms; echo time (TE) = 94.3 ms; field of view (FOV) = 250–350 mm; number of signals averaged (NSA) = 1; acquisition matrix = 144 × 144; and slice thickness = 5 mm with no gap with diffusion sensitizing gradients (b = 1000 s/mm^2) applied in 15 directions, and without diffusion weighting (b = 0 s/mm^2).

Image Analysis

The NCCT and mCTA-venous were assessed by two readers, one expert (PB) and one neuroradiology trainee (AF) for early ischemic changes using ASPECTS. Scores were graded as good (7–10), moderate (4–6) and poor (0–3). The definition of early ischemic changes on NCCT has previously been defined [4, 13].

Each mCTA phase (the 3 time points of the mCTA) was assessed for the time of contrast arrival (arterial, equilibrium, or venous acquisition) described by Rodriguez-Luna et al. [14]. Briefly, for each mCTA phase the ratio of the

Hounsfield Unit values was measured in the proximal middle cerebral artery (MCA) on the normal side and the confluence of sinuses [14]. Perfusion lesions were assessed by measuring hypoattenuation on the arterial and venous acquisitions of the mCTA phase (mCTA-arterial, mCTA-venous). Severe ischemia was indicated by hypoattenuation that persisted into the venous acquisition.

The CTA regional leptomeningeal score collateral (rLMC) score was used to grade the collateral filling by an experienced experienced neurologist (JWE) blinded to clinical and radiological outcomes [15]. The rLMC scale was initially described on single phase CTA only. The rLMC score is a 0–20 point scale where lower numbers represent poorer collateral filling. The scorer rated opacification in pial and lenticulostriate arteries in the 6 cortical ASPECTS regions (M1–M6) plus the anterior cerebral artery, Sylvian fissure and basal ganglia regions [15]. A score of 0–2 for all regions was recorded (0, no collateral filling; 1, less filling; 2, equal or more prominent compared with matching region in contralateral hemisphere), except for the Sylvian fissure which was scored either 0, 2 or 4, respectively. Scores were graded as good (17–20), moderate (11–16) and poor (0–10) [15].

The infarction gold standard was the 24-h follow-up ASPECTS assessed on MRI or on NCCT when MRI was not possible to acquire due to incompatibility or poor patient cooperation by a stroke neurologist (PAB). Any lesion on the DWI scan was counted as a positive region.

Follow-Up Outcomes

The National Institutes of Health Stroke Scale (NIHSS) was scored at time baseline and 24 h follow up (range; 0–42, with higher scores indicating greater stroke severity). The modified Rankin scale (mRS) was scored at 90-day follow-up (range: 0–2 independent, 3–5 dependent to 6 death).

Statistical Analysis

The positive likelihood ratios (LR+) and negative likelihood ratios (LR–) were calculated for the prognostic ability of NCCT, mCTA-rLMC, mCTA-arterial, mCTA-venous against follow-up CT/MRI for each ASPECTS region stratified by reperfusion status using the last run of the DSA post-EVT (TICI 0 vs. TICI 2b or 3). Similarly, the positive predictive values (PPV) and negative predictive values (NPV) were calculated and stratified by reperfusion (TICI) and onset to CT time (<3 h vs. >3 h). The LRs provide a probability of whether a positive or negative test can identify early ischemia. In the situation of using CT for detecting stroke, the LR is the ratio of two probabilities: (i) probability that a given test result may be expected in an ASPECTS region with early ischemia and (ii) probability that the same result will occur in an ASPECTS region without ischemia. It is generally accepted that (LR+) > 10 aids to rule in and (LR–) < 0.2 to rule out. If (LR+) is <10 or (LR–) > 0.1 the test may be considered to have moderate or no value. For this analysis, the rLMC score was binarized, similar to the ASPECTS output, as follows: a score of 0 or 1 was classified as an ischemic positive region, and a score of 2 was classified as an ischemic negative region. The rLMC score for basal ganglia was applied to the ASPECTS caudate region and the Sylvian fissure score was applied to the ASPECTS insula region. There is no score for mCTA-rLMC in the internal capsule or lentiform regions. To determine EVT treatment decisions based on current AHA guidelines, we dichotomized the predictor imaging variables: 1) consider treating with EVT: NCCT and mCTA-venous ASPECT ≥6, mCTA-rLMC ≥11, and 2) consider not treating with EVT: NCCT and mCTA-venous <6 mCTA-rLMC <11 [12]. The PPV, NPV, LR+ and LR– were determined.

Interrater agreement between an experienced stroke specialist (PAB) and a radiology second year resident (AF) was measured for total ASPECTS on all modalities in one third of the cases ($N = 29$). Cohen's kappa (κ) coefficients were calculated for NCCT, mCTA-arterial and mCTA-venous. Interpretation of κ values followed the proposed standards of Landis and Koch: 0–0.2 (slight), 0.21–0.40 (fair), 0.41–0.60 (moderate), 0.61–0.80 (substantial) and 0.81–1.00 (almost perfect) [16].

The machine learning models used to predict the two outcome measurements (24-h NIHSS and 90-day mRS) based on the imaging data (total ASPECTS for NCCT, mCTA-rLMC, mCTA-arterial, mCTA-venous, and follow-up) and other features (sex, age, TICI status, onset to CT time, and baseline NIHSS and mRS) consists of the RRELIEFF feature ranking and selection method and a support vector regression (SVR) model [17, 18]. Non-informative and redundant features potentially downgrade the accuracy of any machine learning model using these features for training. This problem can be overcome by applying a feature ranking and selection approach to the attributes prior to the actual training and testing of a classifier. In this work, the RRELIEFF feature selection algorithm was used for this purpose due its ability to detect conditional dependencies between features but also to estimate the quality of the features in this regression problem [19]. More precisely, the RRELIEFF feature selection algorithm assigns a weight to each attribute, whereas higher feature weights indicate more informative features. After feature ranking using the RRELIEFF feature ranking method, a linear SVR model, which uses the same theoretical basis as a linear kernel support vector machine for classification, was trained based on the ranked attributes. A leave-one-out cross validation approach was used for evaluation of the SVR model and to identify the optimal subset of features individually for the

Table 1 Positive likelihood ratios (LR+) and negative likelihood ratios (LR–) of ASPECTS scoring on NCCT, mCTA-arterial, mCTA-venous and mCTA-rLMC in TICI 0 patients (A) compared to CT/MRI infarction at 24 h, TICI-2b/3 patients (B)

		Caudate	Lentiform	Insula	Internal Capsule	M1	M2	M3	M4	M5	M6
Patients (A)											
NCCT	LR+	9.23	5.82	>10	7.14	5.50	9.54	3.30	>10	>10	>10
	LR–	0.09	0.12	0.20	0.47	0.55	0.05	0.77	0.48	0.19	0.00
mCTA-arterial	LR+	>10	>10	>10	>10	>10	9.09	>10	>10	>10	3.82
	LR–	0.16	0.10	0.08	0.15	0.40	0.10	0.40	0.19	0.10	0.34
mCTA-venous	LR+	7.69	9.58	6.16	8.93	>10	6.36	>10	>10	5.24	7.34
	LR–	0.26	0.29	0.14	0.31	0.52	0.40	0.42	0.29	0.53	0.30
mCTA-rLMC	LR+	>10	–	2.63	–	2.04	2.75	4.07	4.20	4.76	4.24
	LR–	0.19	–	0.35	–	0.61	0.56	0.51	0.47	0.58	0.43
Patients (B)											
NCCT	LR+	>10	4.68	3.00	0.00	7.33	2.54	>10	2.56	8.75	3.84
	LR–	0.54	0.35	0.75	1.02	0.85	0.56	0.78	0.92	0.61	0.85
mCTA-arterial	LR+	8.69	3.06	3.00	>10	2.67	2.08	>10	2.60	1.77	5.13
	LR–	0.08	0.12	0.00	0.00	0.44	0.14	0.31	0.31	0.69	0.29
mCTA-venous	LR+	>10	>10	>10	>10	>10	8.07	>10	9.21	>10	>10
	LR–	0.12	0.11	0.07	0.00	0.18	0.11	0.44	0.16	0.32	0.31
mCTA-rLMC	LR+	7.38	–	1.02	–	2.00	1.10	2.24	1.59	1.72	3.25
	LR–	0.41	–	0.97	–	0.67	0.93	0.55	0.76	0.69	0.51

NCCT non-contrast computed tomography, *mCTA* multi-phase computed tomography angiography, *rLMC* regional leptomeningeal score, *LR* likelihood ratio, *M1* anterior middle cerebral artery cortex, *M2* middle cerebral artery cortex lateral to the insular ribbon, *M3* posterior middle cerebral artery cortex, *M4* anterior cortex immediately rostral to M1, *M5* lateral cortex immediately rostral to M3, *M6* posterior cortex immediately rostral to M3

Table 2 Positive predictive values (PPV), negative predictive value (NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR–) of mCTA-rLMC, NCCT and mCTA-venous to identify follow-up imaging ASPECTS ≥6 and <6. Note mCTA-rLMC scores were dichotomized ≥ 11 i.e. intermediate, good collaterals ($N = 89$)

	mCTA-rLMC	NCCT	mCTA-venous
PPV	0.93	0.89	1.00
NPV	0.55	0.64	0.82
LR+	8.00	6.67	>10
LR–	0.83	0.56	0.29

NCCT non-contrast computed tomography, *mCTA* multi-phase computed tomography angiography, *rLMC* regional leptomeningeal score, *PPV* positive predictive value, *NPV* negative predictive value, *LR* likelihood ratio

two regression problems [19]. More precisely, the accuracy of the regression model was determined in terms of comparing the predicted outcome to the real outcome (90-day mRS or 24-h NIHSS) by calculating the root mean square error as an indicator of regression performance. In doing so, the optimal number of highest ranked features was systematically optimized for each outcome variable by iteratively removing the lowest ranked feature from the training and testing set. The regression results obtained using the attribute subset with the lowest root mean square error were used as the final regression result and for a subsequent qualitative analysis of the selected features.

Results

A total of 89 patients (46 male and 43 female) with a mean age of 68 ± 15 years were included. The mean time from stroke onset to CT was 3 h 10 min ±2 h 55 min. Confirmed on the last run of DSA post-EVT, 33 patients had TICI-0 reperfusion, and 56 had TICI 2b or 3 reperfusion. Out of 89 participants 55 had hypertension, 36/89 had atrial fibrillation, 9/89 had type 2 diabetes and 61/89 were smokers. Of the participants 32 had follow-up MRI and 57 participants had follow-up CT at 24 h. Median (interquartile range IQR) for baseline NIHSS was 17 (12) for TICI 0, and 17 (8) for TICI 2b or 3 sub-groups. Median (IQR) NIHSS at 24 h follow up was 15.5 (15.5) for TICI 0 and 6 (10) for TICI 2b or 3 subgroups. Median (IQR) baseline mRS was 0 (0) for both TICI 0 and TICI 2b or 3 groups. Median (IQR) mRS at 90 day follow-up was 3 (4 (2) TICI 0 and 2 (2) TICI 2b or 3). Median (IQR) ASPECTS for TICI 0 patients at baseline were 6 (4.5) for NCCT, 7 (6.5) for mCTA-arterial, and 8 (5.5) for mCTA-venous. Median (IQR) ASPECTS for TICI 2b or 3 patients at baseline were 8 (3) for NCCT, 5 (4) for mCTA-arterial, 6 (4) for mCTA-venous. Median (IQR) baseline mCTA-rLMC scores were 16 (6) for both TICI 0 and TICI 2b or 3 groups. Median (IQR) 24-hour follow-up MRI/NCCT were 5 for both TICI 0 (5.5) and TICI 2b or 3 groups (4).

Table 3 Inter-observer reliability (weighted Kappa, κ) of ASPECTS scoring on NCCT, mCTA-arterial and mCTA-venous ($N = 29$) between a stroke expert and radiology trainee

	M1	M2	M3	M4	M5	M6	Caudate	Lentiform	Insula	Internal capsule
NCCT	0.61	0.42	0.52	0.63	0.78	0.79	0.93	0.85	0.93	0.42
mCTA-arterial	0.87	0.85	1.00	1.00	0.90	0.89	0.93	0.93	0.86	0.78
mCTA-venous	1.00	1.00	1.00	1.00	1.00	1.00	0.86	0.92	0.91	0.47

NCCT non-contrast computed tomography, *mCTA* multi-phase computed tomography angiography, *rLMC* regional leptomeningeal score, *M1* anterior middle cerebral artery cortex, *M2* middle cerebral artery cortex lateral to the insular ribbon, *M3* posterior middle cerebral artery cortex, *M4* anterior cortex immediately rostal to M1, *M5* lateral cortex immediately rostal to M3, *M6* posterior cortex immediately rostal to M3

Table 4 Machine learning models used to predict the 24-h NIHSS based on the imaging data (total ASPECTS for NCCT, mCTA-rLMC, mCTA-arterial, mCTA-venous, and follow-up) and other features (sex, age, onset to CT time, TICI status and baseline NIHSS and mRS) using the RRELIEFF feature ranking and selection method and a support vector regression (SVR) model ($N = 89$)

	Outcome: 24-h NIHSS Correlation coefficient of model: 0.73 Root mean squared error: 5.55									
Selected variables	TICI	Baseline NIHSS	Baseline mRS	Onset to CT	Age	mCTA-venous	mCTA-arterial	NCCT	mCTA-rLMC	Gender
Relative importance	0.038	0.034	0.032	0.006	0.003	0.001	–0.001	–0.002	–0.004	–0.02
Rank	1	2	3	4	5	6	7	8	9	10

TICI modified Thrombolysis in Cerebral Infarction, *NIHSS* National Institue of Health Stroke Scale, *mRS* Modified Rankin Scale, *CT* computed tomopgrahy, *NCCT* non-contrast computed tomography, *mCTA* multi-phase computed tomography angiography, *rLMC* regional leptomeningeal score

Table 5 Machine learning models used to predict the 90-day mRS based on the imaging data (total ASPECTS for NCCT, mCTA-rLMC, mCTA-arterial, mCTA-venous, and FU) and other features (sex, age, onset to CT time, TICI status and baseline NIHSS and mRS) using the RRELIEFF feature ranking and selection method and a support vector regression (SVR) model ($N = 89$)

	Outcome: 90-day mRS Correlation coefficient of model: 0.55 Root mean squared error: 1.64			
Selected variables	mRS baseline	TICI	Age	mCTA-venous
Relative importance	0.037	0.033	0.021	0.009
Rank	1	2	3	4

TICI modified Thrombolysis in Cerebral Infarction, *mRS* Modified Rankin Scale, *mCTA* multi-phase computed tomography angiography

The 1st mCTA phase most commonly corresponded to the peak arterial ($N = 33$) or equilibrium ($N = 38$), with a minority of images showing early arterial flow ($N = 10$) and peak venous ($N = 7$) time of contrast arrival. The 2nd mCTA phase had fewer cases of peak arterial ($N = 2$), equilibrium ($N = 5$), and increasingly corresponded to peak and late venous ($N = 81$) contrast arrival acquisitions [14].

Table 1 shows the LR+ and LR– on baseline NCCT, mCTA-rLMC, mCTA-arterial and mCTA-venous stratified by TICI 0 (A), and TICI 2b or 3 (B) compared to 24-h MRI or CT ASPECTS. Furthermore, Table 1S shows the PPV, NPV, LR+ and LR– on baseline imaging parameters stratified by TICI compared to 24-h MRI or CT ASPECTS within 3 h of onset to CT and >3 h of onset to CT. In Table 1(A), mCTA arterial has an excellent performance in all ASPECTS regions (LR+ > 10 and LR– < 0.4, range 0.8–0.4), excluding the M6 area for patients unsuccessful reperfusion. The NCCT and mCTA venous phase had a performance in the moderate to excellent range for each ASPECTS region. In Table 1(B), the performance for LR+ in mCTA-arterial is consistently less than for TICI 0 (Table 1A) but the performance for mCTA-venous is in the excellent range in all ASPECTS regions. In both Tables S (A and B), the mCTA-rLMC score revealed inferior performance compared to multi-phase CTA and NCCT, being in the fair to moderate range for comparative ASPECTS regions.

Table 2 shows the PPV, NPV and LR values for the dichotomized imaging predictor variables and follow-up ASPECTS, according to AHA guidelines [12]. When ASPECTS is dichotomized by ≥6 and <6 similar accuracy trends as in Table 1 are reported; improved performance is shown for mCTA-venous (very good to excellent) when

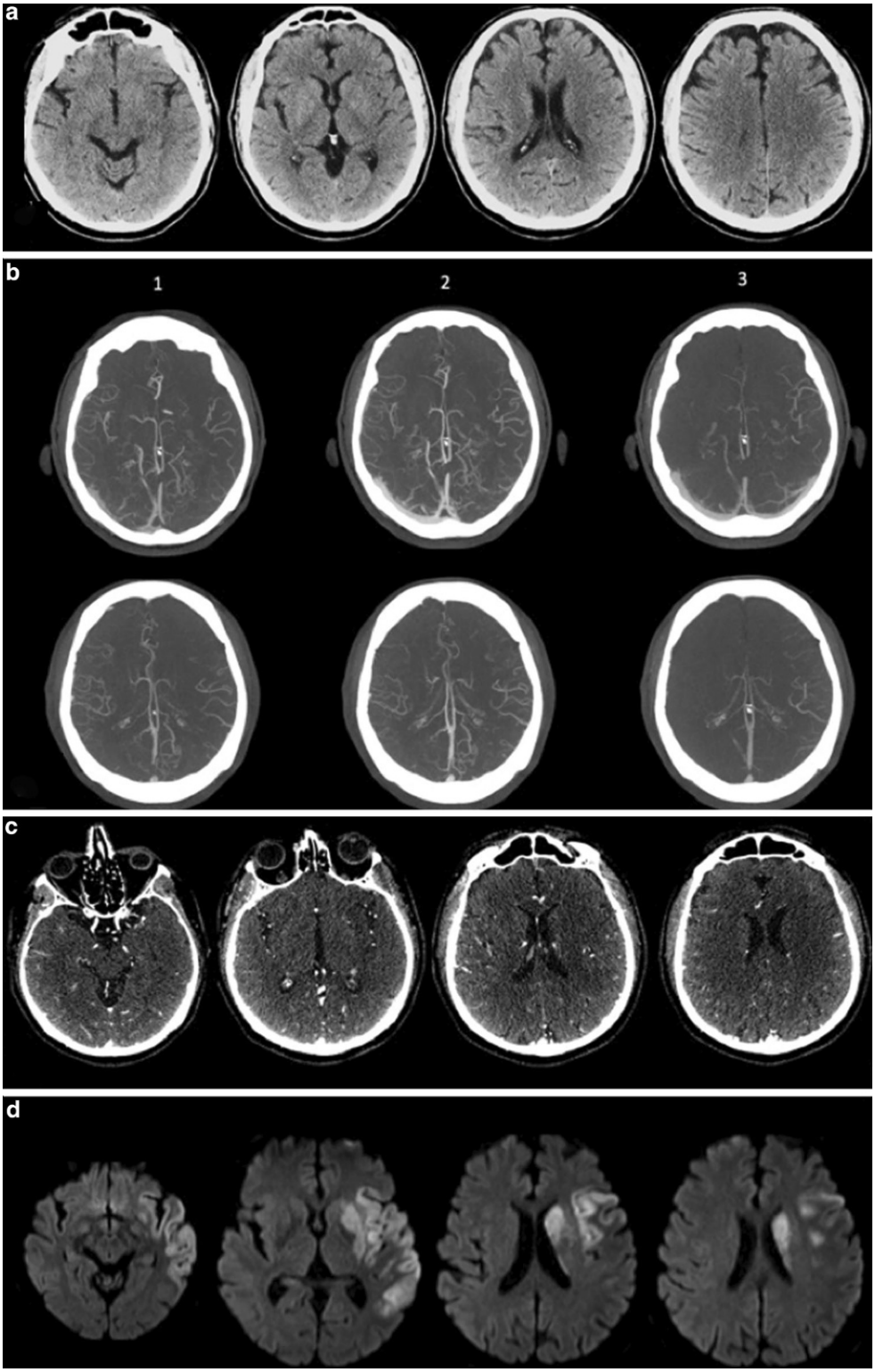

Fig. 1 A 68-year-old male with left anterior middle cerebral artery cortex occlusion which was completely reperfused (TICI-3 score) at 1 h 9 min after admission CT. The patient had a baseline mRS of 0 and a 90-day mRS of 1. **a** NCCT-ASPECTS = 3. **b** The three numbered phases of mCTA-rLMC = 18. **c** mCTA-venous = 5. **d** 24-h MRI ASPECTS = 5

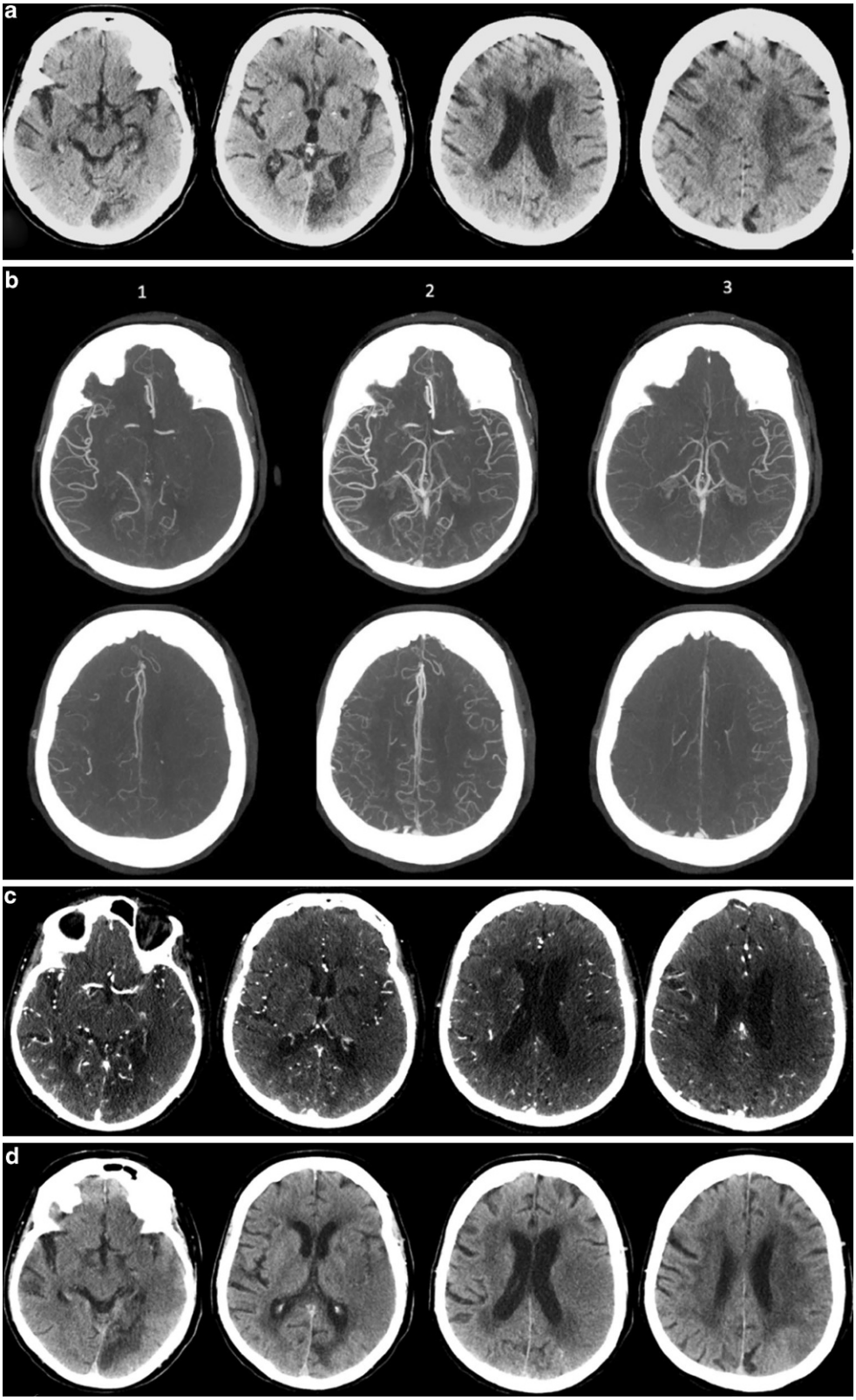

Fig. 2 A 91-year-old female patient with left distal M1 occlusion which was reperfused (TICI-2b) at 45 min after admission CT. Patient had a baseline mRS of 0 and a 90-day mRS of 6 (deceased). **a** NCCT-ASPECTS = 10. **b** The three numbered phases of mCTA-rLMC = 14. **c** mCTA-venous = 3. **d** 24-h CT ASPECTS = 3

compared to NCCT (fair to moderate) and mCTA-rLMC (fair to moderate).

In Table 3, inter-observer reliability (Cohen's Kappa) for ASPECTS on NCCT, mCTA-arterial and mCTA-venous within TICI strata demonstrated that mCTA-venous had superior agreement than NCCT in most ASPECTS regions. The inter-observer reliability of mCTA for both arterial and venous phase is consistently excellent apart from the internal capsule, whereas interobserver reliability for NCCT was disparate with ranges of agreement from fair to excellent.

Tables 4 and 5 show the machine learning results for predictive models to predict 90-day mRS and 24-h NIHSS. Machine learning models are used to predict 24-h NIHSS (Table 4) and, and 90-day mRS (Table 5). In Table 4 ranked imaging data, onset to CT reperfusion status, stoke severity and patient demographics using the RRELIEFF feature ranking and selection method for predicting NIHSS at 24 h. Each demonstrates the importance of reperfusion status, baseline stroke severity and mRS, increasing age and to a lesser degree mCTA-venous ASPECTS for predicting early and 3-month outcome. The mCTA-venous was the highest ranked imaging predictor for both functional outcomes.

Figs. 1 and 2 demonstrate the added benefit of assessing perfusion lesions on mCTA in the acute stroke imaging workflow. Fig. 1 shows the neuroimaging of a patient with a 'good' mCTA-rLMC score of 18 while simultaneously demonstrating a 'moderate' mCTA-venous (ASPECTS-5) score. Although this patient had successful reperfusion at 1 h 9 min following admission (TICI 3), the patient presented with a 'moderate' follow-up MRI (ASPECTS-5). The patient example in Fig. 2 shows a 'good' NCCT score (ASPECTS-10), although radiological interpretation was confounded by movement, white matter disease and an old stroke lesion. This patient simultaneously presented with a poor mCTA-venous (ASPECTS-3) and following successful reperfusion (TICI-2b) at 45 min from admission, had a poor follow-up CT (ASPECTS-3).

Discussion

The results demonstrate that perfusion lesions identified as hypoattenuation on admission mCTA evaluated by ASPECTS had better diagnostic accuracy for follow-up infarction regionally than NCCT-ASPECTS and mCTA-rLMC (pial artery filling). Hypoattenuation persisting into the venous phase on mCTA was confirmed to indicate severe ischemic tissue, which is corroborated by the high LR+ with follow-up infarction regardless of TICI score. The improved LRs for mCTA-arterial within the TICI 0 group may help to identify the ischemic tissue "at risk" when EVT is unsuccessful. With respect to AHA guidelines for EVT decision making, mCTA-venous had the best PPV, NPV, LR+, LR– values when compared to NCCT and rLMCs. Furthermore, this metric was also the highest ranked imaging predictor within the machine learning model outputs for clinical outcome. Interestingly, mCTA-rLMC and NCCT were even deselected from the features used by the 90-day mRS prediction model.

The interobserver reliability of mCTA-venous score was 'almost perfect' ($\kappa = 0.81–1.00$) in all regions except the internal capsule when assessed by a stroke expert and radiology trainee [9]. The mCTA-venous was also scored higher than NCCT in all regions except for the caudate and lentiform. Moreover, the data are consistent with other studies that have shown that the inter-observer agreement improves with contrast-based modalities such as CTA source images and CTP-CBV [9, 10].

This study has important implications for clinical assessment and stroke treatment decision making, imaging work-flow, further study development, and trial design. It demonstrated that the multi-modal CT imaging can characterize different tissue states without additional imaging or post-processing techniques as needed for CT perfusion, which will be especially useful for patients with unknown stroke onset or late arrivals [20, 21]. The purpose of the imaging work flow is to exclude intracranial hemorrhage, demonstrate a target vessel, assess collateral status, assess the extent at risk tissue (hypoattenuation on mCTA-arterial) and ischemic core (mCTA-venous). The imaging parameters measure different pathologies within the ischemic lesion: NCCT: water uptake due to cytotoxic edema, mCTA-perfusion: volume of blood within perfused vascular tissue beds, and mCTA-rLMC: volume of blood within pial arteries. Although related, these pathological metrics can be evident exclusively of each other throughout the duration of ischemia which is exemplified in Figs. 1 and 2.

A limitation of this study is that the groups were highly selected based on TICI reperfusion status with the prime purpose of determining whether the mCTA imaging features were modified by TICI reperfusion. Thus, results may only apply to TICI 0 and TICI 2b or 3 and may not be relevant if reperfusion is delayed beyond 90 min or is partial (e.g. TICI 1–2a). We also recognize that CT is less sensitive for follow-up compared to MRI, but there would be negligible negative implications to the results as an expert neuroradiologist scored the ASPECTS and due to the relatively large sample size of the study.

In summary, this demonstrates the advantage of assessing the delayed phases of mCTA for prediction of tissue outcome and EVT decision-making. The routine use of mCTA would facilitate the selection of stroke patients for EVT beyond current guidelines (extensive early ischemia, i.e. ASPECTS ≤ 6), as this assessment provides further hemodynamic information than NCCT and mCTA-rLMC. Multi-

phase CTA has the advantage of whole brain coverage (as opposed to perfusion CT), is readily and quickly available following scan completion, and has no need for expensive automated software. The current methodology for assessing mCTA perfusion lesion source images is easy to apply and reliable for accurately detecting severe ischemia in each ASPECTS region.

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Compliance with ethical guidelines

Conflict of interest M. Goyal has a patent and licensing agreement with GE Healthcare re: systems of stroke diagnosis. In addition, he has a consulting agreement with Medtronic, Stryker, Microvention, Cenernovus. Medtronic has provided an unrestricted research grant to the University of Calgary for the HERMES collaboration. M. Goyal is the Chair of this collaboration. M. Reid, A.O. Famuyide, N.D. Forkert, A. Sahand Talai, J.W. Evans, A. Sitaram, M. Hafeez, M. Najm, B.K. Menon, A. Demchuk, R. Gupta Sah, C.D. d'Esterre and P. Barber declare that they have no competing interests.

Ethical standards The local ethics boards approved the study. All participants gave informed consent prior to their inclusion in this study. All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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