

MRI as witness for acute stroke patients with unknown onsets

Ona Wu¹, Lawrence L Latour², Shlee S Song³, Karen L Furie⁴, Steven Warach², and Lee H. Schwamm⁴

¹Athinoula A Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Charlestown, MA, United States, ²National Institute of Neurological Diseases and Stroke, National Institutes of Health, Bethesda, MD, United States, ³Department of Neurology, Cedar Sinai Medical Center, Los Angeles, CA, United States, ⁴Department of Neurology, Massachusetts General Hospital, Boston, MA, United States

Introduction: The only current approved pharmacologic therapy for the treatment of acute ischemic stroke is intravenous (IV) alteplase given within 3 to 4.5 hours from when the patient was last known well (LKW). Approximately 25% of stroke patients have unwitnessed strokes, and therefore will typically not be eligible for alteplase treatment. Recent studies suggest that negative FLAIR MRI in conjunction with positive findings on DWI can be used to identify patients with LKW within 3 to 4.5 hours of stroke onset¹⁻⁴. However, controversy exists on the reproducibility of this technique in a clinical setting, potentially limiting its generalizability. One study reported mean kappa (κ) agreement values regarding FLAIR negativity to be only 0.29 among 4 readers³, while other studies involving 2 readers reported kappas ranging from 57%¹, 65%⁴ to 97%². It has been suggested that combining qualitative review of DWI and FLAIR MRI with region of interest (ROI) analysis can improve inter-rater agreement and increase sensitivity for identifying patients in the early stages of stroke. MR WITNESS – a multi-center, open-label, single-arm, Phase IIa clinical trial investigating the safety of giving alteplase to stroke patient with unclear onset times⁵ – uses such an algorithm that combines qualitative assessments of FLAIR MRI with quantitative ROI analysis. We sought to investigate inter-rater and inter-site agreement using this approach among several readers at different sites.

Methods: MRI datasets from patients with witnessed strokes within 24 h of LKW were analyzed. Readers were instructed to first qualitatively classify FLAIR lesions as negative or positive in regions coincident with lesions evident on either DWI (hyperintensity) or apparent diffusion coefficient (ADC) maps (hypointensity) (See Figure). The signal intensity ratio (SIR) of the mean signal intensity (SI) of an ROI on the lesion to the mean SI of an ROI on the opposite side was measured. For ROI placement, readers were instructed to: (1) choose the slice with the greatest FLAIR SI that corresponds to an acute DWI or ADC lesion; (2) select the slice that matches the largest DWI lesion if FLAIR is negative; (3) select the brightest lesion in cases of multiple areas of infarct; (4) limit imaging assessment to lesions at least 1cm in diameter in any direction (but not larger than the DWI lesion), with an exception occurring when all visible lesions are less than 1 cm in dimension; in that case ROIs should be at least 50% of the DWI lesion. Patients were classified as exhibiting MRI patterns consistent with early stage stroke (≤ 3.5 hours from onset) if either FLAIR was negative OR $SIR < 1.15$. Readers at two sites were trained on ten cases, for which example ROIs and FLAIR classification were provided. Readers were then given 20 new cases to evaluate. Fleiss' kappa for FLAIR and combined FLAIR+ROI were calculated. Intraclass coefficient (ICC) was measured for SIR. Readers repeated the test until they individually obtained kappa $> 80\%$ and ICC $> 80\%$ against a "gold-standard" reader. Results from the "gold-standard" reader were excluded from analyses. Coefficients of variation (COV) across the 20 subjects were calculated ($SD/mean * 100$) to evaluate the reproducibility of ROI placement across readers. The performance of each method for correctly classifying whether a stroke was early (≤ 3.5 hours from witnessed onset) or not (> 3.5 hours) was evaluated on the basis of sensitivity and specificity.

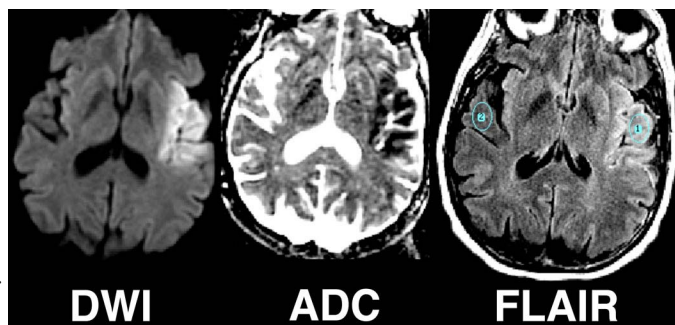


Figure: Example MRI from a stroke patient seen within 4 hours of LKW. The patient would be classified as FLAIR positive, with an $SIR = 1.47$ (blue outlines), and hence consistent with Late stage stroke.

Results: There was a total 15 readers at two sites, 7 readers at site 1 and 8 readers at site 2. Readings from the 4 readers used to develop the MRWITNESS algorithm were excluded. For qualitative FLAIR reads, Fleiss' $\kappa = 74\%$, sensitivity = 79% [95% confidence interval (CI): 71-85%], specificity = 100% [95% CI: 97-100%] across both sites. Site 1 inter-rater $\kappa = 0.68$ while Site 2 inter-rater $\kappa = 0.80$. Using the combined visual inspection of FLAIR and SIR, Fleiss' $\kappa = 0.89$, sensitivity 97% [95% CI: 93-99%], specificity = 97% [95% CI: 92-99%] across both sites. Site 1 inter-rater $\kappa = 0.89$. Site 2 inter-rater $\kappa = 0.90$. This showed an improvement in agreement from good to excellent. Intraclass correlation coefficient for SIR was 0.87 [95% CI: 0.79-0.94]. The COV of the SIR was median 4.7% [IQR 3.9-8.5%]. COV was significantly higher ($P < 0.03$) in patients with late stroke (7.8 [4.4-10.8]%) compared to those with early stroke (4.0% [3.6-5.2]%).

Discussion: With formal rigorous training, combining FLAIR and SIR analysis improved inter-rater agreement for classifying Early and Late stroke patterns while maintaining good sensitivity and specificity. Excellent inter-rater and inter-site agreement was obtained using simple rules that can be easily and rapidly performed at MR consoles without the need for special software. Our findings confirm that the MR WITNESS algorithm is a robust, and reproducible approach for identifying patients with Early stroke onset.

References: 1. Jiang Q, et al. J. Neurol. Sci. 1993; 120, 123-30. 2. Hajnal JV, et al. J. Comput. Assist. Tomogr. 1992; 16, 841-4. 3. Thomalla G, et al. Ann. Neurol. 2009; 65, 724-32. 4. Aoki J, et al. J. Neurol. Sci. 2010; 293, 39-44. 5. <http://clinicaltrials.gov/ct2/show/NCT01282242> Identifier: NCT01282242.