e-ASPECTS software is non-inferior to neuroradiologists in applying the ASPECT score to computed tomography scans of acute ischemic stroke patients

Nagel, Simon; Sinha, Devesh; Day, Diana; Reith, Wolfgang; Chapot, René; Papanagiotou, Panagiotis

Published in:
International Journal of Stroke

DOI:
10.1177/1747493016681020

Publication date:
2017

Document Version
Peer reviewed version

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

Simon Nagel, MD, PhD[1] #, Devesh Sinha, MD[2] #, Diana Day, MSc[3], Wolfgang Reith, MD, PhD[4], René Chapot, MD, PhD [5], Panagiotis Papanagiotou, MD, PhD [6], Elizabeth A. Warburton, MD[7], Paul Guyler, MD[2], Sharon Tysoe, BSc[2], Klaus Fassbender, MD, PhD [8], Silke Walter, MD, PhD [8,16], Marco Essig, MD, PhD [9], Jens Heidenrich, MD, PhD [10] , Angelos A. Konstas, MD[11], Michael Harrison, MPHARM, HSMBA[12], Michalis Papadakis, PhD[13], Eric Greveson, M. Eng, MA[13], Olivier Joly, PhD[13] , Stephen Gerry, MSc[14], Holly Maguire, BA[15] , Christine Roffe, MD[15] , James Hampton-Till, BSc(Hons), PhD[12] , Alastair M. Buchan[16] and Iris Q. Grunwald, MD, PhD [2,13,17]

[1] Department of Neurology, University Hospital Heidelberg, Germany

[2] Southend University Hospital NHS, Essex, UK.

[3] Addenbrooke's Hospital NHS, Cambridge, UK.

[4] Department of Neuroradiology, Saarland University Hospital, Homburg, Germany

[5] Department of Neuroradiology, Alfred Krupp Krankenhaus, Essen, Germany.

[6] Department of Neuroradiology, Bremen Hospital, Bremen, Germany.

[7] Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK.

[8] Department for Neurology, Saarland University Hospital, Homburg, Germany.

[9] Department of Radiology, University of Manitoba, Winnipeg, Canada.

[10] Department of Diagnostic Radiology, Dalhousie University, Nova Scotia, Canada.

[11] Dept. of Radiology, Huntington Memorial Hospital, Pasadena, CA, USA

[12] Clinical Trials Unit, Anglia Ruskin University, Chelmsford, Essex, UK

[13] Brainomix Limited, Oxford, UK.

[14] Centre for Statistics in Medicine, University of Oxford, Oxford, UK.

[15]Stroke Research, North Staffordshire Combined Healthcare NHS Trust, Stoke on Trent, Staffordshire, UK

[16] Acute Stroke Programme, Radcliffe Department of Medicine, University of Oxford, Oxford, UK

[17]Neuroscience Department, Anglia Ruskin University, Chelmsford, Essex, UK

# these authors contributed equally

Short title: automated ASPECTS in ischemic stroke

Key words: ASPECTS, CT, ischemic stroke, machine learning

Word count: 3906

Tables: 2 , **Figures:** 2, **Supplemental Materials**

Corresponding author:

Prof. Dr. I.Q. Grunwald

Neuroscience and Vascular Simulation,

PMI, Anglia Ruskin University,

CM1 1SQ, Chelmsford,

Essex, UK

Email: i.grunwald@gmx.net

Nagel, S., et al (2017) 'e-ASPECTS software is non-inferior to neuroradiologists in applying the ASPECT score to computed tomography scans of acute ischemic stroke patients', *International Journal of Stroke*, vol. 12, no. 6, pp. 615-622. © 2016 World Stroke Organization.
https://doi.org/10.1177/1747493016681020

Abstract

Background: The Alberta Stroke Program Early CT score (ASPECTS) is an established 10-point quantitative topographic CT scan score to assess early ischemic changes. We performed a non-inferiority trial between the e-ASPECTS software and neuroradiologists (NRAD) in scoring ASPECTS on non-contrast enhanced CT images (NCCT) of acute ischemic stroke patients.

Methods: In this multicentre study, e-ASPECTS and three independent NRADs retrospectively and blindly assessed baseline NCCTs of 132 patients with acute anterior circulation ischemic stroke. Follow-up scans served as ground truth to determine the definite area of infarction. Sensitivity, specificity and accuracy (SSA) for region based and score based analysis, ROC curves, Bland-Altman plots and Matthews correlation coefficients (MCC) relative to the ground truth were calculated and comparisons were made between NRADs and different pre-specified e-ASPECTS operating points. The non-inferiority margin was set to 10% for both sensitivity and specificity on region based analysis.

Results: In total 2640 (132 patients x 20 regions per patient) ASPECTS regions were scored. Mean time from onset to baseline CT was 146+/-124 min and median NIHSS was 11 (6-17, IQR). Median ASPECTS for ground truth on follow-up imaging was 8 (6.5-9, IQR). In the region based analysis, two e-ASPECTS operating points (SSA of 44%, 93%, 87% and 44%, 91%, 85%) were statistically non-inferior to all three NRADs (all p-values <0.003). Both MCCs for e-ASPECTS were higher (0.36 and 0.34) than those of all NRADs (0.32. 0.31 and 0.3).

Conclusions: e-ASPECTS was non-inferior to three neuroradiologists in scoring ASPECTS on NCCTs of acute stroke patients.

Introduction

The Alberta Stroke Program Early CT Score (ASPECTS) is a topographic scoring system for acute ischemic damage to brain that divides the middle cerebral artery (MCA) territory into 10 areas of interest (1). It has recently been used for the enrolment of patients in endovascular treatment trials, in which only patients with an ASPECTS of 6 or 7 and above could be included (2-4). However, the interpretation of the ASPECTS on a non-contrast enhanced computer tomography (NCCT) brain scan of patients with an acute ischemic stroke is challenging and variable, even between stroke experts (5, 6). Therefore, standardized and automated assessment of ischemic damage would be useful in clinical practice and research. A proof-of-concept study showed that machine learning methods applied to acute stroke NCCT images offered an improved prediction of symptomatic intracerebral hemorrhage over common prognostic clinical scores (7). The e-ASPECTS software is a commercially available, now CE-marked, standardized and fully automated ASPECTS scoring tool based on a machine learning algorithm (8). Recently, it was shown that e-ASPECTS was more sensitive in detecting early signs of cerebral ischemia than junior stroke physicians, who are usually the first interpreters of a scan of an acute stroke patient. Although the software performed similar to stroke experts, it was not powered to claim non-inferiority (9). In this non-inferiority trial with NCCTs of acute ischemic stroke patients from five different stroke centres, we compared the scoring performance of e-ASPECTS with those of three independent neuroradiologists (NRADs), experienced in diagnosing early ischemic damage.

Methods

Patients

Patients with acute ischemic stroke syndromes in the anterior circulation, as clinically determined, and available baseline and follow-up NCCTs, obtained between 24 and 36 hours after baseline imaging, were eligible. Patients with haemorrhage or severe imaging artefacts on baseline imaging or when consent could not be obtained in accordance with the national procedures stipulated by the respective ethics commissions, were excluded. The Norfolk NRES Committee East of England and Freiburg ethics committee approved the study. All patients were treated according to local in house protocols on the respective local stroke units. For further details on participating centers and CT scanner details please see the suppl. Material.

e-ASPECTS and ASPECTS scoring of NRADs

The ASPECTS score of the ground truth was determined by an independent core lab (Medical Imaging Heidelberg GmbH, Heidelberg, Germany) and based on both the initial imaging as well as on the follow up imaging; i.e. only lesions that were present on baseline imaging and follow-up were scored. e-ASPECTS was run on an Intel ® Core i7 processor. Following pre-processing of the DICOM input images, a registration step corrects for any 3D rotation and tilt. Image features are then extracted and scored with a machine learning classifier to identify early ischemic signs (suppl. Material and 8,9). Pseudonymized baseline NCCT were retrospectively scored by eight different pre-specified e-ASPECTS operating points (OP) as well as by three NRADs (PP, JH and AAK who were not affiliated with the participating clinical sites). Each NRAD had over 10 years' clinical experience in acute stroke imaging and interventional neuroradiology. The e-ASPECTS OPs reflect settings, which essentially determine how much weight is given to misclassifications in the "true positive (damage)" score versus the "true negative (no damage)" score of the algorithm – i.e. modulating sensitivity and specificity and simulating different physicians' behaviour. e-ASPECTS and the human scorers were blinded for any clinical information except that a unilateral ischemic stroke in the anterior circulation was suspected.

Data analysis

Prior to conduction of the study, a sample size calculation was carried out based on the methods of Ying Lu et al. (10) for simultaneous comparison of sensitivity and specificity (suppl. material). The non-inferiority margin was set to 10% for both sensitivity and specificity, based on our previous clinical experience (suppl. material). This calculation yielded 128 necessary patients, i.e. 2560 ASPECTS regions for a region based analysis (see below).

Sensitivity and specificity as well as accuracy based on true positive (TP), true negative (TN), false positives (FP) and false negative (FN) scores were calculated individually over all ASPECTS regions and for the overall ASPECTS score for each e-ASPECTS OP and each NRAD. Since the results were expected to be correlated within patients, two methods for clustered data were used to estimate sensitivity and specificity (and 95% confidence intervals): variance adjustment using a sandwich estimator and generalized estimating equations (GEE) (11). In the GEE approach, the estimated sensitivity (and specificity) is interpreted as the weighted average across the study population ("population averaged"). This approach hence delivers the mean sensitivity and specificity across all patient-specific estimates of sensitivity (and specificity).

Receiver-operating characteristic (ROC) curves were generated for three analysis methods, for the region-based analysis (20*132 regions), the score-based analysis (10 points) and for the dichotomized ASPECTS score of >5 (suppl. material).

Sensitivities and specificities of the region-based analysis were then compared between each e-ASPECTS OP and each NRAD. The non-inferiority (one-sided) statistical test was calculated based on Lu et al (10). The 95% confidence intervals for the difference between e-ASPECTS and scorers are based on the Adjusted Wald Method (12). As a sensitivity analysis, differences and 95% confidence intervals were also calculated using GEE to take account of potential correlations within patients. For each given couple of e-ASPECTS OP and scorers, if the lower 95% confidence interval boundary for the difference of e-ASPECTS minus score does not cross -10% (the non-inferiority margin) for both sensitivity and specificity, then non-inferiority can be concluded; furthermore if in addition the upper boundary for the confidence interval of the difference does not cross +10%, then equivalence can be concluded.

Matthews correlation coefficients (MCC) which range between [-1;1] (0 = random prediction) were also calculated. The MCC summarises in a single value the performance in damage detection in the unbalanced dataset since there are a large number of true negative from the 10 contra-lateral regions for each case. Additionally, Bland-Altman plots and histograms were generated for e-ASPECTS OP#4 and grouped for all NRADs in order to illustrate the distribution of the error in ASPECTS score.

Results

In total 134 patients who met the inclusion criteria were identified. Two patients had to be excluded because the core lab deemed CT imaging artifacts impaired image analyses by NRADs and e-ASPECTS. Finally, 132 patients were included in the study and 2640 ASPECTS regions were analysed. Median age of the patients was 72 years (63-79, IQR) and 55% were male. Mean time from onset to baseline CT was 146+/-124 min and median NIHSS was 11 (6-17, IQR). Three patients were treated with an endovascular approach and 123 patients were treated with intravenous thrombolysis. Median ASPECTS for the ground truth on follow up imaging was 8 (6-9 IQR, Suppl. Figure).

All relevant scoring data, including true positive (TP), true negative (TN), false positive (FP) and false negative (FN) scores as well as respective sensitivity, specificity (with confidence intervals for both methods) and accuracy for all e-ASPECTS OPs and all NRADs in the region based analysis are displayed in table 1.

Importantly, the results for the two analysis methods show no relevant difference. Sensitivity, specificity and accuracy were as follows for the human scorers: NRAD1 - 45%, 89% and 84%, NRAD2 – 27%, 96%, 88% and NRAD3 – 26%, 97% and 89%, respectively. For the three NRADs, sensitivity and specificity are also illustrated (triangles) in the ROC space on the Figure 1A.

Two e-ASPECTS OPs (#4 and#5) were statistically non-inferior to all three NRADs (all p-values <0.003; 44%, 93%, 87% and 45%, 91%, 85% respectively for e-ASPECTS OP#4 and OP#5). The difference between e-ASPECTS (OP#4 and #5) and NRADs is summarised in table 2 together with the p-values for the non-inferiority test.

In summary, both OPs were shown to be non-inferior to all NRADs (except for the GEE analysis of OP#4 and OP#5 vs. NRAD1) for sensitivity and specificity; both OPs were equivalent to NRAD1 (except for GEE analysis for OP#4 and OP#5), for the other comparisons the OPs were equivalent for specificity and superior for sensitivity.

These two e-ASPECTS OPs are also indicated in Figure 1. Two ROC curves illustrate the performance of e-ASPECTS against the human scorers, i.e. Figure 1B which is illustrating performance parameters in the score based analysis and Figure 1C which is illustrating sensitivity and specificity in the ROC space for a dichotomized analysis of ASPECTS>5. Importantly, e-ASPECTS OP#4 identified 97% of patients with an ASPECTS>5 correctly.

For further comparison of e-ASPECTS OP#4 and the manual ASPECTS of all NRAD with the ground truth, Bland-Altman plots and histograms of score difference or score error were generated. In Figure 2, the Bland-Altman graph displays a scatter diagram of the differences between the ASPECTS score and ground truth plotted against the averages of the three scores. This graph allows to visually assess a possible absolute systematic error, respectively the mean error in scoring as compared to the ground truth.

Finally, the Matthews correlation coefficient (MCC), used as a measure of binary classification accuracy, were best (0.36 and 0.34) for e-ASPECTS OP#4 and #5, respectively, thereby showing better prediction of the ground truth by e-ASPECTS (table 1).

Discussion

This is the first trial to demonstrate equivalent specificity and non-inferior or even superior sensitivity of the e-ASPECTS software compared to ASPECTS scoring by experienced neuroradiologists (with specific expertise in acute stroke imaging) of baseline NCCTs from acute ischemic stroke patients. A previous monocentric proof-of concept study already demonstrated superiority of e-ASPECTS to stroke trainees regarding sensitivity of a region based analysis approach (9).

In our multicentre, multiscanner study two different operating points (i.e. OP#4 and OP#5) of e-ASPECTS proved to be statistically non-inferior and equivalent to all three NRADs. Complementary analysis by Bland-Altman plots and MCCs confirmed the equal performance of the software and the human scorers when compared to the ground truth (Figures 1&2).

In the past months, endovascular stroke therapy of the anterior circulation has been labelled as the “new standard of care” for patients with large vessel occlusion (13). Recently, a systematic meta-analysis with 2423 patients supported this enthusiasm through an increased odds ratio of 2.23 for favourable functional outcome (as compared to best medical treatment) when newer generation thrombectomy devices were employed in more than 50% of cases (14). Importantly, the vast majority of patients in these trials were treated based on CT imaging. Selection of the appropriate patient for acute recanalization therapy, i.e. thrombolysis and endovascular treatment is an important process in each acute stroke service or referring hospital, that needs to happen rapidly. Next to the clinical information, i.e. age, time window, concomitant diseases, etc., information from imaging is essential to distinguish between patients likely to benefit and those with a high probability of futile treatment. While the ASPECTS score has previously been shown to be a strong predictor of functional outcome following thrombolytic treatment (1), it has now prospectively and successfully been demonstrated that it also predicts outcome after endovascular treatment. Importantly, the above mentioned, independent meta-analysis showed that both ASPECTS subgroups, 8-10 (minimal ischemic damage) and 5-7 (moderate ischemic damage) on baseline CT imaging were significantly associated with improved outcome (OR 2.1 and 2.04, respectively for mRS 0-2 against best medical treatment) (14). Patients with a low ASPECTS of 0-4 showed no treatment benefit, although it needs to be mentioned that this analysis was only based on 28 patients of the MR-CLEAN trial. The recent ESO-Karolinska “consensus statement on mechanical thrombectomy in acute ischemic stroke” suggests that patients with radiological signs of large infarcts may be unsuitable for thrombectomy and proposes using the ASPECTS (15). Moreover, The Stroke Imaging Research (STIR) group very recently recommended in a consensus statement to use ASPECTS on NCCT in order to determine infarct core size and to focus research on standardizing imaging and on image reconstruction algorithms (16).

J.C. Grotta and W. Hacke, after publication of the thrombectomy trials, pointed out that resources for endovascular treatment are still scarce and that community hospitals swiftly need to establish diagnostic and selection algorithms as well as communication and transportation pathways for eligible patients (17). In this setting, e-ASPECTS might be a valuable tool especially for those referring hospitals, since expert assessment of NCCT imaging or even advanced perfusion CT imaging is rarely available 24/7.

The strengths of this study are the multicentric design, which meant that NCCTs were acquired with various CT scanners indicating generalisation of the results. A limitation is surely that the ground truth was based on the assessment of both the baseline and the follow up CT scan by the core imaging lab and not on expeditious MRI or perfusion CT imaging; however that should not hamper the overall comparison between human NRAD scorers and e-ASPECTS, as any potential bias would affect equally human NRAD scorers and e-ASPECTS. Although e-ASPECTS is CE-marked, careful assessment of each CT scan by the physician to rule out other pathologies and haemorrhage is still mandatory. It is not intended to replace the physician's assessment of the scan but it can be a valuable second opinion and confirmation of the own interpretation on expert level.

Conclusions

In this multicentre trial with 132 patients, e-ASPECTS was shown to be non-inferior to experienced neuroradiologists in applying the ASPECTS score to NCCTs of acute ischemic stroke patients.

Acknowledgements

The authors would like to express their gratefulness to Nicole Mueller (study nurse), Kim Wilde (study nurse) and Oliver Anderson (Trial coordinator). Elizabeth A. Warburton received support from the NIHR BRC.

Source of Funding

This study was funded by Brainomix Ltd and sponsored by the Anglia Ruskin University Higher Education Corporation.

Disclosures

IQG, MP and AMB are co-founders of Brainomix Ltd. EG and OJ are employees of Brainomix. SN has received travel expenses and consulting fees from Brainomix. SG and Medical Imaging Heidelberg GmbH were contracted for this study. All other authors declare no conflict of interest.

Figure 1: Receiver-operating characteristic (ROC) curves for e-ASPECTS and performance of NRADs. (A). ROC curve for ASPECTS on region-based analysis (20 regions) for e-ASPECTS (red dashed line) and performance of NRADs (up-pointing blue triangles). (B). ROC curve for ASPECTS score-based analysis for e-ASPECTS (red dashed line) and performance of NRADs. (C). ROC curve associated to eligibility for endovascular treatment (ASPECTS>5) as determined by e-ASPECTS (red dashed line) and classification by NRADs (blue). OP#4: operating point for e-ASPECTS. Grey dashed diagonals represent the line of no-discrimination associated to random guess.

Figure 2: Bland-Altman plots and associated histograms of score error. Bland-Altman plots (left panel) with mean score error (grey dashed line) and histograms (right panel) of score error for e-ASPECTS (OP#4) (**A**) and NRADs (**B**)

Table 1: Region-based scoring results of e-ASPECTS and the three NRADs. Sensitivities, specificities, accuracies and Matthews correlation coefficient (MCC) are given for all scorers and e-ASPECTS operating points (Fig. 1). Values are given for all regions and for the set of 4 regions at the ganglionic level (L, I, C, IC) and for the set of 6 cortical regions M1-M6.

	e-ASPECTS #1	e-ASPECTS #2	e-ASPECTS #3	e-ASPECTS #4	e-ASPECTS #5	e-ASPECTS #6	e-ASPECTS #7	e-ASPECTS #8	NRAD #1	NRAD #2	NRAD #3
TP	66	73	89	132	137	158	179	192	137	81	79
TN	2269	2246	2226	2163	2119	2053	1916	1820	2073	2254	2267
FP	68	91	111	174	218	284	421	517	264	83	70
FN	237	230	214	171	166	145	124	111	166	222	224
Sensitivity (all regions)	21.78 % (15.7, 27.8)	24.09 % (18.2, 30.0)	29.37 % (23.3, 35.4)	43.56 % (37.0, 50.1)	45.21 % (38.8, 51.7)	52.15 % (45.5, 58.8)	59.08 % (52.6, 65.5)	63.37 % (56.6, 70.2)	45.21 % (38.0, 52.4)	26.73 % (20.9, 32.6)	26.07 % (20.5, 31.7)
Specificity (all regions)	97.09 % (96.2, 98.0)	96.11 % (95.2, 97.0)	95.25 % (94.2, 96.3)	92.55 % (91.3, 93.8)	90.67 % (89.3, 92.1)	87.85 % (86.4, 89.3)	81.99 % (80.4, 83.5)	77.88 % (76.3, 79.4)	88.70 % (87.1, 90.3)	96.45 % (95.3, 97.6)	97.00 % (95.9, 98.1)
Sensitivity GEE	20.79 % (15.0, 26.6)	23.21 % (17.5, 28.9)	28.59 % (22.6, 34.6)	42.01 % (35.5, 48.5)	43.93 % (37.4, 50.5)	50.32 % (43.6, 57.1)	57.04 % (50.4, 63.7)	60.85 % (53.8, 67.9)	44.02 % (36.7, 51.3)	25.70 % (19.9, 31.5)	25.46 % (20.0, 31.0)
Specificity GEE	97.05 % (96.2, 97.9)	96.08 % (95.1, 97.0)	95.22 % (94.2, 96.3)	92.53 % (91.3, 93.8)	90.67 % (89.3, 92.1)	87.8 % (86.4, 89.3)	81.99 % (80.4, 83.5)	77.85 % (76.3, 79.4)	88.72 % (87.2, 90.3)	96.41 % (96.3, 97.5)	96.92 % (95.8, 98.0)
Accuracy (all regions)	88.45 %	87.84 %	87.69 %	86.93 %	85.45 %	83.75 %	79.36 %	76.21 %	83.71 %	88.45 %	88.86 %
Sensitivity (L, I, C, IC)	27.54 %	29.71 %	37.68 %	44.93 %	44.93 %	47.83 %	50.00 %	53.62 %	51.45 %	41.30 %	37.68 %
Specificity (L, I, C, IC)	95.21 %	93.68 %	92.59 %	89.76 %	89.87 %	87.58 %	82.24 %	80.94 %	86.60 %	94.01 %	95.21 %
Accuracy (L, I, C, IC)	86.36 %	85.32 %	85.42 %	83.90 %	84.00 %	82.39 %	78.03 %	77.37 %	82.01 %	87.12 %	87.69 %
Sensitivity (M1-6)	16.97 %	19.39 %	22.42 %	42.42 %	45.45 %	55.76 %	66.67 %	71.52 %	40.00 %	14.55 %	16.36 %
Specificity (M1-6)	98.31 %	97.67 %	96.97 %	94.36 %	91.19 %	88.02 %	81.82 %	75.90 %	90.06 %	98.03 %	98.17 %
Accuracy (M1-6)	89.84 %	89.52 %	89.20 %	88.95 %	86.43 %	84.66 %	80.24 %	75.44 %	84.85 %	89.33 %	89.65 %
Matthews Correlation Coefficient	0.27	0.27	0.3	0.36	0.34	0.34	0.31	0.3	0.3	0.31	0.32
MCC (L, I, C, IC)	0.29	0.27	0.32	0.33	0.33	0.32	0.26	0.27	0.33	0.39	0.39
MCC (M1-6)	0.26	0.26	0.27	0.38	0.34	0.36	0.35	0.32	0.27	0.22	0.25

Table 2: Summary statistics with CI and t-values and p-values for e-ASPECTS #OP4 and #OP5.

	Difference in sensitivities	95% CI	Difference in specificities	95% CI	T statistic for non-inferiority	P-value for non-inferiority
OP#4 - NRAD#1	-0.0165	(-0.0765, 0.0435)	0.0385	(0.0228, 0.0542)	-2.72	0.003
GEE	-0.0263	(-0.1235, 0.0710)	0.0380	(0.0180, 0.0581)		
OP#4 - NRAD#2	0.1683	(0.1120, 0.2246)	-0.0389	(-0.0515, -0.0264)	-8.19	<0.001
GEE	0.1629	(0.0762, 0.2397)	-0.0391	(-0.0560, -0.0222)		
OP#4 - NRAD#3	0.1749175	(0.1165, 0.2334)	-0.0445	(-0.0560, -0.0330)	-8.05	<0.001
GEE	0.1679	(0.0831, 0.2527)	-0.0443	(-0.0609, -0.0276)		
OP#5 - NRAD#1	0	(-0.0624, 0.0624)	0.0197	(0.0024, 0.0370)	-3.29	<0.001
GEE	-0.0078	(-0.1056, 0.0901)	0.0195	(-0.0016, 0.0405)		
OP5# - NRAD#2	0.1848	(0.1251, 0.2445)	-0.0578	(-0.0717, -0.0439)	-5.99	<0.001
GEE	0.1810	(0.0937, 0.2682)	-0.0575	(-0.0756, -0.0394)		
OP#5 - NRAD#3	0.1914	(0.1312, 0.2516)	-0.0633	(-0.0760, -0.0507)	-5.41	<0.001
GEE	0.1859	(0.1007, 0.2712)	-0.0627	(-0.0806, -0.0448)		

References

1. Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. Lancet. 2000;355(9216):1670-4.
2. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. The New England journal of medicine. 2015;372(11):1019-30.
3. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. The New England journal of medicine. 2015;372(24):2296-306.
4. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. The New England journal of medicine. 2015;372(24):2285-95.
5. Menon BK, Puetz V, Kochar P, Demchuk AM. ASPECTS and other neuroimaging scores in the triage and prediction of outcome in acute stroke patients. Neuroimaging clinics of North America. 2011;21(2):407-23, xii.
6. Menon BK, Smith EE, Modi J, Patel SK, Bhatia R, Watson TW, et al. Regional leptomeningeal score on CT angiography predicts clinical and imaging outcomes in patients with acute anterior circulation occlusions. AJNR American journal of neuroradiology. 2011;32(9):1640-5.
7. Bentley P, Ganesalingam J, Carlton Jones AL, Mahady K, Epton S, Rinne P, et al. Prediction of stroke thrombolysis outcome using CT brain machine learning. Neuroimage Clin. 2014;4:635-40.
8. James Hampton-Till MH, Anna Luisa Kühn, , Oliver Anderson DS, Sharon Tysoe, Eric Greveson,, Michalis Papadakis IQG. Automated Quantification of Stroke damage on brain computed tomography scans: e-ASPECTS. European Medical Journal. 2015;2015;3[1]:69-74.
9. Herweh C., Ringleb P.A., Rauch G., Gerry S., Behrens L., Möhlenbruch M., et al. Performance of e-ASPECTS software in comparison to that of stroke physicians on assessing CT scans of acute ischemic stroke patients. Int J Stroke. 2016 Jun;11(4):438-45.
10. Lu Y, Jin H, Genant HK. On the non-inferiority of a diagnostic test based on paired observations. Statistics in medicine. 2003;22(19):3029-44.
11. Genders TS, Spronk S, Stijnen T, Steyerberg EW, Lesaffre E, Hunink MG. Methods for calculating sensitivity and specificity of clustered data: a tutorial. Radiology. 2012;265(3):910-6.

12. Bonett D, Price R. Adjusted Wald Confidence Interval for a Difference of Binomial Proportions Based on Paired Data. Journal of Educational and Behavioural Statistics. 2012;37(No. 4):479-88.

13. Campbell BC, Donnan GA, Lees KR, Hacke W, Khatri P, Hill MD, et al. Endovascular stent thrombectomy: the new standard of care for large vessel ischaemic stroke. The Lancet Neurology. 2015;14(8):846-54.

14. Balami JS, Sutherland BA, Edmunds LD, Grunwald IQ, Neuhaus AA, Hadley G, et al. A systematic review and meta-analysis of randomized controlled trials of endovascular thrombectomy compared with best medical treatment for acute ischemic stroke. International journal of stroke : official journal of the International Stroke Society. 2015.

15. Wahlgren N, Moreira T, Michel P, Steiner T, Jansen O, Cognard C, et al. Mechanical thrombectomy in acute ischemic stroke: Consensus statement by ESO-Karolinska Stroke Update 2014/2015, supported by ESO, ESMINT, ESNR and EAN. International journal of stroke : official journal of the International Stroke Society. 2016;11(1):134-47.

16. Warach SJ, Luby M, Albers GW, Bammer R, Bivard A, Campbell BC, et al. Acute Stroke Imaging Research Roadmap III Imaging Selection and Outcomes in Acute Stroke Reperfusion Clinical Trials: Consensus Recommendations and Further Research Priorities. Stroke 2016;47:1389-1398.

17. Grotta JC, Hacke W. Stroke Neurologist's Perspective on the New Endovascular Trials. Stroke; a journal of cerebral circulation. 2015;46(6):1447-52.