AUTOMATED QUANTIFICATION OF STROKE DAMAGE ON BRAIN COMPUTED TOMOGRAPHY SCANS: e-ASPECTS

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ABSTRACT

Emergency radiological diagnosis of acute ischaemic stroke requires the accurate detection and appropriate interpretation of relevant imaging findings. Non-contrast computed tomography (CT) provides fast and low-cost assessment of the early signs of ischaemia and is the most widely used diagnostic modality for acute stroke. The Alberta Stroke Program Early CT Score (ASPECTS) is a quantitative and clinically validated method to measure the extent of ischaemic signs on brain CT scans. The CE-marked electronic-ASPECTS (e-ASPECTS) software automates the ASPECTS score. Anglia Ruskin Clinical Trials Unit (ARCTU) independently carried out a clinical investigation of the e-ASPECTS software, an automated scoring system which can be integrated into the diagnostic pathway of an acute ischaemic stroke patient, thereby assisting the physician with expert interpretation of the brain CT scan. Here we describe a literature review of the clinical importance of reliable assessment of early ischaemic signs on plain CT scans, and of technologies automating these processed scoring systems in ischaemic stroke on CT scans focusing on the e-ASPECTS software. To be suitable for critical appraisal in this evaluation, the published studies needed a sample size of a minimum of 10 cases. All randomised studies were screened and data deemed relevant to demonstration of performance of ASPECTS were appraised. The literature review focused on three domains: i) interpretation of brain CT scans of stroke patients, ii) the application of the ASPECTS score in ischaemic stroke, and iii) automation of brain CT analysis. Finally, the appraised references are discussed in the context of the clinical impact of e-ASPECTS and the expected performance, which will be independently evaluated by a non-inferiority study conducted by the ARCTU.

Keywords: Ischaemic stroke, Alberta Stroke Program Early CT Score (ASPECTS), e-ASPECTS, automated, computed tomography, patient selection.

INTRODUCTION

Stroke is a devastating disease with a paramount associated social and healthcare cost. In Europe stroke is the second leading cause of mortality, with nearly 1.3 million deaths each year, and the primary cause of disability resulting in long-term residential care. On average, 0.27% of gross domestic product is spent on stroke by national health systems internationally.[1] An ischaemic stroke occurs when a blood vessel in the brain becomes blocked by a blood clot or an embolus. This prevents oxygen and nutrients from reaching nerve cells in the affected area of the brain. These nerve cells can die within minutes and the area of the body that they control may cease to function. This damage can be permanent, especially if the patient is not immediately treated.

Patients who have experienced a stroke will most likely be taken to a nearby hospital. Upon arriving at the hospital, medical staff will attempt to treat the patient, considering the clinical presentation together with information obtained from an emergency non-contrast computed tomography (CT) scan of the patient's brain.[2] The focus of immediate care for patients who have suffered a stroke is to re-establish blood flow (reperfusion) to the brain either by

- thrombolysis, administered within 4.5 hours from symptom onset with recombinant tissue plasminogen activator (rt-PA)
- endovascular treatment with stent-retrievers or aspiration within 8 hours, or
- a combination of both (bridging)

THE DIFFICULTY IN DETECTING EARLY ISCHAEMIC DAMAGE ON BRAIN NON-CONTRAST COMPUTED TOMOGRAPHY SCANS

Eligibility for stroke treatment depends not only upon time from stroke onset, but also on the extent of ischaemic damage on CT scans. Changes on the CT scan denote predominately irreversibly infarcted tissue that appears hypodense, representing the infarct core. In the first 6 hours following stroke onset, stroke detection is challenging[3] and requires significant expertise, as only subtle signs of cerebral ischaemia are present on CT. These include hyperdense artery sign, the insularribbon sign, obscuration of the lentiform nucleus, blurring of grey—white matter differentiation, and sulcal effacement.[4] Even amongst experts quantification of these signs remains highly reader dependent with significant inter and intra-reader variability.[5-7]

Kunst et al.[8] describe that detection of signs of early ischaemia on non-contrast CT is influenced by several factors. These include the severity of the infarct, as measured by clinical examination and National Institutes of Health Stroke Scale (NIHSS), and the time between symptom onset and imaging. The studies that the authors reviewed demonstrated that the detection rate for signs of early ischaemia within the 3-hour time window is 67% or less in most trials, and may be as low as 31%. At 6 hours the rate of detection increased to approximately 82%, but this is outside the therapeutic window for intravenous (IV) rt-PA.

Lack of Experts

A consultant neuroradiologist should ideally carry out proper assessment of the patients' CT scans. However, many hospitals in the UK and around the world do not have 24/7 access to an expert neuroradiologist. Therefore, they are unable to provide an optimal stroke service as they inevitably rely on non-expert interpretation of CT scans during the therapeutic time window.

Inter-Reader Variability

There is discussion on the inter-reader variability in quantifying the extent of infarction. Even experienced clinicians show only 39% agreement in identifying if ischaemic changes on non-contrast CT involve greater than one-third of the middle cerebral artery (MCA) territory.[5] Mullins et al.[9] conducted a systematic review of CT scan interpretation by visual inspection of the scan. It highlighted the general lack of definitions for early infarction signs. Investigators in a substantial proportion of the studies did not define the infarction signs they sought. Looking at the literature it becomes clear that a standardised evaluation method is needed in acute ischaemic stroke.[10-13]

THE DEVELOPMENT OF THE ASPECTS SCORE

The European Cooperative Acute Stroke Study (ECASS) pioneered the importance of assessing early ischaemic changes (EIC) to predict benefit from thrombolysis and introduced the 'one-third' rule.[8] A post-hoc analysis suggested that the extent of EIC is an important predictor of the response to IV thrombolysis.[3] Increased risk of symptomatic intracranial haemorrhage (sICH) was confirmed in secondary analysis of the ECASS-2 CT scans.[14] Given the difficulties with the reliability of the one-third MCA rule[15] the Calgary Stroke Program developed the Alberta Stroke Program Early CT Score (ASPECTS) as a systematic approach to assessing EIC on non-contrast CT.[16] ASPECTS enables a quantitative evaluation of early ischaemic changes in the MCA territory.

The overall inter-observer agreement of ASPECTS seems good compared with that of the one-third MCA rule and provides a systematic method to analyse head CT scans. Clinician agreement was shown to be superior to that of the one-third MCA rule.[10]

ASPECTS is a topographic scoring system that divides the brain hemisphere affected by stroke into ten regions of interest. Areas are weighted according to functional importance with equal weighting given to smaller structures and larger cortical areas. The score is calculated from evaluation of two standardised levels of the affected hemisphere: the basal ganglia level, which includes the caudate, insula, internal capsule, lentiform, and M1-M3, and the supraganglionic level, which includes M4-M6. For each of the defined regions, a single point is subtracted for an area of early ischaemic damage, such as loss of grey—white matter interface, focal swelling, and parenchymal hypoattenuation. Parenchymal hypoattenuation is defined as a region of abnormally decreased attenuation of brain structures relative to attenuation of other parts of the same structures or of the contralateral hemisphere. Focal brain swelling or mass effect is defined as any focal narrowing of the cerebrospinal fluid space due to compression by adjacent structures, such as ventricular compression or effacement of cortical sulci. An ASPECTS score of zero indicates diffuse ischaemic damage. A normal CT scan is assigned an ASPECTS score of ten.

Clinical Validation of the ASPECTS Score as a Selection Tool for Intravenous Thrombolysis

The ASPECTS score is recommended by the American Society of Neuroradiology[17] and was shown to be a reliable and strong predictor of functional outcome and sICH following thrombolytic treatment.[10,16,18,19] Clinical studies have demonstrated that patients with an ASPECTS score >7 were most likely to benefit from treatment,[18] while those scoring <5 were unlikely to see any improved outcome and were exposed to a significantly higher risk of sICH following thrombolysis.[20]

Clinical Validation of the ASPECTS Score as a Selection Tool for Endovascular Treatment

The most relevant study regarding ASPECTS as a selection tool for endovascular stroke treatment is the ESCAPE trial.[21] Patients were selected for treatment by a pre-specified ASPECTS range of 6-10, thereby identifying patients with a small infarct core. In the majority of other trials, ASPECTS has been applied post-hoc, which is of far less clinical significance. In the Interventional Management of Stroke (IMS-1) study, patients with an ASPECTS score >7 were more likely to benefit from the combined IV-intra-arterial (IA) approach than from IV rt-PA alone (based on matched patients from the National Institute of Neurological Disorders and Stroke rt-PA study ASPECTS analysis), with the number needed to treat at ten.[22] Patients with an ASPECTS score of <8 were less likely to benefit from combined IV-IA than from IV thrombolysis, and more likely to be harmed by interventional therapy. Overall, these data are evidence of both a qualitative and quantitative interaction effect with ASPECTS.

AUTOMATION OF BRAIN COMPUTED TOMOGRAPHY ANALYSIS

Recently a new software, e-ASPECTS (Brainomix Ltd., Oxford, UK), for automated detection of acute ischaemic stroke using the validated ASPECTS score was introduced.[23] An independent clinical validation study was conducted by Anglia Ruskin University comparing the performance of the software with expert neuroradiologists. The aim of this study was to demonstrate that e-ASPECTS is non-inferior to experienced neuroradiologists. The CE-marked e-ASPECTS software has been developed to automate the ASPECTS scoring system for ischaemic stroke patients. The algorithm processes brain CT scans in a similar way to a human expert, applying the ASPECTS score. It takes non-contrast brain CT scans as input; the patient's brain is registered to an atlas so that anatomical features of the brain can be recognised and the ASPECTS regions segmented from the 3D data set. A scoring module then looks at each region for signs of ischaemic damage, and the ASPECTS score is generated with a report detailing the overall ASPECTS score, as well as which regions were found to contain ischaemic damage (Figure 1). There is overall agreement in the literature that a standardised, independent, and automated CT assessment tool is needed and could positively impact patient care, although all other publications identified present technologies that have been developed in a research environment with no intention for clinical use.

The first approach to automate stroke detection on CT scans simply compared the whole left-hand side of a brain CT scan with the right-hand side.[24]

Figure 1: Automated scoring output of the electronic Alberta Stroke Program Early CT Score (e-ASPECTS) web interface.
There is fresh ischaemic damage in the left caudate and lentiform. The ASPECTS score is 8.

The proposed method consisted of image enhancement, detection of midline symmetry, and classification of abnormal slices. A windowing operation was performed on the intensity distribution to enhance the region of interest. A two-level classification scheme was used to detect abnormalities using features derived in the intensity and the wavelet domain. The proposed method was evaluated on a limited dataset of 15 patients, giving 90% accuracy and 100% recall in detecting abnormality at patient level. Average precision of 91% and recall of 90% at the slice level was described. The surprisingly high sensitivity and specificity on this small dataset possibly indicates over-fitting.

Tang et al.[25] proposed a novel 'circular adaptive region of interest' method to analyse CT images of the brain. Results indicated that for emergency physicians and radiology residents there was a significant improvement in sensitivity and specificity when using computer-aided detection ($p<0.005$). The authors used an image-feature approach for computer-aided detection of ischaemic stroke with well-described results. Compared with e-ASPECTS the approach was limited to detection of stroke versus no detection, i.e. there is no consideration of the extent of damage.

Boers et al.[26] used a semi-automated delineation of follow-up CT scans. The cerebral infarct volumes of 34 consecutive patients were segmented with an automated, intensity-based, region-growing algorithm, which included partial volume effect correction near the skull, midline determination, and ventricle and haemorrhage exclusion. Damage was assessed based on a seed point selected by a radiologist, thus not addressing the subtle, early ischaemic changes that e-ASPECTS looks for. The Pearson correlation for the automated method compared with the reference standard was similar to the manual correlation (R=0.98). The accuracy of the automated method had a mean difference of 0.5 ml with limits of agreement of -38.0-39.1 ml, which were more consistent than the inter-observer variability of the two observers (-40.9-44.1 ml). However, the Dice coefficients were higher for the manual delineation. The performance was very slow with the technique apparently taking 2 hours per scan.

Rajini et al.[27] looked for small infarcts (e.g. lacunes) only. The proposed method consists of pre-processing, segmentation, tracing the midline of the brain, extraction of texture features, and classification. The application improved efficiency and accuracy of clinical practice with an average overlap metric, average precision, and average recall between the results obtained to the ground truth of 0.98, 0.99, and 0.98, respectively. From the publication it was not clear if the authors had separate training and test sets. The algorithm only tested for the presence or absence of damage on a per-slice basis. The authors only tested a small dataset with the results probably indicating over-fitting.

Bentley et al.[28] evaluated a tool for prediction of sICH following thrombolysis. CT images acted as input into a support vector machine (SVM), along with non-image features (specifically NIHSS score). Predictive performance compared favourably with that of prognostic scores (original and adapted versions: 0.626-0.720; $p<0.01$). The SVM also identified 9 out of 16 sICHs as opposed to 1-5 using prognostic scores, assuming a 10% sICH frequency ($p<0.001$). The dataset appears to be of an adequately high number (n=106), but the algorithm was only tested via cross-validation, which can lead to over-fitting. The authors acknowledged that they could improve their image analysis by using image features rather than all the voxels, which is what e-ASPECTS does with a variety of image features.

Przelaskowski et al.[29] described a system for image enhancement to improve interpretation by the human eye. The system defines a 'stroke window' that adjusts the contrast of the image to better show hypodense areas. They did not automate the actual detection of damage, that is left to radiologists, but the publication does demonstrate that radiologists performed better when looking at their system.

Shieh et al.[30] developed an automatic ASPECTS scoring system using contralateral comparison. Receiver operating characteristic analysis based on evaluation of 103 patients with symptoms of acute stroke showed that the system's dichromatic classification of patients into thrombolysis-indicated or thrombolysis-contraindicated groups achieved a high accuracy, with area under curve equal to 90.2%. The average processing time for a single case was 170 seconds.

CONCLUSION

This literature review underlines the need for standardised image interpretation to identify appropriate treatment options in acute stroke management that translate into clinical benefits for patients. Imaging of the brain parenchyma is a composite surrogate for time elapsed from stroke onset and collateral status, as well as severity of ischaemia and extent of thrombus. However, it must be remembered that imaging is only one factor in a complex equation. Even expert physicians in current practice will often not agree on treatment decisions. As such, they will never use ASPECTS or e-ASPECTS in isolation, but will use it as complementary information.

In the hyperacute setting, ASPECTS has been validated as a predictor of functional outcome in acute ischaemic stroke patients receiving IV alteplase and endovascular treatment. Therefore, integration of the ASPECTS score into a clinical care pathway as a decision-support tool would be reasonable. However, the required expertise that the manual application of ASPECTS carries can limit its use in clinical care. In addition, intra and inter-observer variability is an issue not only in the clinical environment but also in clinical trial enrolment when using image selection criteria. The development of the e-ASPECTS software enables fast and standardised assessment of the brain CT scan using the validated ASPECTS score irrespective of the expertise of the interpreter, thus eliminating inter and intra-observer variability. It will be of great value to assess how standardised use of ASPECTS translates into long-term outcomes that are meaningful to patients in terms of overall health status, functional ability, cognition, and quality of life.

The conclusions about the performance and safety of ASPECTS outlined in this literature review are intended to represent the consensus of a global forum of stroke experts, and to provide a framework for the assessment of acute stroke care provision, using the CE-marked, standardised software e-ASPECTS, with regard to access to care and patient outcomes in both the hyperacute and acute hospital setting, as well as in clinical trial enrolment. The e-ASPECTS non-inferiority study will provide the necessary evidence to demonstrate the reliable performance of e-ASPECTS in a clinical setting.

REFERENCES

1. Evers SM et al. International comparison of stroke cost studies. Stroke. 2004;35(5):1209-15.

2. Lev MH et al. Acute stroke: improved nonenhanced CT detection--benefits of soft-copy interpretation by using variable window width and center level settings. Radiology. 1999;213(1):150-5.

3. Patel SC et al. Lack of clinical significance of early ischemic changes on computed tomography in acute stroke. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. JAMA. 2001;286(22):2830-8.

4. Grunwald IQ, Reith W. Non-traumatic neurological emergencies: imaging of cerebral ischemia. Eur Radiol. 2002;12(7):1632-47.

5. Grotta JC et al. Agreement and variability in the interpretation of early CT changes in stroke patients qualifying for intravenous rtPA therapy. Stroke. 1999;30(8):1528-33.

6. Wardlaw JM et al. Can stroke physicians and neuroradiologists identify signs of early cerebral infarction on CT? J Neurol Neurosurg Psychiatry. 1999;67(5):651-3.

7. Kalafut MA et al. Detection of early CT signs of >1/3 middle cerebral artery infarctions: interrater reliability and sensitivity of CT interpretation by physicians involved in acute stroke care. Stroke. 2000;31(7):1667-71.

8. Kunst MM, Schaefer PW. Ischemic stroke. Radiol Clin North Am. 2011; 49(1):1-26.

9. Mullins ME et al. Influence of availability of clinical history on detection of early stroke using unenhanced CT and diffusion-weighted MR imaging. AJR Am J Roentgenol. 2002;179(1):223-8.

10. Pexman JH et al. Use of the Alberta Stroke Program Early CT Score (ASPECTS) for assessing CT scans in patients with acute stroke. AJNR Am J Neuroradiol. 2001;22(8):1534-42.

11. Menon BK et al. ASPECTS and other neuroimaging scores in the triage and prediction of outcome in acute stroke patients. Neuroimaging Clin N Am. 2011;21(2):407-23.

12. von Kummer R et al. Acute stroke: usefulness of early CT findings before thrombolytic therapy. Radiology. 1997;205(2):327-33.

13. Baek JH et al. Predicting Stroke Outcome Using Clinical- versus Imaging-based Scoring System. J Stroke Cerebrovasc Dis. 2015;24(3):642-8.

14. Hacke W et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). JAMA. 1995;274(13): 1017-25.

15. Mak HK et al. Hypodensity of >1/3 middle cerebral artery territory versus Alberta Stroke Programme Early CT Score (ASPECTS): comparison of two methods of quantitative evaluation of early CT changes in hyperacute ischemic stroke in the community setting. Alberta Stroke Programme Early CT Score. Stroke. 2003;34(5):1194-6.

16. Barber PA et al. 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.

17. Canadian Stroke best practice recommendations. Acute Thrombolytic Therapy 4th edition. 23rd May 2013. www.strokebestpractices.ca/index.php/hyperacute-stroke-management/acute-thrombolytic-therapy-2. Last accessed March 2015.

18. Hill MD, Buchan AM. Thrombolysis for acute ischemic stroke: results of the Canadian Alteplase for Stroke Effectiveness Study. Canadian Alteplase for Stroke Effectiveness Study (CASES) Investigators. CMAJ. 2005;172(10): 1307-12.

19. Shobha N et al. Thrombolysis at 3-4.5 hours after acute ischemic stroke onset--evidence from the Canadian Alteplase for Stroke Effectiveness Study (CASES) registry. Cerebrovasc Dis. 2011;31(3): 223-8.

20. Larrue V et al. Risk factors for severe hemorrhagic transformation in ischemic stroke patients treated with recombinant tissue plasminogen activator: a secondary analysis of the European-Australasian Acute Stroke Study (ECASS II). Stroke. 2001;32(2):438-41.

21. Goyal M et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med. 2015;372(11):1019-30.

22. Demchuk AM et al. Importance of early ischemic computed tomography changes using ASPECTS in NINDS rtPA Stroke Study. NINDS rtPA Stroke Study Group, NIH. Stroke. 2005;36(10):2110-5.

23. 9th World Stroke Congress, 22-25 October 2014, Istanbul, Turkey. Int J Stroke. 2014;9 Suppl 3:2-331.

24. Chawla M et al. A method for automatic detection and classification of stroke from brain CT images. Conf Proc IEEE Eng Med Biol Soc. 2009;2009: 3581-4.

25. Tang FH et al. An image feature approach for computer-aided detection of ischemic stroke. Comput Biol Med. 2011;41(7):529-36.

26. Boers AM et al. Automated cerebral infarct volume measurement in follow-up noncontrast CT scans of patients with acute ischemic stroke. MR CLEAN investigators. AJNR Am J Neuroradiol. 2013;34(8):1522-7.

27. Hema Rajini N, Bhavani R. Computer aided detection of ischemic stroke using segmentation and texture features. Measurement. 2013;46(6):1865–74.

28. Bentley P et al. Prediction of stroke thrombolysis outcome using CT brain machine learning. Neuroimage Clin. 2014;4:635-40.

29. Przelaskowski A et al. Improved early stroke detection: wavelet-based perception enhancement of computerized tomography exams. Comput Biol Med. 2007;37(4):524-33.

30. Shieh Y et al. Computer-aided diagnosis of hyperacute stroke with thrombolysis decision support using a contralateral comparative method of CT image analysis. J Digit Imaging. 2014;27(3):392-406.