**e-ASPECTS software is non-inferior to neuroradiologists in applying the ASPECTS score to CT scans of acute ischemic stroke patients**

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**Supplementary Material:**

**Methods**

Participating centers and patient selection:

The participating centers were: Addenbrookes Hospital, Cambridge, UK (AHC); University Hospital Homburg, Germany (UHH); Alfred Krupp Krankenhaus, Essen, Germany (AKK); Southend University Hospital, Essex, UK (SUH) and University Hospital of North Staffordshire, Stoke-on-Trent, UK (UHNS). In total 132 patients were included in the analysis (AHC: 28, UHH: 8, SUH: 90 and UHNS: 6 patients). For SUH 300 consecutive patients who had the clinical diagnosis of acute ischemic stroke in the anterior circulation, who had received baseline and 24h follow up imaging for acute ischemic stroke in the previous 2 years were approached by letter. This resulted in 81 carer or patient consents. In addition, patients meeting the inclusion, i.e. suspected acute ischemic stroke in the anterior circulation, and not fulfilling the exclusion criteria were approached prospectively and enrolled, if consent was obtained. AHC and UHH retrospectively enrolled patients, UHNS prospectively. AKK was initiated as a trial centre but did not enrol any patients.

CT-scanner details:

Scans were obtained from six different scanners of four different manufacturers: *TOSHIBA (Tokio, Japan)*: Aquilion, *Phillips (Amsterdam Netherlands)*: Brilliance, *GE Healthcare (*[*Chalfont St Giles*](https://de.wikipedia.org/wiki/Chalfont_St_Giles)*, Great Britain)*: LightSpeed VCT and *Siemens (Munich, Germany):* SOMATOM Definition AS+, SOMATOM Definition Flash, Sensation 16. Slice thickness varied from 0.625mm to 5mm and in-plane resolution varied from 0.39 to 0.53mm (matrix of 512x512 for all scans).

e-ASPECTS

e-ASPECTS is based on a combination of advanced image processing and machine learning algorithms. Several image enhancement filters are applied to the input DICOM CT image, to deal with noise, differences between scanners, and image artifacts. A 3D registration module corrects for any tilt, rotation, and other transformations. The ASPECTS regions are then segmented, providing a standardized reference for the cortical regions. The scoring module operates on the standardized 3D images, classifying signs of ischemic damage and assigning them to ASPECTS regions. It applies statistical learning methods to image features to determine whether a region is likely to be damaged.

The e-ASPECTS software is trained and tested with a large dataset of plain CT scans for ischemic stroke patients and negative controls. These have corresponding ground truth data taken within a short time of the plain CT, including gold-standard DWI (Diffusion Weighted Image) MRI and CT perfusion images.

ASPECTS scoring of physicians:

All human scorers were instructed in the correct use of the ASPECTS according to [www.aspectsinstroke.com](http://www.aspectsinstroke.com/). The physicians were allowed to review all available slices of each scan. Early ischemic change was defined as tissue hypoattenuation or loss of gray–white matter differentiation but not isolated cortical swelling, since it has been demonstrated that it is associated with increased cerebral blood volume and may represent threatened but salvageable tissue [1](#_ENREF_1).

Assumptions for sample size calculation:

A number of assumptions were required and these were based on a previous study2 and the literature. We assumed that the sensitivity and specificity for the NRADs are 45% and 92.5% respectively, and for e-ASPECTS are 44% and 92%, respectively. We also assumed that the probability that e-ASPECTS is correct and the NRAD is wrong when truly there is damage in a region was 0.16. Similarly, when there is truly no damage to a region, the probability that e-ASPECTS is correct and the NRAD is wrong was 0.07. The final assumption was that 10% of all regions would truly be damaged. The non-inferior margin was set to 10% based on our previous experience of blinded experts ratings, which tend to be variable for both sensitivity and specificity, as highlighted in our previous trial2. 10% is also a very commonly used margin for non-inferiority trial in diagnostic imaging3.

Receiver-operating characteristic (ROC) curves:

For the region based analysis, the primary endpoint, each region (of 20 for each scan) will be compared between the ground truth and each scorer, i.e. each region will be represented with one of these criteria (TP;TN;FP or FN). The difference in the score-based approach is that only the score itself matters and not which exact anatomical region is actually labelled e.g  a predicted score of 8 with a reference score of 7 yields a derived confusion matrix with 7 TP, 1 FP, 2 TN and 0 FN  => 10 regions. Although this analysis has clinically more relevance, we decided for the region based analysis as primary endpoint, since it is a more accurate assessment of the performance of e-ASPECTS. The dichotomized score based analysis simply considers for each patient whether the predicted ASPECTS score (of each NRAD) is or isn't above the threshold (i.e threshold=5) and a comparison is made with the ground truth ASPECTS score 2.

**Results**

**Suppl. Figure: Bar graph of ground truth ASPECTS on follow-up NCCT.** Distribution of the 132 patients across the different ground truth ASPECTS values. Median score 8.



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