Detection of ischemic changes on baseline multimodal computed tomography: expert reading vs. Brainomix and RAPID software

Petra Cimflova, MD,*,†,# Ondrej Volny, MD, PhD,†,‡,¶,# Prof. Robert Mikulik, MD, PhD,†,§ Bohdan Tyshchenko, Ing,† Silvie Belaskova, PhD,† Jan Vinklarek, MD,¶ Vladimir Cervenak, MD,* Tomas Krivka, MD,* Assoc. Prof. Jiri Vanicek, MD, PhD,* and Prof. Antonin Krajina, MD, CSc||

Purpose: The aim of the study was to compare the assessment of ischemic changes by expert reading and available automated software for non-contrast CT (NCCT) and CT perfusion on baseline multimodal imaging and demonstrate the accuracy for the final infarct prediction. *Methods:* Early ischemic changes were measured by ASPECTS on the baseline neuroimaging of consecutive patients with anterior circulation ischemic stroke. The presence of early ischemic changes was assessed a) on NCCT by two experienced raters, b) on NCCT by e-ASPECTS, and c) visually on derived CT perfusion maps (CBF<30%, Tmax>10s). Accuracy was calculated by comparing presence of final ischemic changes on 24-hour follow-up for each ASPECTS region and expressed as sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The subanalysis for patients with successful recanalization was conducted. *Results:* Of 263 patients, 81 fulfilled inclusion criteria. Median baseline ASPECTS was 9 for all tested modalities. Accuracy was 0.76 for e-ASPECTS, 0.79 for consensus, 0.82 for CBF<30%, 0.80 for Tmax>10s. e-ASPECTS, consensus, CBF<30%, and Tmax>10s had sensitivity 0.41, 0.46, 0.49, 0.57, respectively; specificity 0.91, 0.93, 0.95, 0.91, respectively; PPV 0.66, 0.75, 0.82, 0.73, respectively; NPV 0.78, 0.80, 0.82, 0.83, respectively. Results did not differ in patients with and without successful recanalization. *Conclusion:* This study demonstrated high accuracy for the assessment of ischemic changes by different CT modalities with the best accuracy for CBF<30% and Tmax>10s. The use of automated software has a potential to improve the detection of ischemic changes.

Keywords: Stroke imaging—Early ischemic changes—ASPECTS—e-ASPECTS—CT perfusion—RAPID

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From the *Department of Medical Imaging, St. Annes University Hospital and Faculty of Medicine, Masaryk University, Brno, Czech Republic; †International Clinical Research Centre, Stroke Research Program, St. Annes University Hospital, Brno, Czech Republic; ‡Departments of Clinical Neurosciences, Calgary Stroke Program, Cumming School of Medicine, University of Calgary, Calgary, Canada; ¶Department of Neurology, Faculty Hospital Ostrava, Ostrava, Czech Republic; §Department of Neurology, St. Annes University Hospital and Faculty of Medicine, Masaryk University, Brno, Czech Republic; and ||Department of Radiology, Charles University, Faculty of Medicine and University Hospital, Hradec Kralove, Czech Republic.

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Corresponding author. E-mails: petra.cimflova@fnusa.cz, c.petra@seznam.cz, 214565@mail.muni.cz, mikulik@hotmail.com, bohdan.tyshchenko@fnusa.cz, silvie.belaskova@fnusa.cz, jan.vinklarek@fnusa.cz, vladimir.cervenak@fnusa.cz, tomas.krivka@fnusa.cz, vanicek@fnusa.cz, antonin.krajina@fnhk.cz.

#P.C. and O.V. contributed equally.

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Introduction

The Alberta Stroke Program Early CT Score (ASPECTS) quantifies the extent of early ischemic changes in the middle cerebral artery territory on baseline NCCT scans (1). ASPECTS has been proven to be a significant predictor of clinical outcome in patients with acute ischemic stroke (AIS) in the anterior circulation (2,3). It is also used to select patients for endovascular therapy (4). It represents a validated grading system (3) but the inter-rater variability has been questioned. Even experienced clinicians show only a 39% agreement in the identification of ischemic changes on NCCT involving more than one-third of the MCA territory (5). Hence, there is a trend to develop reliable software tools to help stroke physicians in acute scan reading and subsequent decision making (6,7).

The e-ASPECTS software (Brainomix, Oxford, UK) is a fully-automated ASPECT scoring tool for non-contrast CT (NCCT), which has previously demonstrated a scoring on expert level (8–10). The advantage of e-ASPECTS is its potential to eliminate the inter-rater variability (8,10). CT perfusion (CTP) has a potential to discriminate between irreversibly damaged tissue, infarct core, and tissue at risk of infarction, penumbra (11,12). It has been demonstrated that visual applying of ASPECTS into CTP parametric maps has a strong correlation with good clinical outcome (defined as modified Rankin scale/mRS 0-2), with a prognostic value greater than NCCT ASPECTS (13–16). All previous studies have shown the highest correlation of good clinical outcome with cerebral blood volume (CBV) ASPECTS (13–16).

The most accurate prediction of irreversibly ischemic changes by automatic software post-processing with RAPID was shown for relative cerebral blood flow (CBF) less than 30% in comparison to the mean CBF of normally perfused brain parenchyma (17,18). This threshold was used in the randomized trials with patient selection based on perfusion mismatch (SWIFT-PRIME, EXTEND-AI, DAWN, DEFUSE III) to define ischemic core (19–22).

`Severe hypoperfusion has been associated with irreversible necrosis of the ischemic lesion even after reperfusion (23). In the DEFUSE and EPITHET meta-analysis, large regions of severe delay (>10 s) have been associated with poor outcome after reperfusion (24). This finding suggests that higher Tmax may identify tissue with more severely reduced cerebral blood flow, which may have a substantial impact on the evolution of the acute ischemic lesion (23).

The main aim of our study was to evaluate how accurate the different CT modalities with and without software processing (consensus reading, e-ASPECTS, CBF<30%, Tmax>10s) assess early ischemic changes at baseline and what is their accuracy for final ischemia prediction.

Methods

Patient selection

Ethical approval was obtained from the local Institutional Review Boards (the Boards waived the need for patient consent). All patients with symptoms of AIS and no history of contrast allergy routinely underwent NCCT, multiphase CTA (mCTA) from the aortic arch to the vertex (25) and CTP in our institution. If the diagnosis of AIS was confirmed by this neuroimaging protocol, NCCT was repeated within 24-32 hours to determine the extent and location of ischemia and diagnose potential complications such as hemorrhagic transformation. Radiological data of consecutive patients from March 2017 to September 2017 presenting with symptoms of AIS in the anterior circulation within 6 hours of last seen normal (symptom onset) were retrospectively reviewed. This time period was chosen in order to compare the reliability of the detection of early ischemic changes while the software for automatic detection of early ischemic changes, Brainomix e-ASPECTS, was implemented into our institutional system.

Inclusion criteria were: 1) availability of baseline NCCT with automatic software analysis, baseline CTP and follow-up 24-hour NCCT. Exclusion criteria were: 1) evidence of any intracranial hemorrhage or non-ischemic lesion, 2) negative findings on baseline diagnostic imaging and no ischemic changes on follow-up CT.

We defined patients with successful reperfusion/recanalization angiografically as TICI 2b-3 in patients treated with mechanical thrombectomy (MT) or as >40% decrease in the 24-hour NIHSS score in patients treated with intravenous thrombolysis (IVT) only (26). Subanalysis of this subgroup was conducted.

Imaging Protocol

The imaging protocol set up in our stroke center combines NCCT, mCTA and CTP and both software programs were available during the study period for automatic analysis (Brainomix for NCCT and RAPID for CTP).

NCCT was acquired on a multi-detector scanner (120kV, 328 mAs (419mAs/slice), Brilliance iCT 256; Philips Healthcare, Cleveland, OH) with a section thickness of 0.9mm and an image reconstruction of 3mm.

For the CTP protocol, 40 ml of contrast agent (Iomeron 300; Mallinckrodt Pharmaceuticals; Dublin, Ireland) was power injected at 5 ml/s followed by a saline chase of 50 ml at 5 ml/s. Sections of 8cm thickness were acquired at 10 mm slice thickness. Scanning began after a delay of 5s from contrast injection in every 1.8s for 75s. After 24 hours, a NCCT was acquired for final infarct delineation in all patients.

Image Processing

NCCT scans were automatically analysed by the e-ASPECTS software (version 6.0, Brainomix, Oxford, UK). The e-ASPECTS software is a standardized, fully-automated, CE mark-approved ASPECTS scoring tool for NCCT, which has previously demonstrated scoring on an expert level (8–10). The e-ASPECTS software is based on a combination of advanced image-processing and machine-learning algorithms. Its scoring module operates on the standardized 3D images, classifying signs of ischemic damage and assigning them to ASPECTS regions (9).

CT perfusion studies were post-processed using the RAPID software (iSchemaView, Menlo Park, CA, USA) to generate perfusion maps of cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), and time to the maximum of the residue function (Tmax). The RAPID software also automatically segmented and calculated volumes of the ischemic core (relative regional CBF<30%) and the critically hypoperfused tissue (Tmax>6s) (27).

Image review

Early ischemic changes were assessed on baseline NCCT by two experienced readers (a consultant neuroradiologist, PC, and a stroke neurologist, OV)* using the ASPECTS score defined by Barber et al. (3) previously, blind to the results of the e-ASPECTS analysis, as well as to other baseline imaging modalities and follow-up NCCT.

Automatic segmentations of ASPECTS regions on e-ASPECTS derived scans were visually checked to avoid any severe inaccuracy. Otherwise, the given e-ASPECTS score were not modified and the original e-ASPECTS was noted.

CTP maps were superposed on the CT-ASPECTS template and visually assessed by an experienced reader (PC). Ischemic changes on CTP maps were evaluated using the ASPECTS as follows: 1) on the CBF map as the area with CBF<30 % when compared to the contralateral hemisphere and 2) on the Tmax map as the area with Tmax>10s delay in the maximum contrast filling within the region of interest when compared to the contralateral hemisphere (**Fig. 1**). The reader was blind to findings on NCCT, perfusion baseline scans available in the summary of RAPID analysis were visually controlled to exclude any false positive CTP findings (e.g. chronic infarction).

The final infarction was assessed on a 24-hour follow-up NCCT with consensus of the two readers (PC, OV), during a different session, one month after the previous assessment of the early ischemic changes on baseline NCCT.

To support the reliability of the consensus reading, two radiologists (VC, TK) evaluated ASPECTS of 40 random admission NCCT and 40 follow-up scans (of different patients). The inter-rater agreement with the consensus was counted using weighted kappa (κ_w) and Krippendorf's alfa (α) (28). The moderate agreement between raters was demonstrated for baseline NCCT (κ_w=0.53-0.54; α=0.72) and good to excellent agreement for follow-up imaging (κ_w=0.78-0.88; α=0.94)**.

*PC and OV have 6-year experience with stroke imaging evaluation, 5-year experience in comprehensive stroke centre and both were trained in ASPECTS reading as members of the Calgary Stroke Program.

** Detailed data are available upon request.

Statistical Analysis

Clinical and imaging baseline characteristics were summarized using descriptive statistics.

The accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for particular ASPECTS regions (81 patients x 10 ASPECTS regions) at baseline imaging (e-ASPECTS, expert consensus reading, CBF<30%, Tmax>10s) in comparison with ASPECTS regions at the follow-up CT. The Bland-Altman plots were calculated to compare the differences between each baseline imaging method and follow-up ASPECTS.

The sensitivity analysis of pooled data for the group with determined successful reperfusion/recanalization was conducted; clinical and imaging baseline characteristics were summarized using descriptive statistics and compared to the group with non-determined recanalization/reperfusion using Wilcoxon rank sum test; the accuracy, sensitivity, specificity, PPV, NPV as well as Bland-Altman plots were calculated. To compare the two subgroups, we calculated residuals between follow-up ASPECTS and each baseline ASPECT score method (e-ASPECTS, expert consensus reading, CBF<30%, Tmax>10) and analysed these residuals using Wilcoxon rank sum test.

This study provides hierarchically structured data with 3 levels: subject ID, imaging modalities (e-ASPECTS, expert consensus reading, CBF<30%, Tmax>10s, and follow-up ASPECTS); and ASPECTS regions (M1-M6, Insula, Lentiform, Capsula, Caudate). We regarded regions as a fixed effect. The generalized estimating equation accommodating clustering at the subject ID level was used (PROC GENMOD; SAS Institute Inc, Cary, NC). LS-means estimates of fixed effect "region" computed from generalized mixed model were graphically illustrated.

All analyses were performed in Stata 16.1 (StataCorp LLC, College Station, TX, USA) and SAS 9.3 (SAS Institute, Cary, NC, USA).

Results

Baseline scans of 263 patients were retrospectively reviewed; 16 patients with intracranial hemorrhage and 166 patients with either negative findings on all imaging modalities or missing follow-up imaging were excluded.

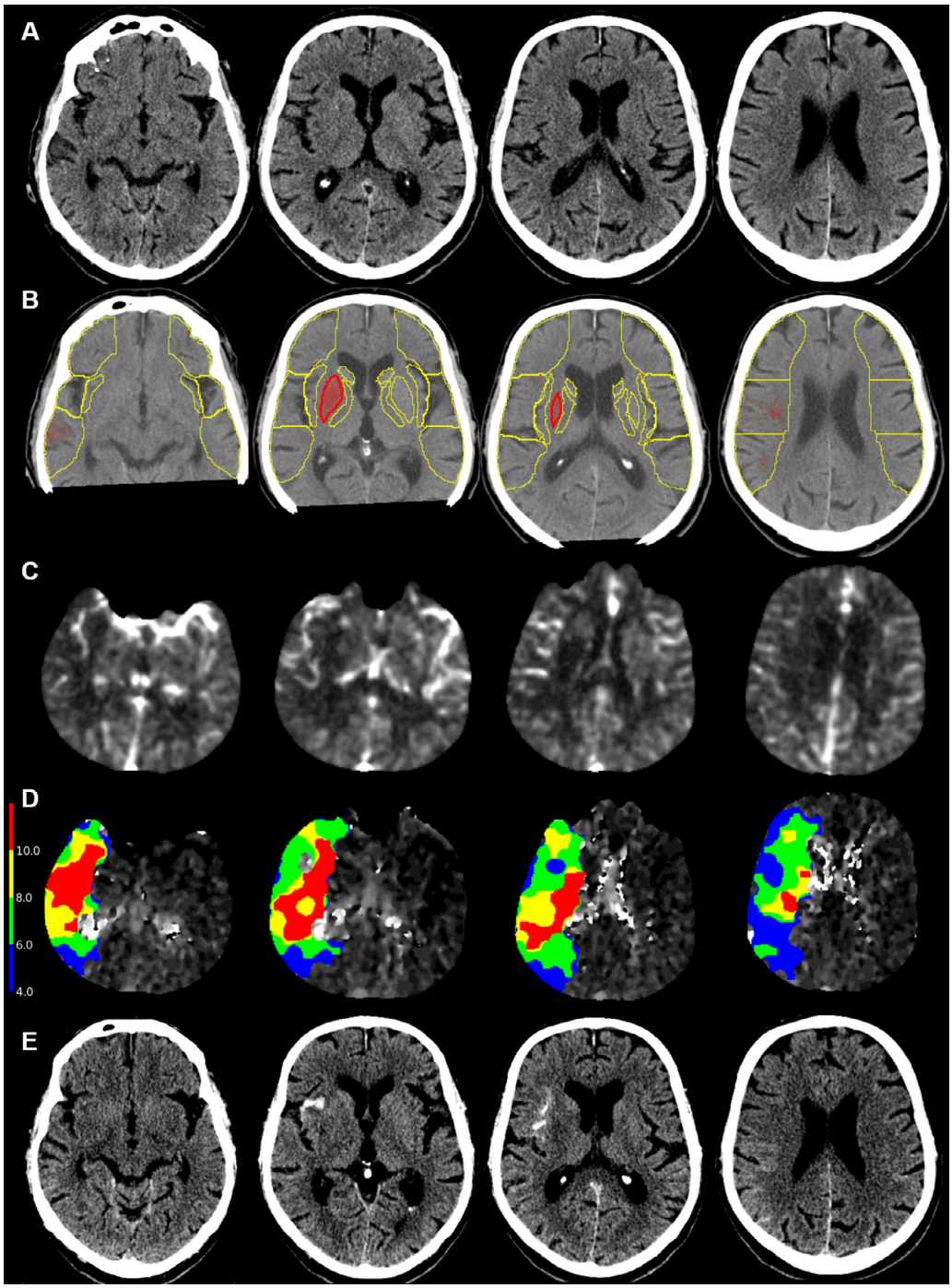

Fig. 1. *Comparison of CT imaging modalities and evaluation of early ischemic changes. Legend: Baseline ASPECTS was assessed as follows: 9 points (lentiform) on NCCT by expert reading (A), 9 points (lentiform) by automatic e-ASPECTS (B), 10 points on CBF<30% (C) and 6 points (M2, M3, insula, lentiform) on Tmax>10s CTP maps (D). Follow-up CT (E) shows the ischemic changes within insula, lentiform and M5 (ASPECTS 7); and hemorrhagic transformation within the right insula.*

Overall, 81 patients met all the criteria and were included into the analysis.

Mean age was 70 years (standard deviation [SD] 14 years, range 30-92 years), 38 (46,9%) were women. Median baseline NIHSS was 9 (interquartile range [IQR] =4 – 17). The median time interval from symptom onset to CT was 156 mins (IQR=71-220); there were 12 patients with the unknow time of symptom onset or wake-up stroke. Median baseline ASPECTS was 9 for all tested modalities (IQR=8-10 for e-ASPECTS, IQR=7-10 for consensus, IQR=7-10 for CBF<30%, IQR 6-10 for Tmax>10s, median ASPECTS on follow-up NCCT was 8, IQR=5-9), left hemisphere was affected in 44 cases (54.3%). Fifty patients received intravenous thrombolysis and 19

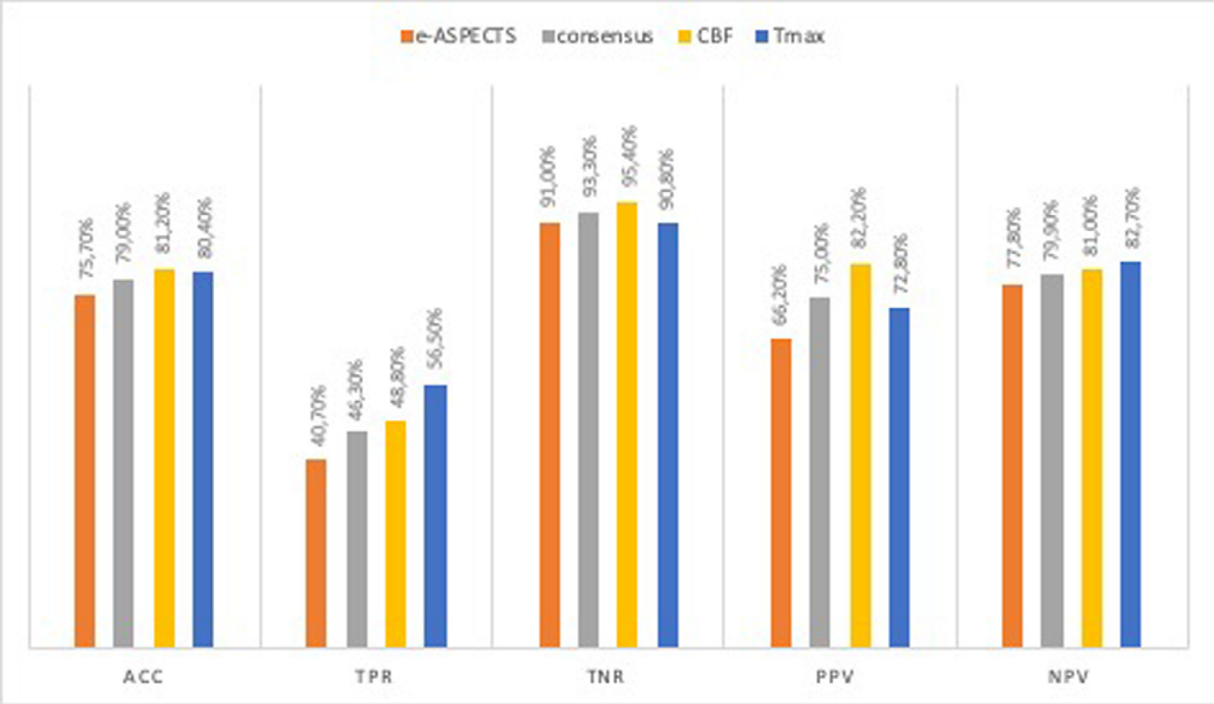

Fig. 2. *Accuracy, sensitivity, specificity, positive predictive value, negative predictive values of baseline ASPECTSs evaluated by e-ASPECTS, consensus (expert reading), CBF<30% and Tmax>10s). Legend: ACC – accuracy; TPR – true positive value/sensitivity, TNR – true negative value/specificity, PPV – positive predictive value, NPV – negative predictive value*

patients had mechanical thrombectomy. Reperfusion was achieved in 11 patients in the mechanical thrombectomy group and in 22 patients in the IVT group, the data from mechanical thrombectomy and intravenous thrombolysis groups were pooled for further analysis (as determined recanalization).

Accuracy of baseline ASPECTS and follow-up ASPECTS was 0.76 for e-ASPECTS, 0.79 for expert consensus, 0.81 for CBF<30% and 0.8 for Tmax>10s. Sensitivity and specificity were 0.41 and 0.91 for e-ASPECTS; 0.46 and 0.93 for expert consensus; 0.49 and 0.95 for CBF<30%; 0.57 and 0.91 for Tmax>10s respectively. PPV and NPV were 0.66 and 0.78 for e-ASPECTS; 0.75 and 0.8 for expert consensus; 0.82 and 0.81 for CBF<30%; 0.73 and 0.83 for Tmax>10s, respectively, Fig. 2 (**Suppl. table 1** in supplemental material).

Bland-Altman plots comparing differences in scores of baseline ASPECTS and follow-up ASPECTS are demonstrated in Fig. 3. The mean difference between e-ASPECTS and follow-up was -1.16 ± 2.52 (median undercall of ASPECTS was -1), expert consensus and follow-up -1.16 ± 2.23 (median undercall was -1), CBF<30% and follow-up -1.15 ± 1.77 % (median undercall was -1), and Tmax>10s and follow-up -0.59 ± 1.86 (median undercall was 0). The ASPECTS was rated as lower on baseline imaging in 15/81 cases for e-ASPECTS, 11/81 for expert consensus, 6/81 for CBF<30, and in 15/81 cases for Tmax>10s.

Sensitivity analysis

Clinical and imaging baseline characteristics for patients with determined successful recanalization were not significantly different in comparison to the subgroup of patients with non-determined recanalization (**Suppl. table 2)**. The results of the subgroup analysis in patients with successful reperfusion/recanalization are graphically demonstrated in Fig. 4 (**Suppl. table 3**). Accuracy of baseline ASPECTS and follow-up ASPECTS was 0.79 for e-ASPECTS, 0.81 for expert consensus, 0.83 for CBF<30% and 0.82 for Tmax>10s. Sensitivity and specificity were 0.51 and 0.90 for e-ASPECTS; 0.53 and 0.92 for expert consensus; 0.55 and 0.94 for CBF<30%; 0.66 and 0.89 for Tmax>10s, respectively. PPV and NPV were 0.67 and 0.82 for e-ASPECTS; 0.73 and 0.83 for expert consensus; 0.77 and 0.84 for CBF<30%; 0.7 and 0.87 for Tmax>10s, respectively.

Bland-Altman plots for the subgroup analysis comparing differences in scores of baseline ASPECTS and follow-up ASPECTS are demonstrated in Fig. 5. The mean difference between e-ASPECTS and follow-up was -0.70 ± 2.48 (median undercall of ASPECTS was -1), expert consensus and follow-up -0.79 ± 2.33 (median undercall was 0), CBF<30% and follow-up -0.82 ± 1.77 (median undercall was -1), and Tmax>10s and follow-up -0.21 ± 1.74 (median undercall was 0). The ASPECTS was lower on baseline imaging in 7/33 cases for e-ASPECTS, 6/33 for

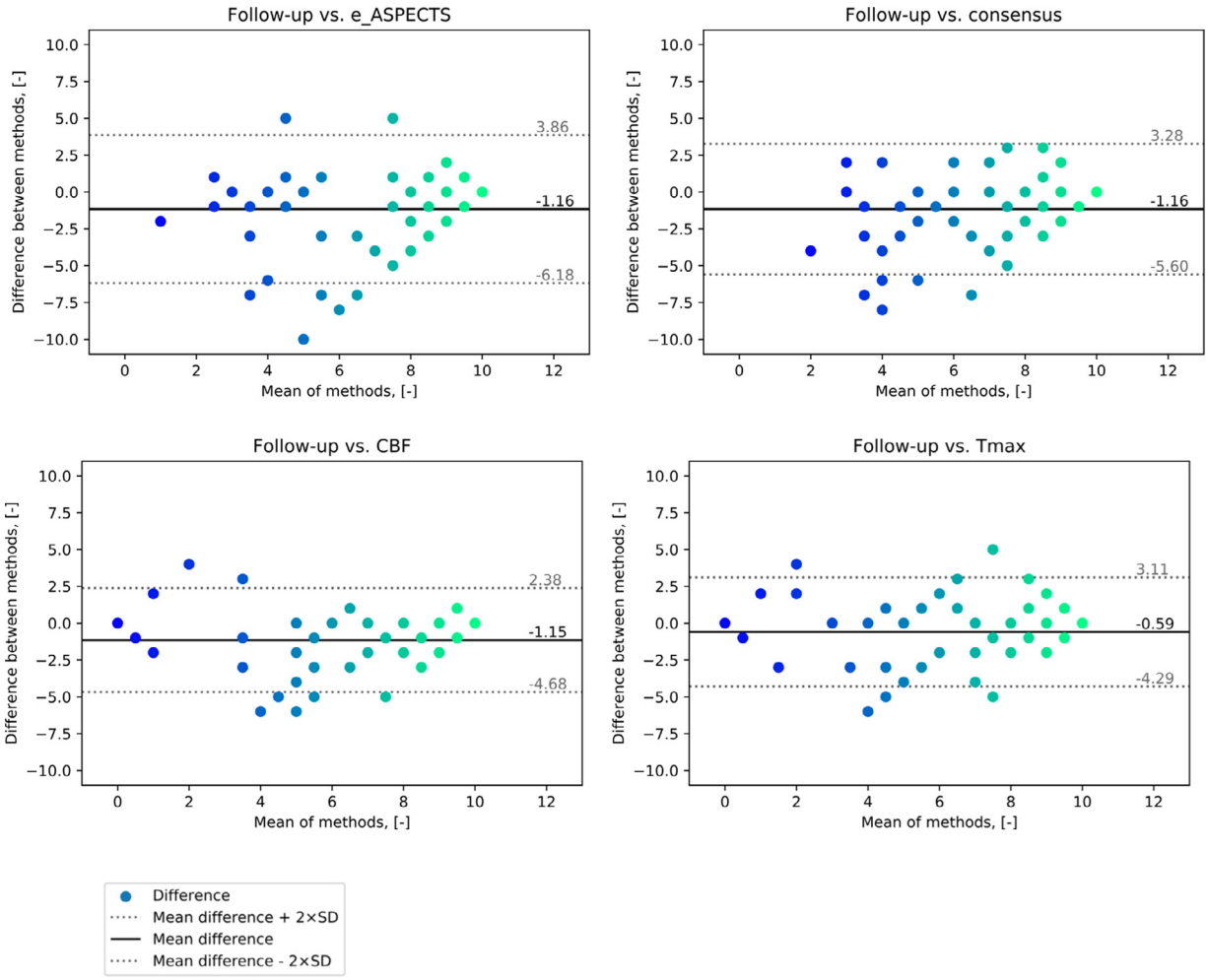

Fig. 3. *Bland-Altman plots. Bland-Altman plots illustrating the level of agreement between the baseline and follow-up ASPECTS for different baseline CT modalities and means of evaluation (software vs. expert reading). Solid line indicates the mean difference between the baseline and follow-up, dashed lines indicate the limits of the agreement.*

expert consensus, 5/33 for CBF<30%, and in 9/33 cases for Tmax>10s.

There was no significant difference between residuals of the follow-up ASPECTS and each baseline ASPECTS for the two subgroups (determined recanalization versus non-determined recanalization group), the median undercall of baseline ASPECT scores was -1 point in comparison to the follow-up ASPECTS for the baseline methods in the subgroup with non-determined recanalization and for CBF<30% and e-ASPECTS in the subgroup with determined recanalization. There was a trend observed for Tmax>10s that show a higher precision in the subgroup with determined successful recanalization with the median undercall of 0 points. (**Suppl. table 4**).

Results from generalized mixed model are illustrated in Fig. 6.

Discussion

In this study we demonstrated high sensitivity and specificity for detection of acute ischemic changes for CT imaging modalities including assessment of acute ischemic changes by experienced readers and clinically available software. Unlike in previous studies, we have focused on CTP parameters representing either ischemic core (CBF<30%) or severely hypoperfused tissue (Tmax>10s), parameters that were not analyzed previously in the perspective of ASPECT scoring. CBF <30% is nowadays widely accepted to represent the ischemic core with the high sensitivity and specificity and with low overestimation of the core, that could result in unwarranted exclusion of patients who could benefit from reperfusion (17). In contrast to Tmax>6s, which is used to define penumbra, we evaluated a more severe delay, Tmax>10s, representing the critically hypoperfused tissue, which is associated with irreversible necrosis of the ischemic lesion even after reperfusion (23).

The highest specificity was observed for CTP parameter, rCBF<30%, assessed visually on CTP maps processed by RAPID software. This CTP parameter also showed the highest positive predictive value for final ischemic changes.

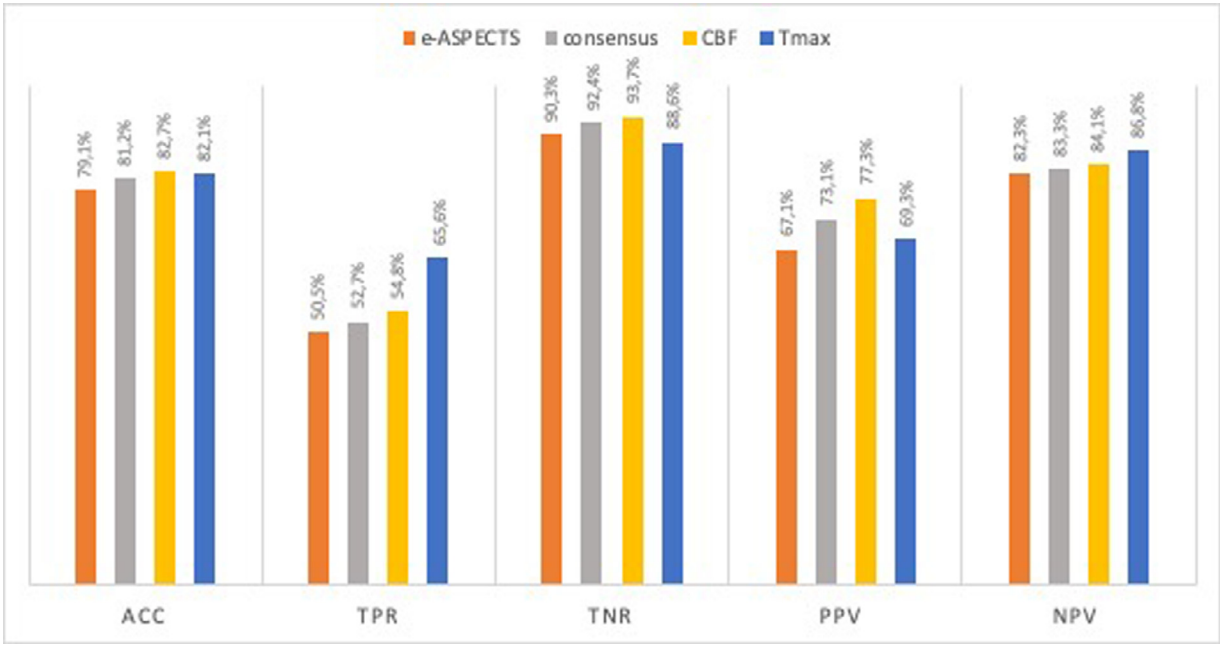

Fig. 4. *Subgroup analysis of patients with successful reperfusion – accuracy, sensitivity, specificity, positive predictive value and negative predictive value for baseline assessment (e-ASPECTS, consensus, CBF<30% and Tmax>10s) and final ischemic changes on follow-up NCCT. Legend: ACC – accuracy; TPR – true positive value/sensitivity, TNR – true negative value/specificity, PPV – positive predictive value, NPV – negative predictive value*

Moreover, the CTP parameter of Tmax delay >10s, representing a severe hypoperfusion, showed the highest sensitivity and high accuracy for prediction of final ischemic lesion (within the whole dataset as well as in the subgroup analysis of successful reperfusion/recanalization). Tmax delay >10s was studied previously – the association of large Tmax>10s lesion and malignant MCA profile was showed in previous studies (18,29). Tmax volumes at a delay of >8s and >10s were strongly correlated with clinical outcome.(30) Our findings support the importance of this parameter in the detection of irreversible ischemic changes on baseline neuroimaging. We demonstrated that both CBF <30% and Tmax>10s have high accuracy in detection of early ischemic changes as shown previously for CBV (13–16) and these changes could be easily assessed on the derived perfusion maps from RAPID analysis.

The Blant-Altman plots showed the lowest difference in baseline ASPECTS and follow-up ASPECTS for Tmax>10s. The other baseline methods showed similar differences in baseline and follow-up ASPECTS with the median undercall of the baseline score of 1 point (these findings did not differ when we analyzed the residuals between follow-up ASPECTS and baseline ASPECTS for the subgroups with determined/non-determined recanalization). The CBF <30% and Tmax>10s also demonstrated the lowest data dispersion for baseline and follow-up ASPECTS. This indicates that these perfusion parameters may represent irreversibly affected tissue with higher accuracy in comparison to detectable changes on baseline NCCT. Nevertheless, the semi-automated analysis showed similar results with expert reading. This finding suggests a comparable diagnostic value of the software evaluation and expert reading in the acute stroke management.

Although e-ASPECTS showed the lowest accuracy and sensitivity among the tested baseline methods, the accuracy of 0.76 could still be considered as good, the sensitivity analysis also did not show any significant difference between baseline methods for the tested subgroups. The comparable findings for e-ASPECTS and other studied imaging methods implicates the benefit of software evaluation for less experienced readers.

We observed a certain level of variability in assessment of particular ASPECTS regions. The highest odds for agreement in evaluation of baseline ischemic changes and final ischemia was demonstrated for insula regardless the baseline imaging modality and the way of ASPECT scoring. It was demonstrated previously that the insular ribbon sign represented a very early ischemic change in the middle cerebral artery strokes (31). Contrarily, the lowest odds for agreement between multimodal baseline and follow-up imaging was observed in the internal capsule. That might be explained by difficulties in the visual assessment of hypoattenuation within this region as the internal capsule is naturally less hypodense on NCCT (32). This small subcortical region might also be challenging to be distinguished on the CTP maps as hypoperfused. Additionally, there was low variability demonstrated for all cortical ASPECTS regions, caudate and lentiform. It may reflect that early ischemic changes of the insula are easy to detect even with the low

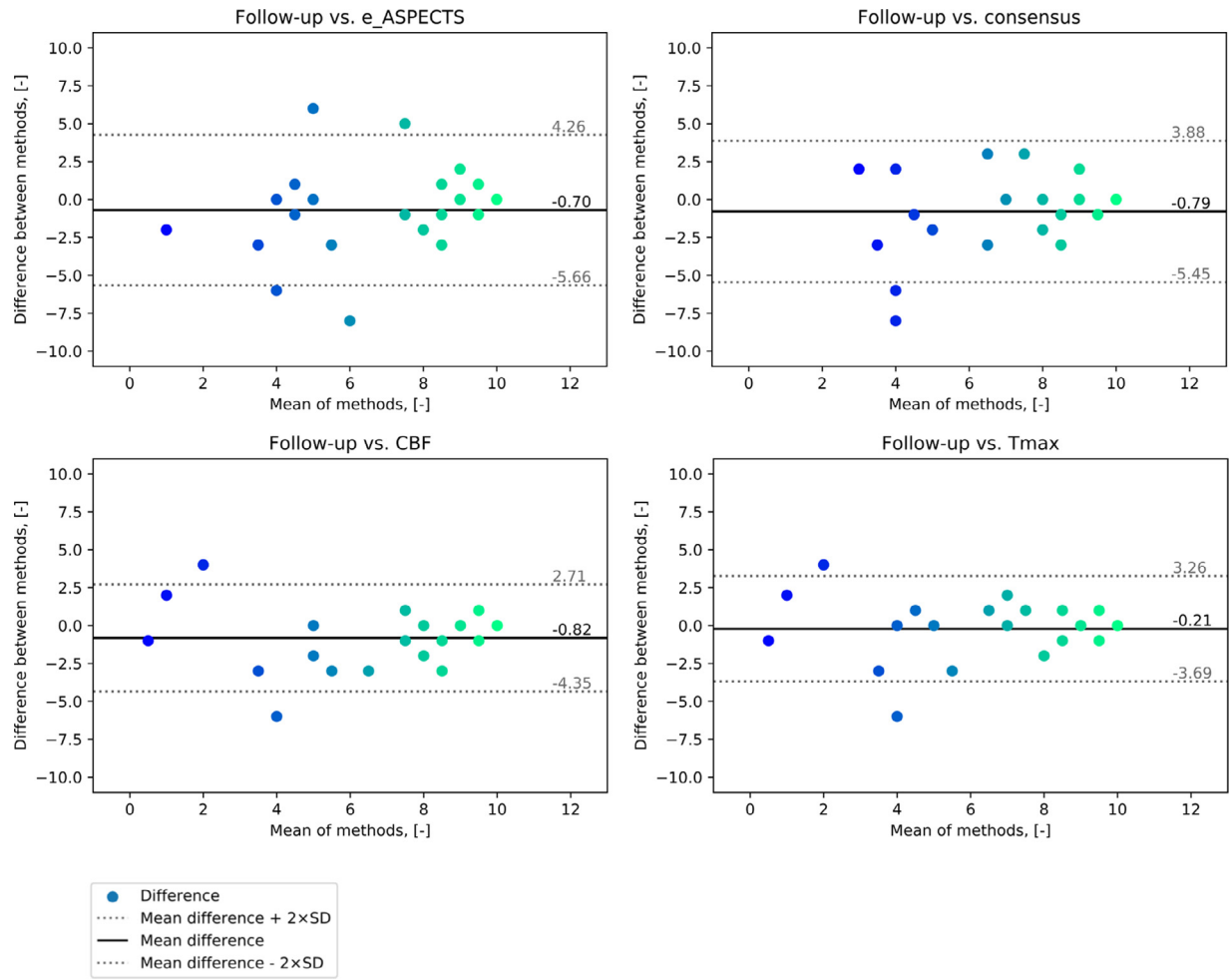

Fig. 5. *Bland-Altman plots for the subgroup analysis of patients with successful recanalization/reperfusion (MT and IVT group pooled data). Bland-Altman plots compare the baseline ASPECTS and follow-up ASPECTS for baseline CT modalities and different means of assessment. Solid line indicates the mean difference between baseline and follow-up, dashed lines indicate the limits of the agreement.*

experience, but assessment of early ischemic changes within the internal capsule might be problematic also for experienced readers.

We are aware of some limitations of this study. First of all, this was a single center observational study. The patients were not selected according to the recanalization rate. Information about the recanalization status was available only in patients indicated to mechanical thrombectomy. Nevertheless, due to a limited (6-months) period when the e-ASPECTS software was available at our institution, we decided to include all patients meeting our inclusion criteria regardless of the treatment or recanalization status. We also did not focus on the correlation of ASPECTS and final clinical outcome, as this relationship has been studied in other work (33). The main purpose of this work was to evaluate the accuracy of ASPECTS assessment on baseline multimodal imaging.

We are also aware of a possible misinterpretation of particular regions caused by visual application of ASPECTS regions into the CTP maps processed by RAPID software. At the time of the patient recruitment, the RAPID CTP software presented only the volumes of impaired tissue perfusion (not co-registered within the ASPECTS regions). The automatic segmentation of ASPECTS regions on e-ASPECTS scans also has its limitations and beside the visual control to avoid any severe inaccuracy we did not tend to correct the automatic segmentation and given ASPECTS scoring as we aimed to test the accuracy of commercially available version of the software.

There are a few potential pitfalls in regard of the detection of acute ischemic changes with automatic analysis. There might be a false positive finding on CTP maps in patients with a subacute or chronic infarction. The RAPID software automatically segments and removes areas with very low CBF, such as CSF spaces and other extra-parenchymal tissue, so in most cases subacute/chronic infarction is also excluded. Another known pitfall is that CTP maps do not display an infarcted area if the reperfusion was achieved ahead of the imaging, even though there is evidence of the infarction on NCCT (34). These potential pitfalls highlight the necessity of a visual control of CTP

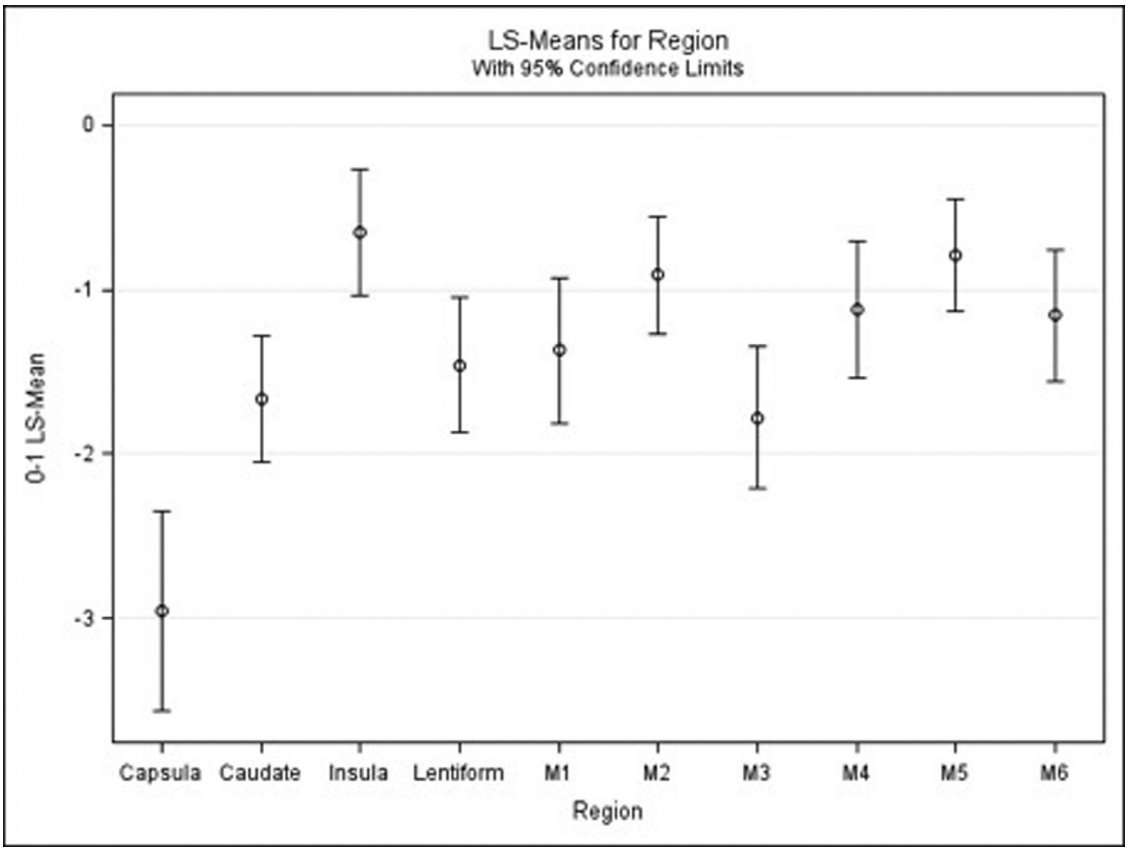

Fig. 6. *Least square means estimates of fixed effect "region" computed from generalized mixed model. The least square means (Ls-means) estimates were computed from a generalized mixed model (fixed effect was ASPECTS region). Follow-up NCCT was used as a reference grid. Results expressed on a logit scale demonstrate the highest agreement for final ischemia in insula and M5 region regardless the used CT modality and scoring approach. The lowest odds were demonstrated for internal capsule, which also showed the highest variability in scoring.*

derived maps with NCCT or other available imaging as well as a control of the correct placement of arterial input function and venous output function.

Conclusions

Our study demonstrated high accuracy for the evaluation of early ischemic changes by different CT modalities with the best accuracy for CBF<30% and Tmax>10s. The use of automated software in everyday clinical practice has a potential to improve detection of extent of early ischemic changes.

Funding

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Informed consent

Informed consent was obtained from all individual participants included in the study.

Ethical Approval

All procedures performed in studies involving human participants 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.

For this type of study formal consent is not required.

Declaration of Competing Interest

PC is a consultant for iSchemaView, Inc.; other authors declare that they have no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2020.104978.

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