# Does b1000–b0 Mismatch Challenge Diffusion-Weighted Imaging–Fluid Attenuated Inversion Recovery Mismatch in Stroke?

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***Background and Purpose***—Our aim was to explore whether the mismatch in lesion visibility between b1000 and b0 images is an alternative to mismatch between diffusion-weighted imaging and fluid-attenuated inversion recovery imaging as a surrogate marker of stroke age.

***Methods***—We analyzed patients from the European multicenter I-KNOW database. Independent readers assessed the visibility of ischemic lesions of the anterior circulation on b0 and fluid-attenuated inversion recovery imaging images. The signal-intensity ratio for b0 and fluid-attenuated inversion recovery imaging images was also measured from the segmented stroke lesion volume on b1000 images.

***Results***—This study included 112 patients (68 men; mean age, 67.4 years) with stroke onset within (n=85) or longer than (n=27) 4.5 hours. b1000–b0 mismatch identified patients within 4.5 hours of stroke onset with moderate sensitivity (72.9%; 95% confidence interval [CI], 63.5–82.4) and specificity (70.4%; 95% CI, 53.2–87.6), high positive predictive value (88.6%; 95% CI, 81.1–96.0), and low negative predictive value (45.2%; 95% CI, 30.2–60.3). Global comparison of b1000–b0 mismatch with diffusion-weighted imaging–fluid-attenuated inversion recovery imaging mismatch (considered the imaging gold standard) indicated high sensitivity (85.9%; 95% CI, 78.2–93.6), specificity (91.2%; 95% CI, 76.3–98.1), and positive predictive value (96.7%; 95% CI, 88.0–99.1) and moderate negative predictive value (73.8%; 95% CI, 60.5–87.1) of this new approach. b0 signal-intensity ratio ($r$=0.251; 95% CI, 0.069–0.417; $P$=0.008) was significantly although weakly correlated with delay between stroke onset and magnetic resonance imaging.

***Conclusions***—b1000–b0 mismatch may identify patients with ischemic stroke of the within 4.5 hours of onset with high positive predictive value, perhaps constituting an alternative imaging tissue clock. (***Stroke***. 2016;47:877-881. DOI: 10.1161/STROKEAHA.115.011501.)

**Key Words:** biomarkers ■ diffusion magnetic resonance imaging ■ magnetic resonance imaging ■ sensitivity and specificity ■ stroke

Intravenous tissue-type plasminogen activator administration is currently approved only for patients who present within 4.5 hours of ischemic stroke onset.[1] Tissue-clock biomarkers are, thus, needed for stroke with unknown onset time in which penumbra salvage may improve clinical outcome.[2] Diffusion-weighted imaging (DWI)/fluid-attenuated inversion recovery (FLAIR) mismatch has been proposed for magnetic resonance imaging (MRI) estimation of lesion age in acute stroke[3] but still presents some drawbacks.[4–8] To circumvent the subjectivity of the visual rating of images using this method, different approaches have been proposed with conflicting results,[4,6,8–12] and further studies are needed to verify their utility.

Our purpose was to explore whether the mismatch in lesion visibility between b1000 and b0 images (b1000–b0

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mismatch) could serve as a potential alternative approach to DWI–FLAIR mismatch as a surrogate marker of stroke age.

## Materials and Methods

### Patients

We retrospectively analyzed patients from the prospective multicenter I-KNOW study (http://www.i-know-stroke.eu), who underwent sequential MRI for anterior circulation acute ischemic stroke. Regional ethics committees approved the protocol, and informed consent was obtained from all patients.

### MRI Protocol

Multiparametric admission MRI included both DWI (3 or 12 directions; repetition time, >6000 ms; median echo time, 91 [77–102] ms with 2 $b$-values [b0 and b1000 s/mm$^2$]) and FLAIR images (repetition time, 8690 ms; echo time, 109 ms; inversion time, 2500 ms).

### Imaging Analysis

Qualitative b0 and FLAIR analysis was performed by independent blinded readers (2 different readers for each sequence). Parenchymal FLAIR signal intensity was initially dichotomized as positive (frank hypersignal) or negative (absent or subtle hypersignal), in line with recent data.[13] b0 images were in turn divided initially in b0 positive (including both subtle and frank hypersignal, accounting for the intrinsic lower resolution/contrast of this sequence) or b0 negative (no detectable lesion). A consensus was reached in cases of disagreement.

The extent of leukoaraiosis was evaluated on b0 images by 1 reader using the Kappeler adapted scale of Fazekas and Schmidt.[14] Scores of >1 on either of the subscales defined severe leukoaraiosis.[3]

b1000, b0, and FLAIR images were postprocessed using MATLAB 2010b (MathWorks Inc, Natick, MA), SPM8 (Wellcome Trust Center for Neuroimaging, University College of London, London, United Kingdom), and Medical Image Processing, Analysis, and Visualization (version 7.0.1; National Institutes of Health). After image coregistration and using a semiautomated software, masks of the acute b1000 lesion (DWI mask) and the contralateral hemisphere (mirror DWI mask) were generated. At each step, masks were visually checked and corrected to avoid inclusion of ventricles or sulci. The masks were superimposed on b0 and FLAIR images and signal intensities within their volume of interest calculated. Finally, signal-intensity ratios (SIRs) for both b0 and FLAIR images were calculated as the ratio of ipsilateral and contralateral voxel intensity.

### Statistical Analysis

Quantitative data are presented as median and interquartile range and categorical data as frequencies and percentages. Group comparison according to b0 or FLAIR status was performed using the Wilcoxon signed-rank test, $\chi^2$, or Fisher exact test, as appropriate. Logistic regression was used to identify independent predictors of b1000–b0 and DWI–FLAIR mismatches.

Interobserver agreement and Cohen $\kappa$ coefficients were calculated for the qualitative rating of images.

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value of b0-negative and FLAIR-negative images for identifying patients with stroke onset ≤4.5 hours were calculated with 95% confidence intervals (CIs). The accuracy was also calculated to compare the performance of the b1000–b0 mismatch with the DWI–FLAIR mismatch.

Correlation of SIR with the delay between stroke onset and MRI was calculated using Pearson correlation coefficient and 95% CI.

Analyses were performed with SAS software (version 9.2; SAS Institute Inc, Cary, NC). The significance level was set at $P=0.05$.

## Results

### Patients

Of the 167 patients included in the I-KNOW cohort, 55 were excluded because of missing relevant data (n=38) or insufficient imaging quality/alignment (n=17). One hundred twelve of 167 patients (67%) were included in the final analysis. Eighty-five (75.9%) were imaged at 0 to 4.5 hours after stroke onset and 27 (24.1%) at 4.5 to 12 hours after stroke onset, using either a 3.0-T (n=11; 9.8%) or a 1.5-T (n=101, 90.2%) magnet. Global baseline and subgroup characteristics are presented in Table.

### Qualitative Analysis

After final consensus, the differences between classifications using the 2 mismatches involved 14/112 (12.5%) patients, occurring in 8 of 85 (9%) and in 6 of 27 (22%) of cases presenting before and after 4.5 hours of symptom onset, respectively. Interobserver agreement on lesion conspicuity was good for both b0 (92.0%; $\kappa=0.83$; 95% CI, 0.72–0.93; $P<0.001$) and FLAIR evaluation (88.4%; $\kappa=0.72$; 95% CI, 0.58–0.87; $P<0.001$).

Subgroups were similar except for onset-to-MRI delay, which was significantly longer ($P<0.001$) in b0-positive and FLAIR-positive patients and was an independent predictor of b0 ($P=0.032$) and FLAIR ($P<0.001$) positivity on multivariate analysis.

Sensitivity, specificity, PPV, and negative predictive values for identification of patients within 4.5 hours of stroke onset

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**Table.    Global and Subgroup Baseline Characteristics**

| | All Patients, n=112 | b0-Negative, n=70 (62.5%) | b0-Positive, n=42 (37.5%) | P Value | FLAIR-Negative, n=78 (69.6%) | FLAIR-Positive, n=34 (30.4%) | P Value |
|---|---|---|---|---|---|---|---|
| Age, y | 70.5 (60.5–77.5) | 72.5 (62–78) | 66 (57–73) | 0.110 | 72 (61–78) | 67 (60–759) | 0.489 |
| Men, n (%) | 68 (60.7) | 44 (62.9) | 24 (57.1) | 0.540 | 48 (61.5) | 20 (58.8) | 0.787 |
| NIHSS at admission | 10 (6–15) | 10 (6–14) | 11 (6–17) | 0.204 | 10 (6–14) | 11 (6–17) | 0.470 |
| DWI lesion volume, mm$^3$ | 11 063.7 (3250.0–24 899.3) | 7340.6 (2594.5–23 547.4) | 13 791.0 (8226.6–31 590.0) | 0.334 | 10 098.4 (2970.7–22 508.8) | 14 543.7 (6868.0–33 496.9) | 0.108 |
| Fazekas scale, relevant, n (%) | 66 (59) | 32 (45.7) | 14 (33.3) | 0.197 | 35 (44.9) | 11 (32.4) | 0.216 |
| Onset-to-MRI delay, min | 152.5 (111.5–267.0) | 137.5 (105–182) | 255 (148–363) | <0.001* | 141.5 (106–188) | 273 (148–403) | <0.001* |

DWI indicates diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; and NIHSS, National Institutes of Health Stroke Scale.

*Value statistically significant ($P<0.05$).
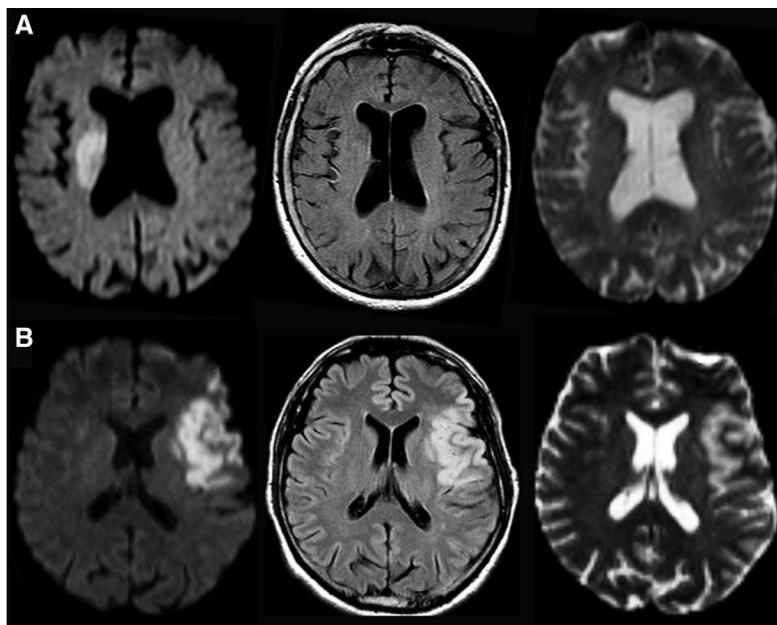
**Figure 1.** Examples of positive (**A**) and negative (**B**) b0–b1000 and diffusion-weighted imaging–fluid-attenuated inversion recovery imaging mismatches.

were 72.9% (95% CI, 63.5–82.4), 70.4% (95% CI, 53.2–87.6), 88.6% (95% CI, 81.1–96.0), and 45.2% (95% CI, 30.2–60.3) for the b1000–b0 mismatch and 80.0% (95% CI, 71.5–88.5), 63.0% (95% CI, 44.8–81.2), 87.2% (95% CI, 79.8–94.6), and 50.0% (95% CI, 33.2–66.8) for the DWI–FLAIR mismatch, respectively. The accuracy results were similar for both mismatches after exclusion of 3-T examinations (n=11), with maintenance of high PPV (86.9% [95% CI, 78.4–95.4] for the b1000–b0 mismatch and 85.3% [95% CI, 76.9–93.7] for the DWI–FLAIR mismatch).

When compared with DWI–FLAIR mismatch (currently considered the imaging gold standard for age estimation in stroke of unknown onset), b1000–b0 mismatch showed globally a good performance, with a sensitivity of 85.9% (95% CI, 78.2–93.6), a specificity of 91.2% (95% CI, 76.3–98.1), a PPV of 96.7% (95% CI, 88.0–99.1), and a negative predictive value of 73.8% (95% CI, 60.5–87.1). Figure 1 presents examples of concordance between the 2 methods.

### Quantitative Analysis

Median SIR within the ischemic lesions (when compared with the normal contralateral hemisphere) increased by 7% in b0 images (SIR, 1.07; interquartile range, 1.02–1.14) and by 11% in FLAIR images (SIR, 1.13; interquartile range, 1.06–1.18), and it was significantly higher ($P<0.001$) in both b0 and FLAIR-positive groups.

We detected significant although weak correlations with onset-to-MRI delay for both b0 SIR ($r=0.251$; 95% CI, 0.069–.417; $P=0.008$) and FLAIR SIR ($r=0.358$; 95% CI, 0.185–0.510; $P=0.001$; Figure 2).

### Discussion

After arterial occlusion, cytotoxic edema can be detected within minutes via DWI, whereas vasogenic edema increases slowly, inducing progressively higher T2 relaxation time measures that significantly correlate with time from symptom onset.[8,15] As b0 images also present a long echo time, we have hypothesized that an ischemic lesion would appear brighter on b1000 sooner than on b0 images and that this difference would disappear over time.

This study confirmed that patients with acute ischemic stroke with lesions detected on b1000 but not on b0 were likely to be within the current therapeutic time window for acute stroke, with a high PPV. The main drawback of this method is its moderate sensitivity and specificity, as well as low negative predictive value; however, these values were similar to values previously reported with DWI–FLAIR mismatch[3,5–7] and that we have also obtained.

Quantitative analysis of b0 SIR confirmed changes detected through visual inspection, indicating a relative increase in the signal in the affected hemisphere when compared with the contralateral. This signal was also on average higher in b0-positive patients than in other patients. Median b0 SIR significantly but weakly correlated with onset-to-MRI delay, as seen with median FLAIR SIR in our study and in previous reports.[6,8,10]

b1000–b0 method is itself easy to perform, does not require sophisticated or time-consuming postprocessing, and exhibits a good inter-rater agreement.

Furthermore, time constraints constitute a central factor on stroke MR–based protocols, and as most centers use at least b0 and b1000 values for obtaining standard DWI images, b0 sequences are available without additional acquisition delay.

Importantly, as b0 is part of DWI sequence, it is more directly comparable with b1000 images in terms of colocalization of signal intensities, artifacts, voxel size, and slice position than FLAIR images.

Finally, because DWI sequences have fast acquisition times and patients with stroke are frequently agitated, b0 images are less prone to movement artifacts than FLAIR images.

As a drawback, b0 presents poorer resolution and contrast than FLAIR images but their overall quality still allows evaluation of major stroke mimics, namely tumors. Furthermore,

**A**

**B**
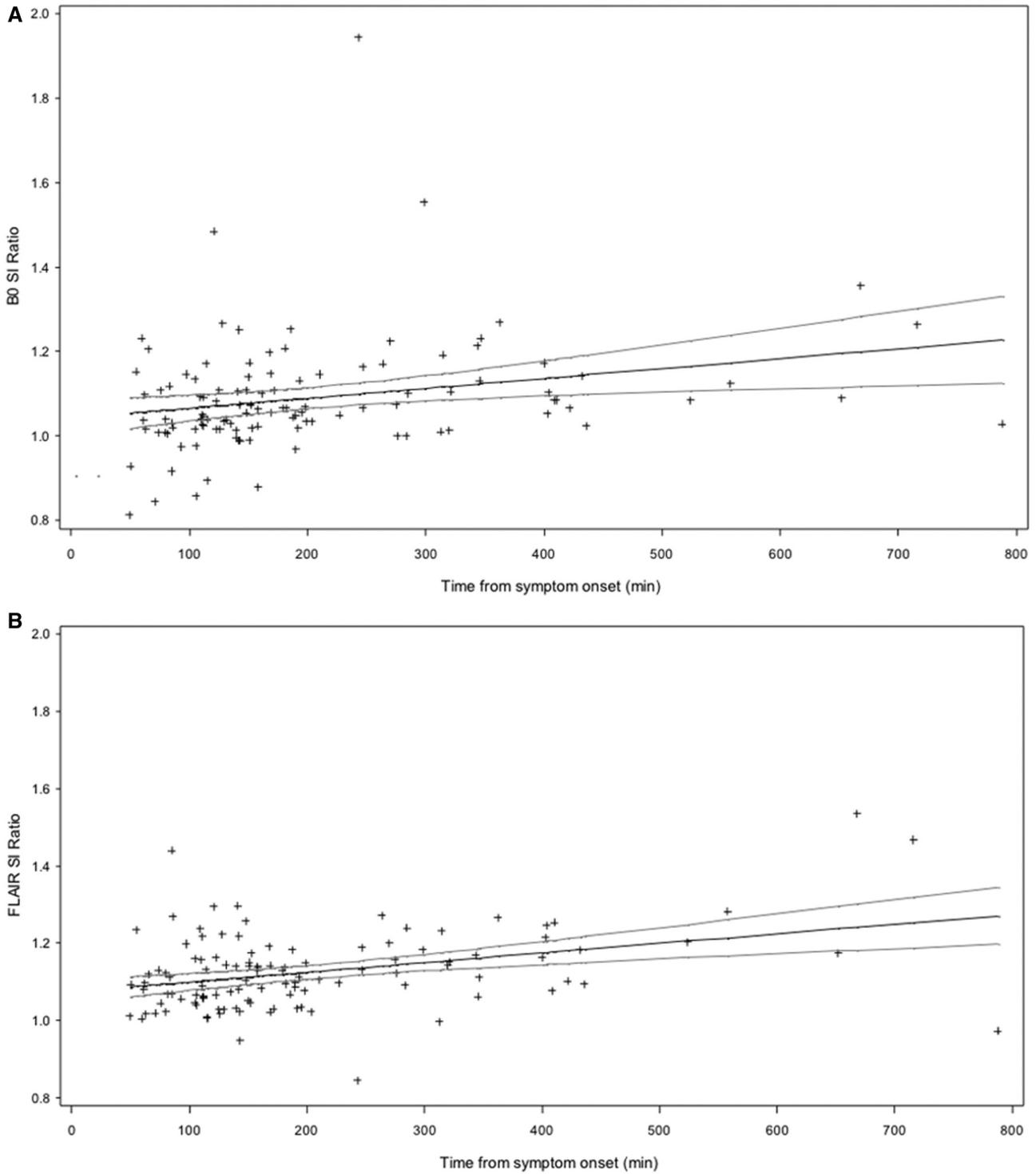
**Figure 2.** Scatterplots of b0 signal-intensity (SI) ratio (**A**) and fluid-attenuated inversion recovery imaging SI ratio (**B**) plotted against onset-to-magnetic resonance imaging delay (regression line and 95% mean confidence intervals are shown).

although the absence of cerebrospinal fluid suppression in b0 images raises some difficulties in the evaluation of subtle signal-intensity changes in the cortical region, these FLAIR hyperintensities have not been taking in account in many studies applying the DWI–FLAIR mismatch, particularly in this anatomic location.[4,13] Thus, this can in fact be a positive aspect of our method, intrinsically excluding early subtle signal anomalies that may cause a false-negative DWI–FLAIR mismatch.

Our study has some limitations, mainly because of the imbalance of patients assessed within 4.5 to 12 hours versus <4.5 hours. In addition, our examinations were performed with both 1.5-T and 3-T MRI scanners, and field strength can affect lesion visibility on both DWI and FLAIR images.[7] Nevertheless, the vast majority of patients underwent MRI at 1.5 T, and after exclusion of 3.0-T examinations, measures of accuracy remained similar. Consequently, this method seems reliable at least for 1.5-T scans.

Finally, as our study only included infarcts of the anterior circulation, generalization of results for posterior circulation or lacunar infarcts cannot be performed.

Our results show that b0 signal abnormalities in patients with stroke lesions on the anterior circulation correlate both qualitatively and quantitatively with onset-to-MRI delay. The use of this neuroimaging pattern may constitute a possible alternative to DWI–FLAIR as a potential stroke tissue clock, specially to provide reassurance of radiologists whenever there is a dubious judgment of subtle hyperintensities on FLAIR or FLAIR sequences are degraded by artifacts.

## Sources of Funding

## Disclosures

None.

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