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ORIGINAL RESEARCH
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Automated Assessment of DWI-FLAIR Mismatch in Patients with Acute Ischemic Stroke: Added Value to Routine Clinical Practice

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ABSTRACT

BACKGROUND AND PURPOSE: DWI-FLAIR mismatch is used to determine thrombolytic eligibility in patients with acute ischemic stroke (AIS) when time since stroke onset (TSS) is unknown. Commercial software packages have been developed for automated DWI-FLAIR classification. We aimed to use e-Stroke software (Brainomix, Oxford, UK) for automated classification of DWI-FLAIR mismatch in a cohort of patients with AIS and in a comparative analysis with two expert neuroradiologists.

MATERIALS AND METHODS: In this retrospective study, patients with AIS who had MRI and known TSS were included. DWI-FLAIR mismatch was evaluated by two neuroradiologists blinded to TSS and automatically by e-Stroke software. After 4 weeks, the neuroradiologists reevaluated the MRIs, this time equipped with automated predicted e-Stroke results as a computer assisted tool (CAT). Diagnostic performances of e-Stroke software and neuroradiologists were evaluated for prediction of DWI-FLAIR mismatch status.

RESULTS: A total of 157 patients met inclusion criteria. A total of 82 patients (52%) had TSS ≤ 4.5 hours. Using consensus reads, 81 patients (51.5%) had DWI-FLAIR mismatch. The diagnostic accuracy (AUC/sensitivity/specificity) of e-Stroke software for determination of DWI-FLAIR mismatch was 0.72/90.0/53.9. The diagnostic accuracy (AUC/sensitivity/specificity) for neuroradiologist 1 and 2 was 0.76/69.1/84.2 and was 0.82/91.4/73.7 respectively, both significantly ($p<0.05$) improved to 0.83/79.0/86.8 and 0.89/92.6/85.5 respectively following the use of e-Stroke predictions as CAT. The interrater agreement (K) for determination of DWI-FLAIR status was improved from 0.49 to 0.57 following the use of CAT.

CONCLUSIONS: Automated quantitative approach for DWI-FLAIR mismatch provides comparable results to human experts and can improve diagnostic accuracies of expert neuroradiologists in determination of DWI-FLAIR status.

ABBREVIATIONS: AIS: Acute ischemic stroke; CAT: Computer assisted tool; TSS: Time since stroke onset.

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SUMMARY SECTION

PREVIOUS LITERATURE: In patients with acute ischemic stroke (AIS), DWI-FLAIR mismatch has been used as an imaging biomarker for tissue clock that can guide and expand the use thrombolytic therapies. However, due to its binary nature, DWI-FLAIR mismatch is subjected to modest interobserver agreement and limited reproducibility among human interpreters since heterogenous and wide range of FLAIR signal may be present within an infarction bed. Advances in image segmentation and quantitative analysis of MR imaging hold promise for automated analysis in determination of DWI-FLAIR status as they are made available commercially.

KEY FINDINGS: Automated DWI-FLAIR status assessed by e-Stroke software provides improved diagnostic accuracy and interrater

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agreement for determination of tissue clock when used in conjunction by human interpreters. Significant ($p<0.05$) improvement in diagnostic assessment of DWI-FLAIR status achieved for both neuroradiologists after using e-Stroke software predictions as computer assisted tool.

KNOWLEDGE ADVANCEMENT: Fully automated quantitative approach provided by e-Stroke software can improve the diagnostic performance of neuroradiologists in assessment of DWI-FLAIR mismatch in patients with AIS. If its potential is realized, it can be used to supplant human interpretation to aid thrombolytic decision making equally in all patients.

INTRODUCTION

In patients with acute ischemic stroke (AIS), stroke-onset time (TSS) < 4.5 hours has been used as a criterion for thrombolytic eligibility < 4.5[1]. Recently, advanced imaging has played a critical role in showing that a greater number of patients may benefit from thrombolytic therapy when using a "tissue clock" concept rather than considering TSS alone. For example, in EXTEND (Extending the Time for Thrombolysis in Emergency Neurological Deficits) trial [2], perfusion imaging was successfully used to extend the thrombolytic window up to 9 hours in patients who had salvageable brain tissue.

DWI-FLAIR mismatch has been used as a tissue clock imaging biomarker that may better guide appropriate use of thrombolytic therapy than TSS alone[1, 3]. Generally, stroke lesions become more visible on FLAIR images as time passes from stroke onset. This concept was used in the design of WAKE UP trial (A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial to Test Efficacy and Safety of Magnetic Resonance Imaging-Based Thrombolysis in Wake-up Stroke) [3], which showed the benefit of thrombolytic treatment in AIS patients with unknown onset or wake up stroke as long as they had DWI-FLAIR mismatch. However, DWI-FLAIR mismatch has some limitations. These include its subjective nature that introduces variability among human interpreters, which may in part depend on the level of expertise. A binary reporting standard of negative or positive is also limiting since the signal intensity difference between DWI and FLAIR often has a range and may be weakly positive or weakly negative rather than absolute. These limitations have resulted in modest interobserver agreement and diagnostic accuracies[4, 5].

Advances in image segmentation and machine learning (ML) techniques have shown promising results in an automated analysis of MR images to determine DWI-FLAIR status [6, 7,8]. In this study, we aimed to use an automated image segmentation algorithm that is now commercially available (e-Stroke software, Brainomix, Oxford, UK) to automatically classify DWI-FLAIR mismatch in a cohort of patients with AIS and to perform a comparative analysis with expert neuroradiologists. Specifically, the following was performed: 1) Comparison of the diagnostic accuracy of e-stroke DWI-FLAIR mismatch output with expert neuroradiologists in determination of TSS; 2) Assessment of the diagnostic accuracy of e-stroke DWI-FLAIR mismatch output in prediction of tissue-clock as determined by consensus reads of two experts neuroradiologists; 3) Evaluation of the added value of e-Stroke DWI-FLAIR mismatch output when used as computer-assisted tool to the diagnostic performance of experts neuroradiologists.

MATERIALS AND METHODS

Study Design and Patient Selection

In this retrospective study, consecutive patients with AIS who had pretreatment MRI and known TSS were included between September 2011 to August 2021. Institutional review board approval was obtained. The clinical characteristics such as age, sex, NIHSS, TSS and time to imaging (MRI), and location of arterial occlusion if known were documented. Patients were excluded if they had unknown or questionable TSS and poor MR image quality that impaired diagnostic evaluation by neuroradiologists.

Image Acquisition

MR imaging was performed on either a 1.5T MR scanner (Avanto, Siemens, Erlangen, Germany) or a 3T MR scanner (Trio, Siemens, Erlangen, Germany) within our hospital. DWI was acquired using a single-shot spin-echo EPI sequence (TR/TE, 4900/98 ms [1.5T] or 4100/95 ms [3T]; FOV, 220 × 220 mm; matrix, 128 × 128 mm; slices, 30 × 5 mm). Diffusion gradients were applied along 3 orthogonal directions with b=0 and 1000 s/mm2. The FLAIR images were acquired using a TR/TE of 9000/89 ms at 1.5T and 9000/122 ms at 3.0T; matrix, 256 × 256 mm; slices, 30 × 5 mm. The inversion time (TI) was 2504 ms at 1.5T and 2500 ms at 3.0T.

Image Analysis

For automated image analysis, MR diffusion and FLAIR images were uploaded to e-Stroke software (Brainomix, Oxford, UK) (e-MRI module, version 11.1) for automated image processing and quantitative analysis. The software used an ADC threshold of 620 ×10−6 mm2 to guide segmentation and generated a volume of interest that was used as an infarction mask [9]. The FLAIR images were spatially realigned in three dimensions with b0 image from the DWI dataset. The process of realignment used a standard 3D rigid registration to determine the image transformation function with 6 degrees of freedom consisting of 3 rotations and 3 translations [10, 11]. Then, the co-registered flipped FLAIR images were used to compute the voxel-wise relative FLAIR maps. The co-registered flipped FLAIR images were first smoothed with a 3D median filter (size: 7mm, 7mm, 1mm in x, y, z dimension). Tissue masks were generated by thresholding the b0 image to remove the CSF. The threshold was obtained by K-means algorithm to group the voxels within the brain mask region to two clusters (CSF range and tissue range) [12]. For each voxel within the brain, the voxel value from the intensity normalized FLAIR image was divided by the corresponding intensity value in its contralateral voxel and resulted in a relative FLAIR map. Voxel-based relative signal

intensity ratios (rSIR) from the infarction mask were computed from these relative FLAIR maps and the values were reported as median and inter quartile range within the infarction mask. Following calculation of rSIRs, the software automatically assigned each case as match or mismatch using median rSIR cutoff of ≥1.15 for match [13].

Two board-certified neuroradiologists (with 10 and 18 years of experience) blinded to TSS and the results of automated analysis independently assessed the MRI studies to classify DWI-FLAIR mismatch status for each patient. Mismatch was assigned when there was reduced diffusion on DWI with no signal on FLAIR and match-assignment was for cases where there was corresponding FLAIR signal along the infarction territory. All disagreements were subsequently resolved by consensus between two neuroradiologists. This consensus read was used as the reference of standard for assessment of diagnostic accuracy.

In a subsequent follow up analysis approximately 4 weeks after the initial readout session, the neuroradiologists were instructed to reclassify the DWI-FLAIR mismatch status while using e-Stroke predicted results as a computer-assisted tool (CAT).

The final consensus reads of two neuroradiologists were used as the reference of standard for final assignment of DWI-FLAIR mismatch status.

Statistical Analysis

Data were presented as mean ± SD for continuous data and as median- interquartile range (IQR) with relative frequencies (percentages) for categorical data. Receiver operator characteristic (ROC) analysis was performed, and the area under the curve was calculated for the prediction of TSS and tissue clock with accuracy measures including sensitivity and specificity. Interobserver agreement between readers was evaluated using a weighted kappa test. For prediction of TSS, the accuracy of DWI-FLAIR mismatch status was compared against dichotomized stroke-onset time using TSS ≤ 4.5 or > 4.5 hours. For prediction of tissue-clock, the consensus reads of two neuroradiologists were used as the standard of reference. The diagnostic performance of e-Stroke software, and each neuroradiologists before and after using e-Stroke as CAT were then analyzed against the consensus reads. Added value of e-Stroke predictions to accuracy of each neuroradiologist was evaluated using comparative ROC analysis and tested by Delong test. The significance level was defined as $p<0.05$. Statistical analyses were performed with MedCalc® statistical software (version 20.008, MedCalc Software Ltd, Ostend, Belgium).

RESULTS

Clinical Characteristics of Patient Population

A total of 157 patients met our inclusion criteria. Average age (mean ± SD) was 68.7± 16.3 years, and a total of 79 (50.3%) were female. The severity of stroke determined by NIHSS (median, IQR) was 10 (5-16). A total of 151 (96%) patients had an identifiable intracranial arterial occlusion, including of the internal carotid artery (n=18, 11.5%), M1 (n=100, 63.7%), M2 (n=19, 12%), anterior cerebral artery (n=2, 1.2%), or posterior cerebral artery (n=12, 7.6%). Three (2%) patients had lacunar infarction and the other 3 (2%) patients had multiple small foci of infarctions in more than two vascular territories likely related to embolic shower. The infarct volume was 18.0 ± 25.6 ml (mean ± SD). TSS was 267.4 ± 269.2 min (mean ± SD). Using 4.5 hours as a threshold for thrombolytic treatment eligibility, a total of 75 (48%) patients had TSS > 4.5 hours, while 82 (52%) patients had TSS ≤ 4.5 hours.

Determination of DWI-FLAIR status

Automated image analysis by e-Stroke software using FLAIR rSIR showed matched DWI-FLAIR in 49 patients and mismatch in 108 patients. Neuroradiologis-1 assigned 89 patients as matched and 68 patients as mismatched while neuroradiologist-2 identified 63 matched and 94 as mismatched for DWI-FLAIR status. The interobserver agreement for determination of DWI-FLAIR mismatch status was moderate (K, 95% CI): (0.49, 0.36-0.62).

After obtaining consensus between two readers, a total of 76 patients were assigned as matched and 81 patients as mismatched, which was used as the reference for assessment of diagnostic performance.

Diagnostic accuracy (AUC/sensitivity/specificity) of e-Stroke software for determination of DWI-FLAIR mismatch against consensus reads was 0.72/90.0/53.9 ($p<0.001$).

For neuroradiologist 1, the diagnostic performance (AUC/sensitivity/specificity) of the initial interpretation was 0.76/69.1/84.2 which was significantly ($p=0.003$) improved to 0.83/79.0/86.8 in the second interpretation following the use of e-Stroke predictions as CAT.

For neuroradiologist 2, the diagnostic performance (AUC/sensitivity/specificity) of the initial interpretation was 0.82/91.4/73.7 which was significantly ($p=0.005$) improved 0.89/92.6/85.5 after using e-Stroke predictions as CAT.

The interrater agreement (K, 95% CI) for determination of DWI-FLAIR status following the use of CAT was also modestly improved to 0.57 (0.44-0.72).

Table 1 shows the breakdown of correctly identified patients with matched and mismatched DWI-FLAIR status in addition to diagnostic performances for e-Stroke software, each neuroradiologists alone and in conjunction with CAT.

Figure 1 shows comparative ROC analysis for each neuroradiologist alone and in conjunction with CAT.

In a sub-analysis to assess the diagnostic performance in determination of TSS (≤ or > 4.5 hours), the AUC/sensitivity/specificity were 0.63/81.7/45.3 ($p<0.001$) for e-Stroke software, 0.67/57.3/76.0 for neuroradiologist 1 ($P<0.001$) and 0.70/69.5/70.7 for neuroradiologist 2 ($P<0.001$). There was no statistically significant difference between the neuroradiologists and e-Stroke software in prediction of TSS. Delong test showed p-values of 0.51 for e-Stroke software versus neuroradiologist 1, 0.13 for e-Stroke software versus neuroradiologists 2, and 0.38 between the two neuroradiologists.

Figure 2 shows an example of a patient with TSS < 4.5 hours who was correctly classified by both neuroradiologists as DWI-FLAIR mismatch and automatically assigned as mismatch by e-Stroke software.

Figure 3 shows an example in a patient who had weak FLAIR signal associated with infarct region resulting in discrepant interpretation of DWI-FLAIR status between two neuroradiologists during the initial assessment. This case was subsequently corrected after using e-Stroke prediction as CAT to match the consensus reads.

Table 1: The breakdown of correctly identified matched and mismatched DWI-FLAIR status in addition to diagnostic performances for e-Stroke software, each neuroradiologists alone and in conjunction with CAT.

	Consensus interpretation		AUC/Sensitivity/specificity	P value**
	* Matched (n=76)	* Mismatch (n=81)		

e-Stroke	41 (56.5%)	73 (90.1%)	0.72/90.0/53.9	<0.001
R1	64 (84.2%)	56 (69.1%)	76/69.1/84.2	<0.001
R1-CAT	66 (86.8%)	64 (79.0%)	0.83/79.0/86.8	<0.001
R2	56 (73.7%)	74 (91.3%)	0.82/91.4/73.7	<0.001
R2-CAT	65 (85.5%)	75 (92.5%)	0.89/92.6/85.5	<0.001

* Data are numbers and percentages of correctly identified patients as DWI-FLAIR matched or mismatch against final consensus read

** Indicates the significance of diagnostic performance against the consensus interpretation of two neuroradiologist using ROC analysis

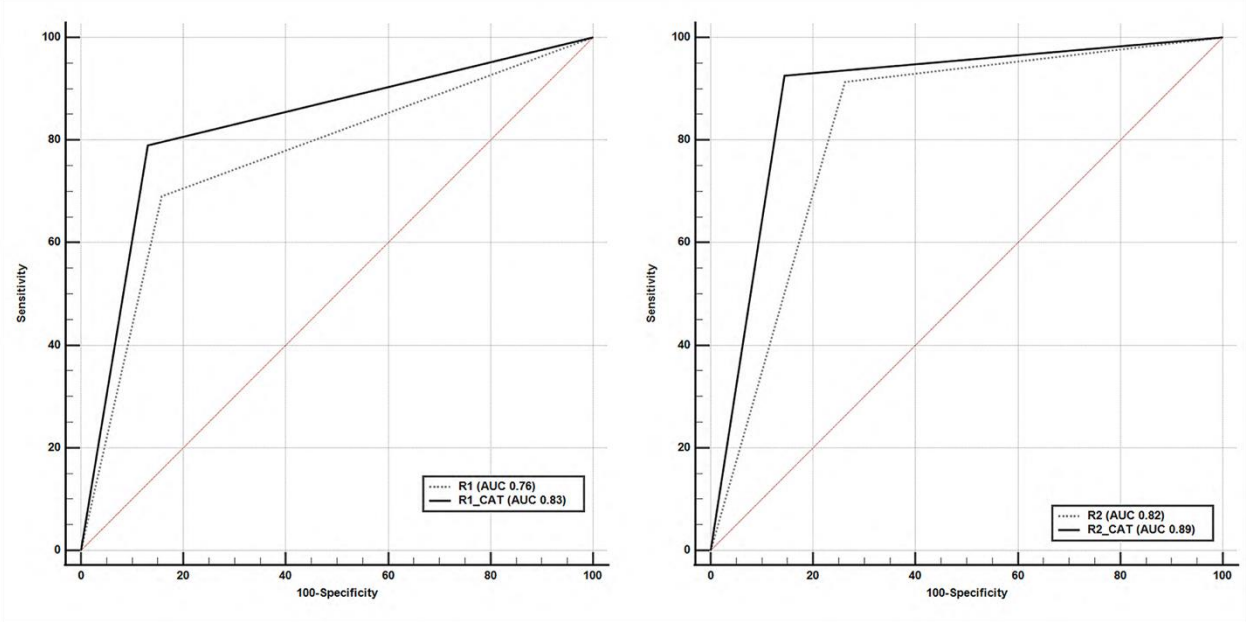

FIG 1. Comparative analysis of ROC curves for diagnostic performance of each neuroradiologist alone (R1, R2) and in conjunction with predicted results of e-Stroke software used as computer-assisted tool (CAT) (R1-CAT, R2-CAT). The diagnostic performance of both neuroradiologists in determination of DWI-FLAIR status was significantly improved when compared against the consensus interpretations.

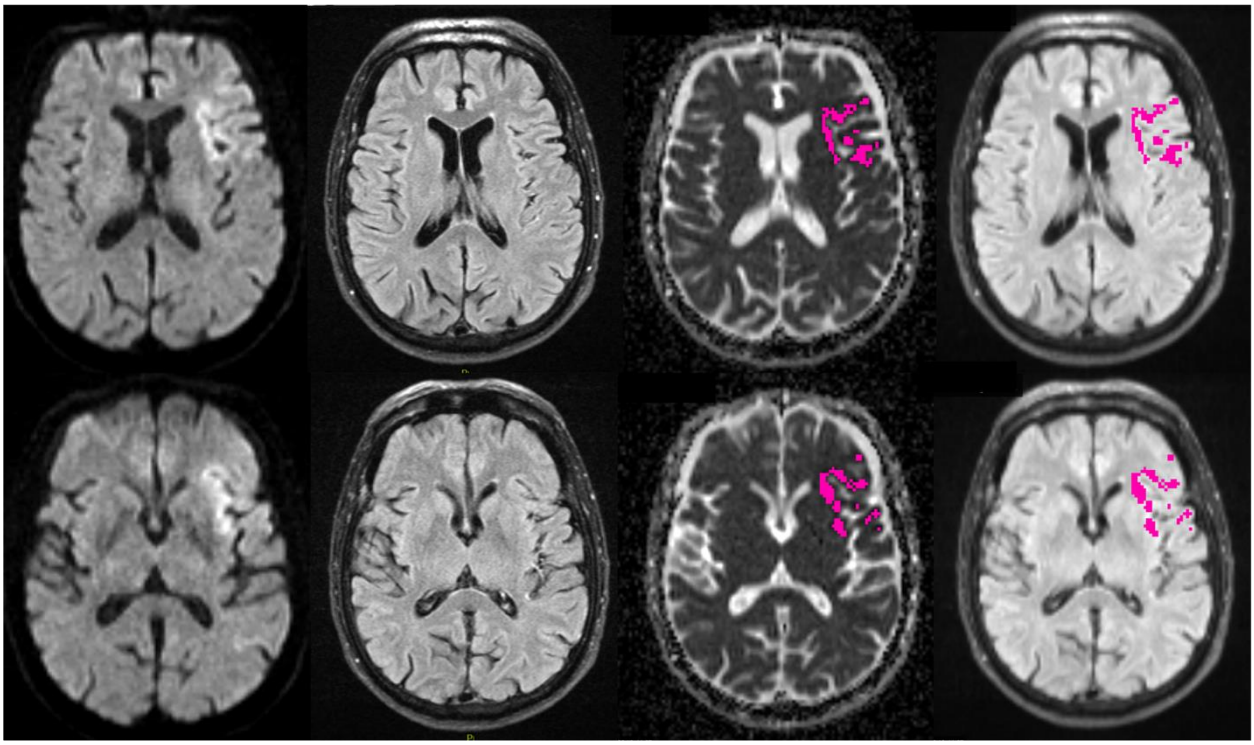

FIG 2. 73 year old man with left MCA-M1 occlusion who presented within 117 minutes from stroke onset. There is infarction involving the left frontal lobe, opercular region, and insula with reduced diffusion that is negative on FLAIR (i.e., DWI-FLAIR mismatch). The infarction was automatically segmented by e-Stroke software (highlighted in purple), and relative signal intensity of infarction bed was calculated from corresponding FLAIR images at 1.03, rendering DWI-FLAIR mismatch classification, concordant with both neuroradiologists and TSS.

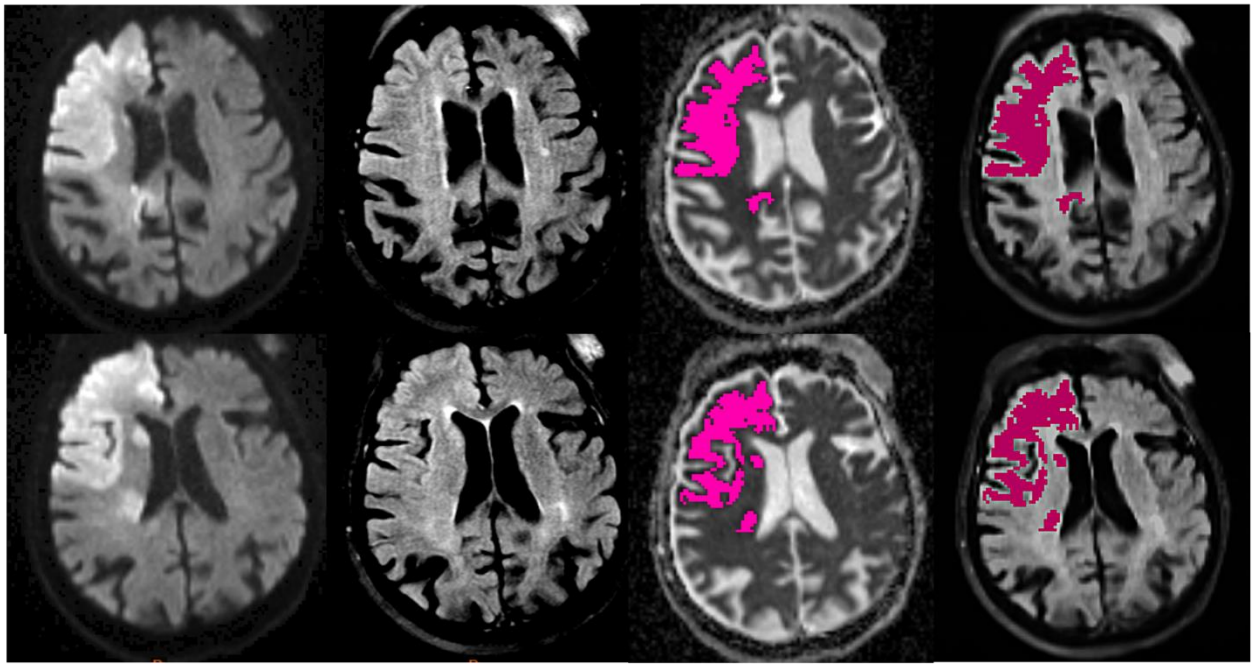

FIG 3. 90 year old woman with right internal carotid occlusion presented 190 minutes from stroke onset. The SIR calculated automatically by e-Stroke software at 1.14, rendering the correct assignment of DWI-FLAIR mismatch. The weak FLAIR signal associated with the infarct region resulted in discrepant interpretation between two neuroradiologists. However, the neuroradiologist who initially classified this case as match; changed his interpretation to mismatch after using e-Stroke software as a computer assisted tool, which was concordant with the consensus read.

DISCUSSION

Our results showed that automated image analysis afforded by advanced and streamlined image segmentation techniques that are now commercially available can provide similar results to human experts in determination of DWI-FLAIR mismatch as a biomarker for tissue clock. We would like to highlight two major findings in our results.

Our first finding is that e-Stroke software provided improved diagnostic accuracy and interrater agreement for determination of tissue clock when used in conjunction by human interpreters. Assessment of DWI-FLAIR mismatch is a difficult task that requires extensive training. Due to the binary reporting nature (negative or positive) of DWI-FLAIR mismatch, current human assessment does not consider the wide range of signal intensities on FLAIR images. The heterogeneity of FLAIR signal intensity change across the infarction bed is one of the major contributing factors resulting in inconsistent and possible disagreements in interpretation of DWI-FLAIR mismatch status [4, 5]. This limitation is reflected in modest interobserver agreement (k= 0.49), similar to previously reported values ranging from 0.4-0.6 by human observers[4, 5]. However after using e-Stroke prediction as CAT, the interrater agreement was improved to k=0.57. Furthermore the use of e-Stroke prediction as CAT resulted in significant improved in diagnostic accuracy of DWI-FLAIR mismatch (tissue-clock) assignment with approximately 10% increased sensitivity for one neuroradiologist and 11% increased specificity for the other.

Comparable diagnostic accuracies for e-Stroke software in determination of tissue clock (DWI-FLAIR mismatch) to the consensus reads of two expert neuroradiologists highlight the potential for this solution to aid thrombolytic decision making, to supplant human interpretation when used as a decision support tool. By leveraging automated analysis tools in e-Stroke, the potential benefit may be even more relevant in settings where there is lack of neuroimaging expertise to ensure efficient and consistent assessment can be obtained for treatment decisions equally in all patients.

Our second finding is that e-Stroke software provided comparable results to expert neuroradiologists in prediction of TSS using cut off value of 4.5 hours. Prior reports have shown that approximately 27%–50% of patients with stroke have positive FLAIR findings within 3 hours and 93% at > 6 hours[14-16]. Our results are concordant with the results of prior reports showing only modest sensitivity in the range of 60% for TSS prediction by human observers [15, 17, 18]. While the diagnostic performance of e-Stroke software in prediction of TSS was comparable to expert neuroradiologists, the automated TSS prediction provided by e-Stroke resulted in higher sensitivity (81.7%) in comparison to the modest sensitivity of human experts but at a cost of lower specificity.

Although the 4.5 hours cut off for TSS remains a thrombolytic eligibility criterion, there is now a transition towards accepting tissue status rather than TSS alone for thrombolytic decision making at least for patients with unknown TSS or wake up strokes[3]. In addition, there are some stroke patients who may become FLAIR positive in < 4.5 hours and others who could remain FLAIR negative even after 6 hours. Therefore, the classification of TSS based on 4.5 hours cut off is imperfect [19] and a fading cause.

Application of advanced image processing techniques and artificial intelligence has shown promising potential to provide more consistent results for prediction of TSS and DWI-FLAIR status while mitigating the variability issues related to human observers[6-8]. However, these algorithms are yet to become commercially available for broad clinical use. Automated image processing and segmentation by e-Stroke solution that is now commercially available provides an opportunity for routine use to support treatment decisions if its potential is realized in a broader clinical setting.

Our study has several limitations. First, it was a retrospective study, which may introduce unknown bias. Second, this was a single institutional study with MR images included from a limited number of scanners. Including data from multi-center studies with greater variability in image acquisition parameters and MRI scanners will be required to further generalize our results. Third, we were unable to test how e-Stroke software could affect treatment decisions in our retrospective design. In our cohort, the decision for thrombolysis was based solely on TSS, which was determined at the time of patient presentation. We did not screen for patients with extensive white matter disease, and it is plausible that underlying leukoaraiosis could confound quantitative assessment of SIR in a subset of our patients. Although the software algorithm takes into account the presence of non-normal voxels such as CSF and older white matter lesions, this potential mitigating effect of the software was not tested systematically for the presence of significant white matter disease. Lastly, the gold standard for ischemic brain tissue status was consensus reads of DWI-FLAIR mismatch by two neuroradiologists. This is less than ideal but the best practical reference of standard that could be adopted for our study since DWI-FLAIR mismatch has been used a surrogate for tissue clock.

CONCLUSIONS

In conclusion, our study demonstrates the potential diagnostic utility of a fully automated quantitative approach provided by e-Stroke software to assess DWI-FLAIR mismatch in patients with AIS. We showed that the automated software provides comparable diagnostic accuracies to expert neuroradiologists. Importantly, when used by neuroradiologists as a computer-assisted tool, the automated software significantly improved the diagnostic performance of neuroradiologists for more accurate classification of DWI-FLAIR mismatch as a surrogate for tissue clock.

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