

MR Imaging Helps Predict Time from Symptom Onset in Patients with Acute Stroke: Implications for Patients with Unknown Onset Time¹

Mina Petkova, MD
 Sebastian Rodrigo, MD, PhD
 Catherine Lamy, MD
 Georges Oppenheim, PhD
 Emmanuel Touzé, MD, PhD
 Jean-Louis Mas, MD
 Jean-François Méder, MD, PhD
 Catherine Oppenheim, MD, PhD

Purpose:

To assess the value of magnetic resonance (MR) imaging parameters as surrogate markers of stroke duration.

Materials and Methods:

The study was approved by the Ethics Committee of Ile de France III and was found to conform to generally accepted scientific principles and ethical standards. The authors studied 130 patients with acute stroke of known onset time who underwent 1.5-T MR imaging within 12 hours of the onset of stroke symptoms. Fluid-attenuated inversion recovery (FLAIR), diffusion-weighted (DW) imaging, and apparent diffusion coefficient (ADC) ratios were computed by using three-dimensional regions of interest to outline signal intensity changes on DW images and then projecting them onto the contralateral hemisphere. Imaging ratios in 63 patients who underwent imaging 0–3 hours after symptom onset were compared with those in 67 patients who underwent imaging more than 3 hours after onset by using the Student *t* test and receiver operating characteristic curves. The accuracy (sensitivity, specificity, and 95% confidence intervals [CIs]) of lesion visibility on FLAIR images in the prediction of a stroke onset time of less than 3 hours was assessed by two independent observers.

Results:

Differences in imaging ratios between patients imaged 0–3 hours after symptom onset and those imaged more than 3 hours after onset were statistically significant ($P < .001$). The FLAIR ratio showed a positive correlation with the time from symptom onset (Pearson correlation coefficient, 0.63). Receiver operating characteristic curves indicated that the FLAIR ratio could reliably identify patients imaged 0–3 hours after symptom onset, reaching 90% sensitivity (95% CI: 83%, 98%) and 93% specificity (95% CI: 86%, 99%) when using a 7% cutoff. Stroke imaged within 3 hours could also be identified by means of visual inspection of FLAIR and DW MR images, with 94% sensitivity (95% CI: 88%, 100%) and 97% specificity (95% CI: 93%, 101%).

Conclusion:

Signal intensity changes on 1.5-T FLAIR MR images can be used as a surrogate marker of stroke age, either qualitatively or quantitatively. This suggests that MR imaging might be used as a “clock” for determining stroke age in patients with an unknown onset time, potentially increasing the number of patients who are eligible for thrombolysis.

¹From the Departments of Radiology (M.P., S.R., J.F.M., C.O.) and Neurology (C.L., E.T., J.L.M.), Université Paris Descartes, Centre de Psychiatrie et Neurosciences, INSERM U894, Centre Hospitalier Sainte-Anne, 1 rue Cabanis, 75014 Paris, France; and the Department of Statistics, Université Paris-Est Marne-la-Vallée, Marne-La-Vallée, France (G.O.). Received March 5, 2010; revision requested May 10; revision received June 7; accepted June 16; final version accepted July 14. **Address correspondence to** C.O. (e-mail: c.oppenheim@ch-sainte-anne.fr).

At the acute phase of stroke, one of the major contraindications to thrombolysis is an unknown stroke onset time (1). Indeed, up to one-quarter of patients have been excluded from thrombolytic trials because the stroke was noticed on awakening or the onset was not witnessed. However, previous studies have reported an early morning predominance of stroke (2), suggesting that many patients who wake up with stroke may in fact wake up at the time of stroke itself. In addition, the clinical and neurologic imaging features or origin of stroke in patients with stroke on awakening do not seem to differ from those with stroke while awake (3–5). Some authors have suggested that certain treatment options should not be systematically excluded just because the time of stroke onset is unknown (6) and proposed a more rational management based on information provided with neurologic imaging techniques, such as magnetic resonance (MR) imaging (5,6). Multiparametric MR imaging can be used as a screening tool for thrombolysis without causing unacceptable delays in treatment (7). Some MR imaging–derived parameters, such as the mismatch between lesions at perfusion-weighted imaging and diffusion-weighted (DW) imaging, can help estimate the amount of at-risk, yet salvageable, ischemic tissue. Its potential in the identification of candidates for thrombolysis beyond the current guidelines has been thoroughly

studied in patients with known onset time and, occasionally, in those with unknown onset time (8).

For the time being, however, the time elapsed from stroke onset remains the key parameter in determining a patient's eligibility for thrombolysis, given that the effect of thrombolysis is time dependent (9). Consequently, a tool that could help estimate the age of stroke would be of great value in cases of unknown stroke onset time. In view of the linear variation of T2 relaxation time measurements in the first few hours of ischemia, the estimation of stroke age could rely on T2-weighted sequences (10–15). Recently, the absence of a signal intensity increase on fluid-attenuated inversion recovery (FLAIR) MR images in the presence of a corresponding area of high signal intensity on DW images has been shown to help identify patients within 3 hours after stroke onset with high specificity but low sensitivity (16). This is consistent with the reported safety of thrombolysis in patients with unknown stroke onset time who fulfilled MR imaging–specific criteria (eg, absence of well-developed changes on FLAIR images of acute diffusion lesions) (8). However, another group recently reported a random distribution of FLAIR signal intensity with regard to time after stroke, which sounds a note of caution when trying to estimate time of onset on the basis of FLAIR images (17). These studies relied on images acquired at different magnetic field strengths, including patients in different time windows

and, more important, those with differing degrees of stroke severity. Further studies are thus needed before one can recommend the use of FLAIR signal intensity changes for estimating the time from stroke onset.

We therefore compared the predictive values of FLAIR MR imaging, DW MR imaging, and apparent diffusion coefficient (ADC) measurements and tested the accuracy of the visual analysis of signal intensity changes on FLAIR and DW images in the identification of patients imaged within 3 hours of symptom onset. Our purpose was to assess the value of MR imaging parameters as surrogate markers of stroke duration.

Materials and Methods

Patients

We retrospectively studied the images obtained in consecutive patients with acute stroke admitted to our hospital between May 2006 and October 2008. The patients were identified from a prospectively collected stroke registry of consecutive patients. Patients were included in this study if they had acute ischemic stroke; if they had a well-defined stroke onset time; if they had undergone MR imaging (including DW and FLAIR imaging) within 12 hours

Advances in Knowledge

- Within the first 12 hours after stroke, signal intensity changes seen on fluid-attenuated inversion recovery (FLAIR) MR images in the acute ischemic area increase progressively and are correlated with the time from symptom onset.
- Qualitative or quantitative analysis of stroke signal intensity changes on FLAIR images can help determine, with a sensitivity and specificity of more than 90%, whether patients were imaged within the first 3 hours after stroke onset.

Implications for Patient Care

- MR imaging at 1.5 T could be used to estimate stroke age to support the interpretation of images in patients in whom the time from symptom onset is unknown.
- Such an MR imaging–based tool might increase the number of candidates for thrombolytic therapy if used in patients with unknown stroke onset time, provided that such patients are transferred urgently to a hospital after stroke recognition.

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Abbreviations:

ADC = apparent diffusion coefficient
 A_z = area under the receiver operating characteristic curve
 CI = confidence interval
 DW = diffusion-weighted
 FLAIR = fluid-attenuated inversion recovery
 NIHSS = National Institutes of Health Stroke Scale
 ROI = region of interest

Author contributions:

Guarantors of integrity of entire study, M.P., G.O., J.L.M., J.F.M., C.O.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, M.P., J.L.M., J.F.M., C.O.; clinical studies, all authors; statistical analysis, M.P., G.O., E.T., J.L.M., J.F.M., C.O.; and manuscript editing, C.L., E.T., J.L.M., J.F.M., C.O.

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of stroke onset; and if they had a National Institutes of Health Stroke Scale (NIHSS) score at admission of greater than 3. Patients with stroke on awakening were excluded. The study was approved by the Ethics Committee of Ile de France III and was found to conform to generally accepted scientific principles and ethical standards.

Among 907 consecutive patients admitted for acute ischemic stroke, 777 (85.7%) were excluded for the following reasons: the NIHSS score was 3 or less ($n = 518$, 57.1%), the stroke onset-to-MR imaging delay was more than 12 hours ($n = 215$, 23.7%), the stroke onset time was unknown ($n = 19$, 2.1%), screening was performed with computed tomography (CT) ($n = 23$, 2.6%), or the FLAIR images had major artifacts ($n = 2$, 0.2%). The remaining 130 patients (14.3%) comprised the study group. There was no difference between the excluded patients and the study group with regard to age (mean age $\pm$ standard deviation, 64.9 years $\pm$ 15.7 and 64.7 years $\pm$ 16.7, respectively; $P = .9$) or sex (40.2% [312 of 777 patients] and 40.8% [53 of 130 patients], respectively, were women; $P = .8$).

For each patient, we recorded the demographic details, stroke onset-to-MR imaging delay, NIHSS score at admission, arterial distribution (anterior or posterior circulation), infarct size on DW images (large or small [<5.0 cm³]), affected side (left, right, or bilateral), presence of motion artifacts on FLAIR images, treatment with thrombolysis, and outcome (modified Rankin score at discharge from hospital). Patients were classified into two groups according to the time between stroke onset and MR imaging: those imaged 0–3 hours after stroke onset (hyperacute group) and those imaged more than 3 hours after onset (acute group).

MR Imaging

MR imaging was performed with a 1.5-T unit (Signa EchoSpeed; GE Healthcare, Madison, Wis) by using a gradient strength of 33 mT/m and an eight-channel head coil. A T2-weighted baseline image ($b = 0$ sec/mm²) and the DW images were acquired with a single-shot echo-planar spin-echo sequence with the

following parameters: 6400/85.4 (repetition time msec/echo time msec), 24×24 -cm² field of view, 128×128 matrix, two signals acquired, 24 sections, 6-mm-thick sections, and no gap. The trace images were calculated from three DW acquisitions with gradients sequentially applied along each of the three orthogonal axes ($b = 1000$ sec/mm²). FLAIR images were obtained with the following parameters: 9802/155.5/2300 (repetition time msec/echo time msec/inversion time msec), 256×192 matrix, and one signal acquired; all other parameters were identical to those given earlier. The total acquisition time was less than 7 minutes.

Quantitative Analysis

DW and FLAIR images were processed by using FSL software (Functional Magnetic Resonance Imaging of the Brain Software Library, Oxford University, Oxford, England). Image processing was performed with the following steps (Fig 1): (a) rigid registration of FLAIR images to the DW images; (b) extraction of brain tissue from the T2-weighted images obtained at baseline ($b = 0$ sec/mm²); (c) manual three-dimensional definition of a mask encompassing the area of high signal intensity on DW images followed by automatic three-dimensional stroke segmentation (Functional Magnetic Resonance Imaging of the Brain automated segmentation tool) (briefly, this corresponded to segmentation of the DW voxels within the mask into six gray-level classes, keeping only voxels of the two highest classes); (d) affine registration of the DW images to the MNI152 brain atlas (Montreal Neurologic Institute, Montreal, Canada) (the quality of this registration was visually checked to search for outliers); (e) projection of the three-dimensional segmented stroke onto the MNI152 brain atlas and then flipping it onto the contralateral normal MNI152 brain to obtain normal signal intensity values for the contralateral brain (considered as the reference); and (f) back-projection of these three-dimensional regions of interest (ROIs) onto DW images, FLAIR images, and ADC maps. All ROIs were visually checked by one reader (S.R., with 7 years of ex-

perience) and manually corrected to avoid areas of leukoaraiosis (on FLAIR images) or contralateral stroke lesions. The ADC maps were available for comparison to rule out the presence of subacute or chronic vascular changes, which produce areas of high signal intensity on FLAIR images and T2 shine-through effects on DW images. Except for mask definition and visual inspection of the DW images, MNI152 registration, and final ROIs, the procedure was fully automatic. Image processing was performed within 15 minutes for each patient (Fig 2). Signal intensity or ADC values within stroke and contralateral reference ROIs were used to compute imaging ratios as follows: (stroke – reference)/(stroke + reference) $\times 100$.

Qualitative Analysis

Two neuroradiologists (M.P. and C.O., with 3 and 13 years of experience, respectively), who were blinded to the time from stroke onset but aware of clinical information, independently assigned patients to the hyperacute group or the acute group by simultaneously reviewing FLAIR and DW images, which were randomly presented on a dedicated workstation. ADC maps were available. The observers searched for signal intensity changes on FLAIR images in the area corresponding to the signal intensity changes on the DW images. They were asked not to take into account vascular areas of high signal intensity related to slow flow adjacent to the ischemic cortex (18–20). Patients without high signal intensity on FLAIR images were assigned to the hyperacute group. Reviewers were aware that patients with large signal intensity changes on DW images (ie, changes in more than half of the vascular territory) are more likely to develop early signal intensity changes on FLAIR images (16,17). In such cases, provided that signal intensity changes remained subtle and were limited to the external part of the cortex on FLAIR images, these areas were noted but ignored and patients were assigned to the hyperacute group (Figs 3, 4). All other patients were assigned to the acute group (Fig 5). To determine comparability between

studies, we also tested a binary classification approach used by others (16,17), that is, use of no signal intensity changes on FLAIR images versus all other FLAIR patterns, including subtle and definite signal intensity changes.

Statistical Analysis

Group comparison.—The two groups were compared for age, sex, initial NIHSS score, arterial distribution, affected side, lesion size, artifacts on FLAIR images, imaging ratios, and outcome. The unpaired Student *t* test was used for comparison of continuous variables, and the χ^2 test was used for categorical variables.

Qualitative analysis.—The interobserver agreement, sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios, and 95% confidence intervals (CIs) for the detection of patients imaged 0–3 hours after stroke were computed for the classification algorithm illustrated in Figure 4 and the binary approach.

Quantitative analysis.—For the imaging ratios, the areas under the receiver operating characteristic curve (A_z) were compared for the identification of patients imaged 0–3 hours after stroke and the best cutoff values determined. Values favoring specificity were used to minimize the risk of patients being wrongly classified into the hyperacute group. With use of these cutoff values, the sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios, and 95% CI in the identification of patients imaged 0–3 hours after stroke were assessed for each imaging ratio.

The correlations between imaging ratios and the time between stroke onset and MR imaging (in minutes) were analyzed by using Pearson correlations.

A software package (SPSS, version 15.0 for Windows; SPSS, Chicago, Ill) was used for statistical analysis. MedCalc (version 11.2.1.0; Mariakerke, Belgium) was used for comparisons of A_z . $P < .05$ was considered statistically significant. This study was carried out in accordance with the Standards for Reporting of Diagnostic Accuracy recommendations (21).

Figure 1

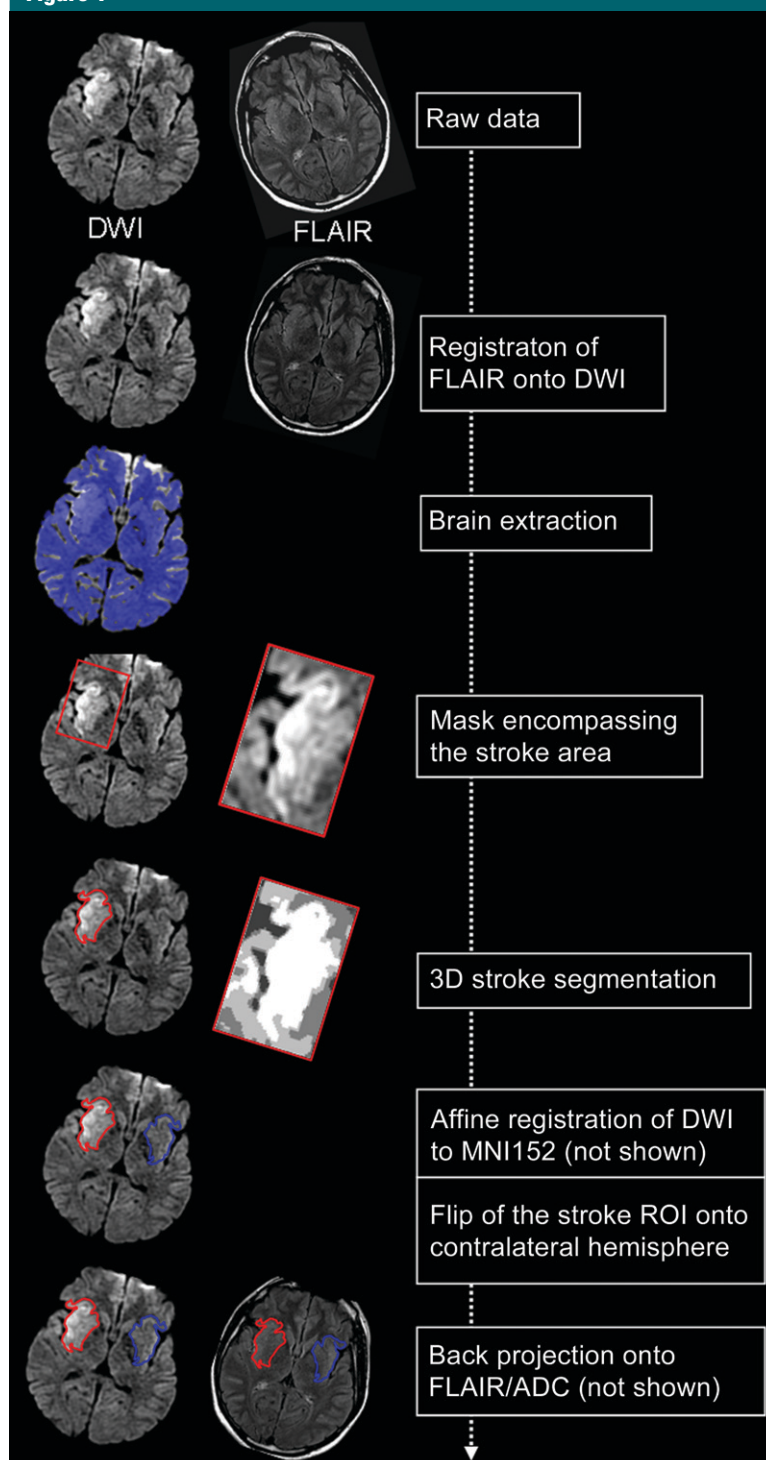


Figure 1: Diagram of quantitative processing steps. DWI = DW image, MNI152 = MNI152 brain atlas, 3D = three-dimensional.

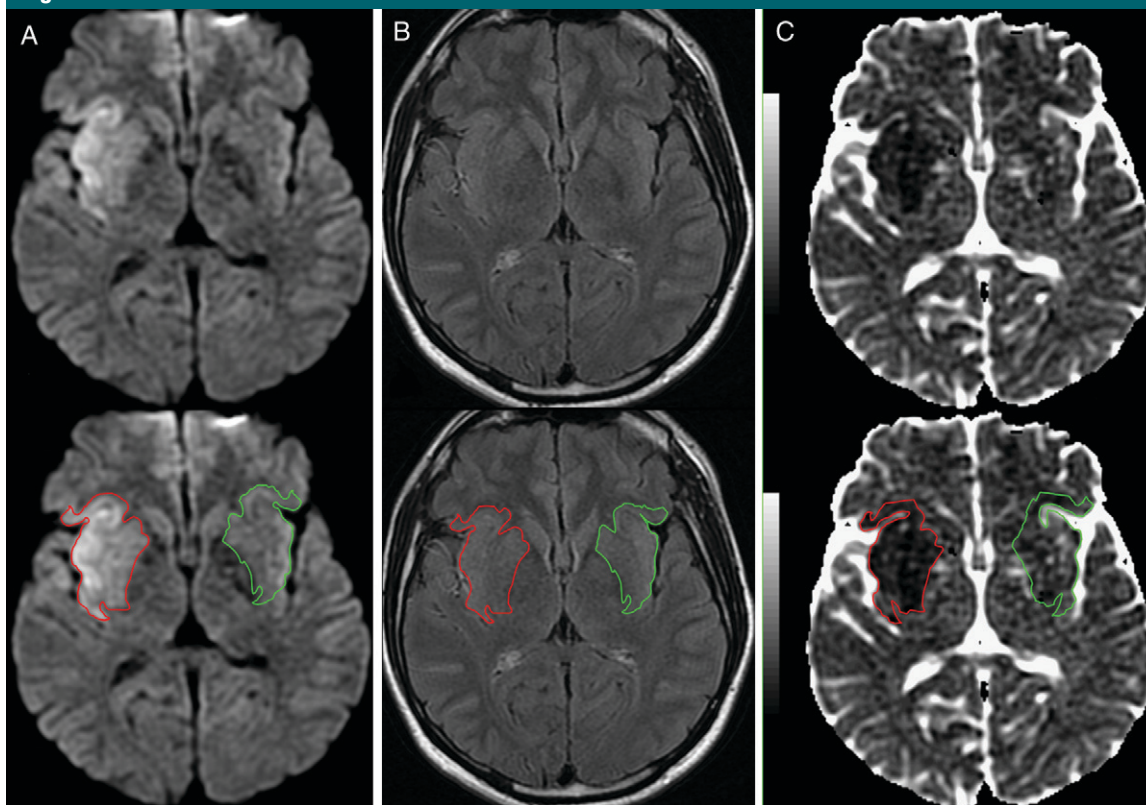
Figure 2

Figure 2: Axial, *A*, DW MR images, *B*, FLAIR MR images, and, *C*, ADC maps obtained 70 minutes after symptom onset in a 41-year-old man with right insular and putaminal ischemic infarct. The red line corresponds to the manually corrected ROI outlining the ischemic infarct on one section of the DW image and then projected onto the FLAIR image and the ADC map; the green line corresponds to the manually corrected ROI flipped onto the contralateral brain (reference ROI).

Results

The study group was composed of 130 patients aged 23–93 years (mean age, 64.7 years $\pm$ 16.7). There were 77 men aged 27–93 years (mean age, 61.8 years $\pm$ 15.6) and 53 women aged 23–93 years (mean age, 68.8 years $\pm$ 17.5). Sixty-three patients were imaged 0–3 hours after stroke onset (39 men with a mean age of 63.5 years $\pm$ 14.8 and 24 women with a mean age of 70.5 years $\pm$ 15.1; $P = .073$). The remaining 67 patients (38 men with a mean age of 60.1 years $\pm$ 16.3 and 29 women with a mean age of 67.3 years $\pm$ 19.4; $P = .10$) were imaged 3–12 hours after stroke onset. Thirteen of those patients were imaged 3–4.5 hours after onset. Forty-three of the 63 patients imaged 0–3 hours after stroke onset and one patient imaged more than 3 hours after onset underwent intravenous thrombol-

ysis, in each case after completion of MR imaging.

Group Comparison

Compared with patients who underwent imaging more than 3 hours after stroke onset, patients imaged 0–3 hours after onset had a higher mean NIHSS score at admission, had a higher frequency of large infarcts, and were more prone to motion artifacts on FLAIR images. All imaging ratios were significantly different between the two groups, with the strongest difference obtained for the FLAIR ratio (Table 1).

Qualitative Analysis

The interobserver agreement in the differentiation between the two groups of patients was almost perfect ($\kappa = 0.97$; 95% CI: 0.93, 1.0; $P < .001$). Of note, all seven patients with large stroke on DW images and subtle signal intensity

changes on FLAIR images were correctly assigned to the hyperacute group by both reviewers. Seven other patients were misclassified by at least one reader. Of these seven patients, three patients who underwent imaging more than 3 hours after stroke onset were wrongly assigned to the hyperacute group: One patient was imaged 190 minutes after stroke onset and the other two, who had artifacts on FLAIR images and extensive chronic vascular areas of high signal intensity adjacent to the ischemic area on FLAIR images, were imaged at 275 and 360 minutes. Four patients imaged within 3 hours of stroke onset were wrongly assigned to the acute group: One patient had a large stroke in the posterior circulation imaged at 120 minutes, two patients had a small stroke in the anterior circulation imaged at 120 and 140 minutes, and one patient had a small stroke in the posterior circulation imaged at 90 minutes.

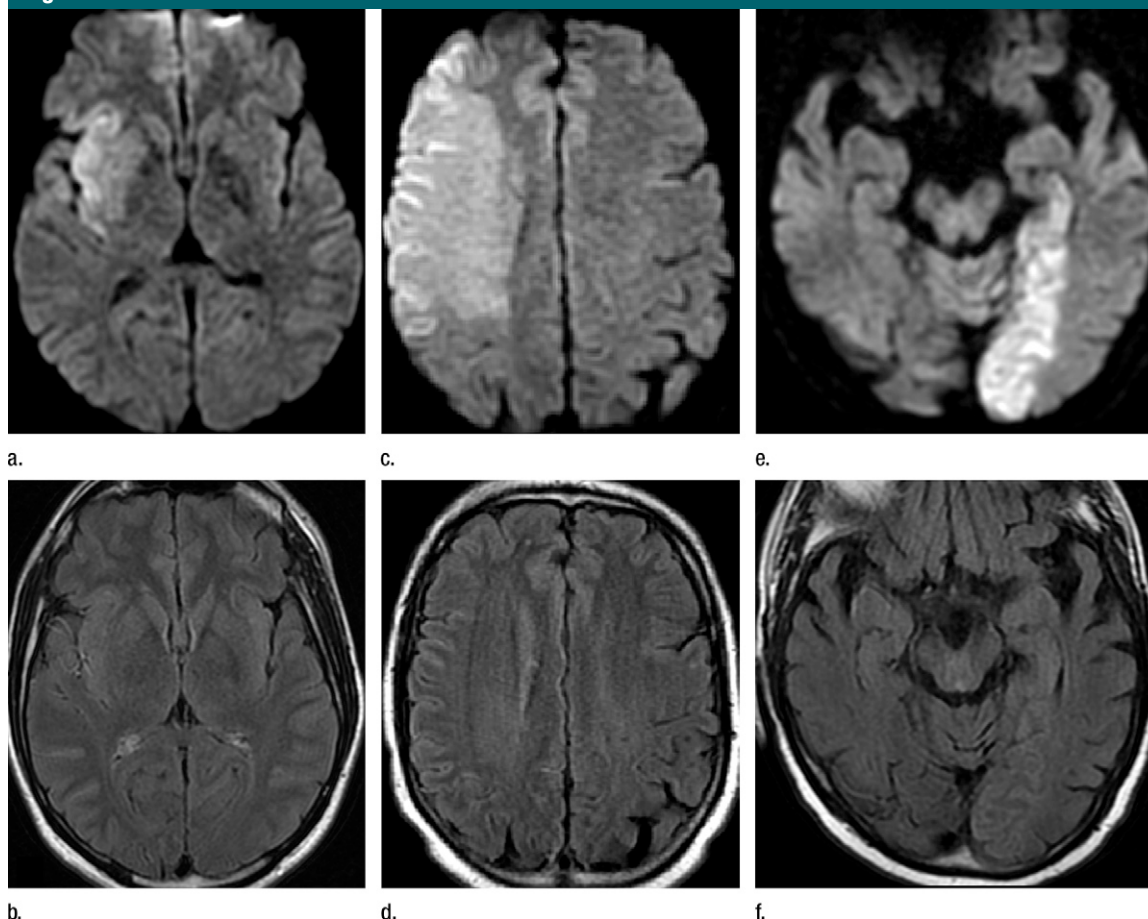
Figure 3

Figure 3: Axial (a) DW and (b) FLAIR images obtained 70 minutes after symptom onset in a 41-year-old man with right insular and putaminal ischemic infarct. Because the area of high signal intensity seen on the a image was absent from b, this patient was assigned to the hyperacute group. Axial (c) DW and (d) FLAIR images obtained 90 minutes after symptom onset in a 58-year-old man with a large right frontoparietal ischemic infarct. Axial (e) DW and (f) FLAIR images obtained 150 minutes after symptom onset in an 83-year-old man with a left occipital ischemic infarct. Because the subtle changes in signal intensity on d and f were limited to the external part of the cortex, the patients were assigned to the hyperacute group.

The classification algorithm presented in Figure 4 resulted in a sensitivity, specificity, and positive and negative predictive value of at least 94% (Table 2). The binary algorithm assigning only patients with strictly normal FLAIR findings to the hyperacute group, that is, reassigning the seven patients with large stroke and subtle signal intensity changes on FLAIR images to the acute group, resulted in a sensitivity of 82% (52 of 63 patients) with a specificity of 97% (65 of 67 patients).

Quantitative Analysis

Comparison of the A_z values indicated that the FLAIR ratio ($A_z = 0.964$;

95% CI: 0.933, 0.995) was more accurate than the DW imaging ratio ($A_z = 0.749$; 95% CI: 0.666, 0.831; $P < .001$) or ADC ratio ($A_z = 0.735$; 95% CI: 0.651, 0.819; $P < .001$) in the differentiation of patients imaged 0–3 hours after stroke onset from those imaged later (Fig 6). There was no significant difference in the A_z between the DW imaging ratio and the ADC ratio ($P = .77$). The best cutoff values for differentiating patients imaged 0–3 hours after stroke onset from those imaged later were 7% for the FLAIR ratio (Fig 7), 19% for the DW imaging ratio, and 14% for the ADC ratio. For instance, classification of patients with use of FLAIR alone would assign all patients

with a FLAIR ratio of 7% or less to the hyperacute group. Interestingly, all but one of the seven patients with subtle signal intensity changes on FLAIR images at the qualitative analysis had a corresponding FLAIR ratio below the 7% cutoff (median, 5.7%; range, 4.8%–8.0%). Comparison of the predictive values based on these cutoff values showed that the FLAIR ratio achieved a much higher predictive performance than did the other two imaging ratios (Table 2).

Finally, the FLAIR ratio ($R = 0.63$, $P < .001$), DW imaging ratio ($R = 0.53$, $P < .001$), and ADC ratio ($R = 0.47$, $P < .001$) all showed positive correlation with the time from stroke onset (Fig 8).

Figure 4

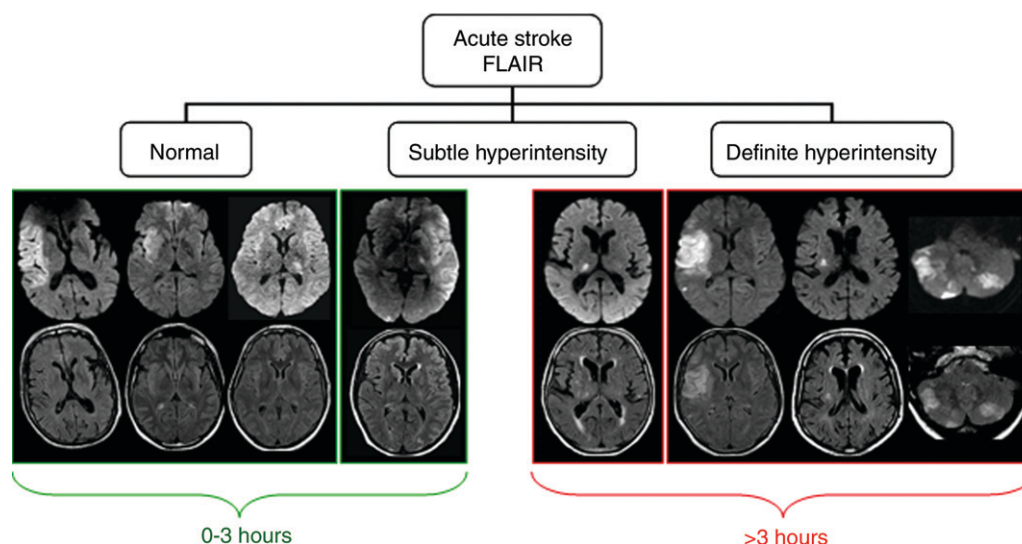


Figure 4: Diagrammatic presentation of the qualitative classification algorithm used to assign patients to the hyperacute group.

Discussion

Our results, which were drawn from a precisely defined suddenly symptomatic stroke population in which the exact time of insult was known, indicated that FLAIR MR imaging was better than DW imaging or ADC mapping in the identification of patients imaged 0–3 hours after stroke. Visual analysis of FLAIR and DW images or the use of a 7% FLAIR ratio cutoff offered sensitivity and specificity of at least 90% in the differentiation of a symptom duration of greater than or less than 3 hours. Consequently, multiparametric MR imaging could be used as a surrogate marker of stroke age when the onset time of stroke is unknown. In patients in whom the onset time is unknown or uncertain, MR imaging can help identify those who are highly likely to be within the 3-hour time window—namely, the time window for which intravenous thrombolysis has proved effective, is approved, and is recommended by international guidelines.

Our results provide quantitative evidence that signal intensity changes on FLAIR images were slower and more gradual than those on DW images or ADC maps in a group of 130 patients imaged within 12 hours of stroke onset. In animal models, the ADC was found to decrease to about half the normal

value within 30 minutes after stroke induction, followed by a slow decrease over the subsequent 6 hours (22,23). After this initial decrease, it is likely that the magnitude of any time-dependent changes in the ADC within the first 12 hours is modest in experimental and human stroke (4,14,24–28). The regional and interindividual heterogeneity of ADC is another impediment to estimating stroke age (4,24). We, like others (14), found that the time dependence of ADC was weaker than that of other imaging parameters.

Estimation of stroke age on the basis of FLAIR images seems possible, in line with our initial hypothesis, on the basis of several lines of evidence: (a) The net water uptake measured with use of CT attenuation shows a continuous linear decrease during the 6-hour period (27); (b) the MR correlate of CT attenuation in the infarct core, that is, the increase of T2 relaxation time, is linearly dependent on the time elapsed from stroke onset (10,13–15,29,30), accounting for the accuracy of quantitative T2 measurements in the prediction of time from stroke onset (14); (c) owing to a heavily T2-weighted sequence combined with cerebrospinal fluid cancellation, FLAIR is more sensitive to ischemia than are other T2-weighted sequences; and (d) the sensitivity of FLAIR is time

dependent within the first hours after the onset of symptoms (14,16,31,32). We found a positive linear correlation ($R = 0.63$) between the FLAIR ratio and the time from stroke onset (in minutes), and this correlation was stronger than that reported by Siemonsen et al (14) between time and quantitative T2 measurements at 1.5-T imaging ($R = 0.43$). Whereas Siemonsen et al used two-dimensional ROIs, our results were based on three-dimensional ROIs that covered the entire stroke volume and are likely to be more representative of the heterogeneous changes of stroke.

Our quantitative analysis of MR signal intensity provides additional evidence that the detectability of acute ischemic lesions on 1.5-T FLAIR images is dependent on time (16). We found that a 7% cutoff value for the FLAIR ratio in the identification of patients with a stroke onset time of 0–3 hours maximized specificity (92%) while keeping sensitivity at 90%. This 7% FLAIR ratio cutoff supports the allocation of patients with large lesions at DW imaging and minimal changes at FLAIR imaging to the hyperacute group; such patients were classified in the “3–6-hour” group in a recent study (16). We confirmed that such binary classification according to lesion visibility at FLAIR imaging had a lower sensitivity than a slightly

Figure 5

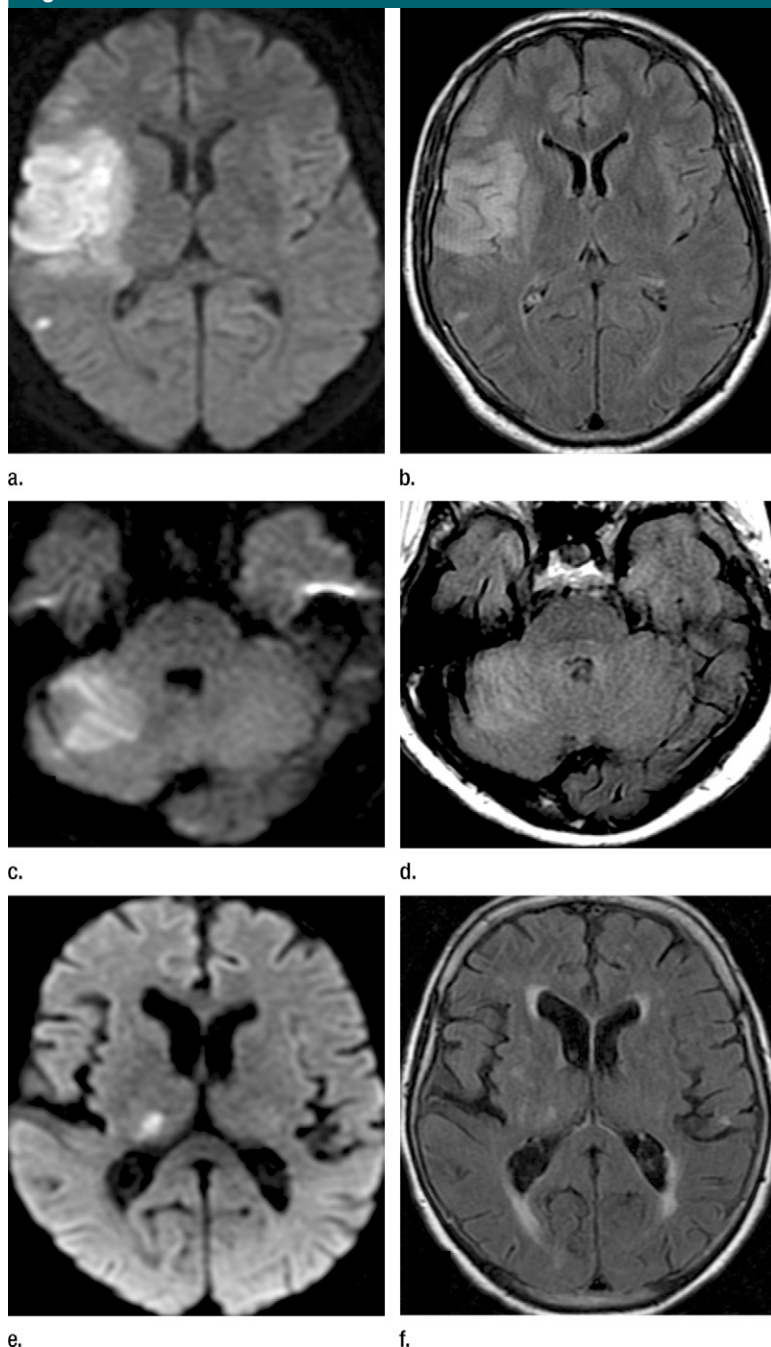


Figure 5: Axial (a) DW and (b) FLAIR MR images obtained 400 minutes after symptom onset in a 40-year-old man with right insular and putaminal ischemic infarct. Axial (c) DW and (d) FLAIR images obtained in a 78-year-old woman with right cerebellar ischemic infarct 420 minutes after symptom onset. Axial (e) DW and (f) FLAIR images obtained in a 75-year-old man with right thalamic ischemic infarct 250 minutes after symptom onset. On the basis of the areas of high signal intensity on FLAIR images, all of these patients were assigned to the acute group.

Figure 6

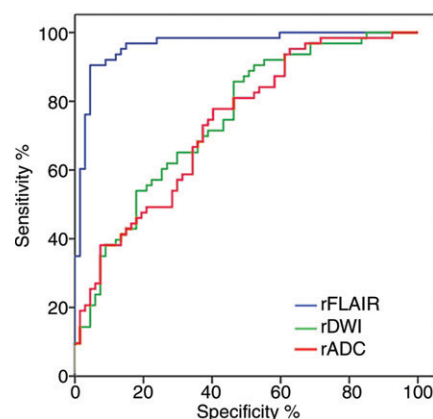


Figure 6: Receiver operating characteristic curves for imaging ratios in the prediction of patient assignment to the hyperacute group. Of the three ratios, the FLAIR ratio (*rFLAIR*) enabled the best discrimination between the two patient groups. *rADC* = ADC ratio, *rDWI* = DW imaging ratio.

Figure 7

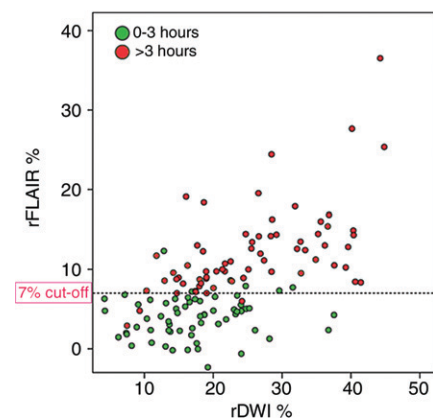


Figure 7: Scatterplot shows FLAIR ratios (*rFLAIR*) plotted against DW imaging ratios (*rDWI*) for the entire study population. The dotted line represents the cutoff value for the FLAIR ratio that enables the best differentiation between patients imaged 0–3 hours after stroke onset and those imaged more than 3 hours after stroke onset. The two groups could not be differentiated on the basis of the DW imaging ratio cutoff.

different classification algorithm that considered separately cases with subtle signal intensity changes. The distinction between normal and subtle signal intensity changes may help explain the moderate agreement that was previously obtained with the interpretation of FLAIR images (16); we reported better

agreement when subtle signal intensity changes in large strokes were overlooked and patients subsequently assigned to the hyperacute group. Moreover, in the case of minimal signal intensity changes on FLAIR images, the additional quantification of the FLAIR ratio signal intensity could help with definite group assignment and counterbalance the subjectivity of qualitative FLAIR analysis (8). Given that larger strokes on DW images and longer time from onset are both independent factors for lesion visibility on FLAIR images (16), a reliable FLAIR classification diagram should integrate the size of the ischemic lesion.

We confirmed the results of a previous study (16) showing that qualitative FLAIR MR imaging at 1.5 T has excellent specificity and extended the time to symptom onset to 12 hours. The accuracy of DW imaging–based prediction of stroke age was better than that with ADC and lower than that with FLAIR. This was not unexpected given that both diffusion restriction, measured with use of ADC, and T2 changes contribute to the changes seen at DW imaging.

The reliability of stroke age estimation with 1.5-T MR imaging might have practical implications. First, it might increase the number of patients eligible for thrombolysis (5) if used as a “clock” for stroke of unknown onset time. It provides scientific evidence for the MR imaging–based treatment algorithm used in some stroke centers that consider patients with unknown stroke onset time to be potential candidates for thrombolysis provided that FLAIR and/or T2-weighted images are normal and a large perfusion-weighted imaging–DW imaging mismatch is present (33,34). Of interest, a single-center study (6) suggested that thrombolysis may be safe in patients who wake up with stroke. In that study, the outcomes of patients who woke up with stroke and who did and did not undergo thrombolysis were compared with those in patients with stroke who were treated with intravenous thrombolysis within 3 hours of onset. In line with this, Cho et al (8), in a retrospective Korean study, suggested that thrombolysis may be safely performed in patients with

Table 1

Comparison of Clinical and Imaging Findings in the Hyperacute and Acute Groups

Parameter	Hyperacute Group (n = 63)*	Acute Group (n = 67)†	P Value
Age (y)	66 ± 15	63 ± 18	.32
Sex‡			.38
M	39	38	
F	24	29	
NIHSS score	13 ± 6.7	9 ± 5.6	<.001
Time between stroke onset and MR imaging (min)	116.8 ± 34.2	463.3 ± 173.7	...
Territory‡			.17
Anterior	54	51	
Posterior	9	16	
Side‡			.01
Right	35	21	
Left	27	41	
Bilateral	1	5	
DW imaging volume (cm ³)	25.3 ± 32.3	16.8 ± 24.7	.09
Lesion size‡			.04
Large (>5 cm ³)	53	46	
Small (≤5 cm ³)	10	21	
FLAIR artifacts‡	20	11	.04
Imaging ratio (%)			
FLAIR	4.0 ± 2.6	12.2 ± 5.5	<.001
DW imaging	17.4 ± 7.2	25.6 ± 9.5	<.001
ADC	12.8 ± 6.1	19.1 ± 7.4	<.001
Modified Rankin score§	3.2 ± 1.4	2.8 ± 1.2	.17

Note.—Unless otherwise indicated, data are means ± standard deviations.

*Imaging was performed 0–3 hours after stroke onset.

†Imaging was performed more than 3 hours after stroke onset.

‡Data are numbers of patients.

§At hospital discharge.

unknown onset stroke who fulfill certain MR imaging–specific criteria (eg, positive perfusion-weighted imaging–DW imaging mismatch and the absence of well-developed changes on FLAIR images). Our results confirm that further, prospective multicenter studies in which the safety of thrombolysis is assessed in patients with unknown stroke onset time should integrate, among other things, parameters used to estimate stroke age on the basis of FLAIR imaging. FLAIR imaging is part of most current MR stroke protocols, and the qualitative analysis of these images can be performed online, without delaying the decision to treat. Because of its excellent interobserver reliability, sensitivity, and specificity, visual inspection of FLAIR and DW MR images is a valuable alternative to the quantification of T2

relaxation time (10,14,35) or brain sodium concentration (22,23,36). Finally, like other investigators, we would further like to point out that we provided no evidence to suggest that patients with a defined stroke onset time be excluded from thrombolysis if lesions are visible on FLAIR images, although, according to a recent study (8), the presence of focal areas of high signal intensity within acute infarcts at FLAIR imaging may be associated with an increased risk of symptomatic hemorrhage after thrombolysis.

Our study had limitations. First, although MR imaging seems to be a reliable means of estimating stroke age regardless of the arterial distribution, we must be wary of drawing any definite conclusions because only 25 of our 130 patients (19%) had a stroke in the posterior circulation. Second, the quantitative

Table 2

Diagnostic Performance of MR Imaging–based Prediction

Image Analysis	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Positive Likelihood Ratio	Negative Likelihood Ratio
Qualitative						
Observer 1	94 (59/63) [88, 100]	97 (65/67) [93, 101]	97 (59/61) [92, 101]	94 (65/69) [89, 100]	25.3 [7.5, 85.5]	0.07 [0.03, 0.18]
Observer 2	95 (60/63) [90, 100]	96 (64/67) [91, 100]	95 (60/63) [90, 101]	96 (64/67) [91, 101]	18.4 [6.6, 51]	0.06 [0.02, 0.16]
Quantitative						
FLAIR ratio*	90 (57/63) [83, 98]	92 (62/67) [86, 99]	92 (57/62) [85, 99]	91 (62/68) [84, 98]	11.1 [5, 24.9]	0.1 [0.05, 0.2]
DW imaging ratio†	65 (41/63) [53, 77]	70 (47/67) [59, 81]	67 (41/61) [56, 79]	68 (47/69) [57, 79]	2.2 [1.4, 3.2]	0.5 [0.4, 0.7]
ADC ratio‡	56 (35/63) [43, 68]	70 (47/67) [59, 81]	64 (35/55) [52, 76]	63 (47/75) [51, 74]	1.8 [1.2, 2.8]	0.6 [0.5, 0.9]

Note.—Numbers in parentheses are numbers of patients. Numbers in brackets are 95% CIs.

*Cutoff was 7%.

†Cutoff was 19%.

‡Cutoff was 14%.

Figure 8

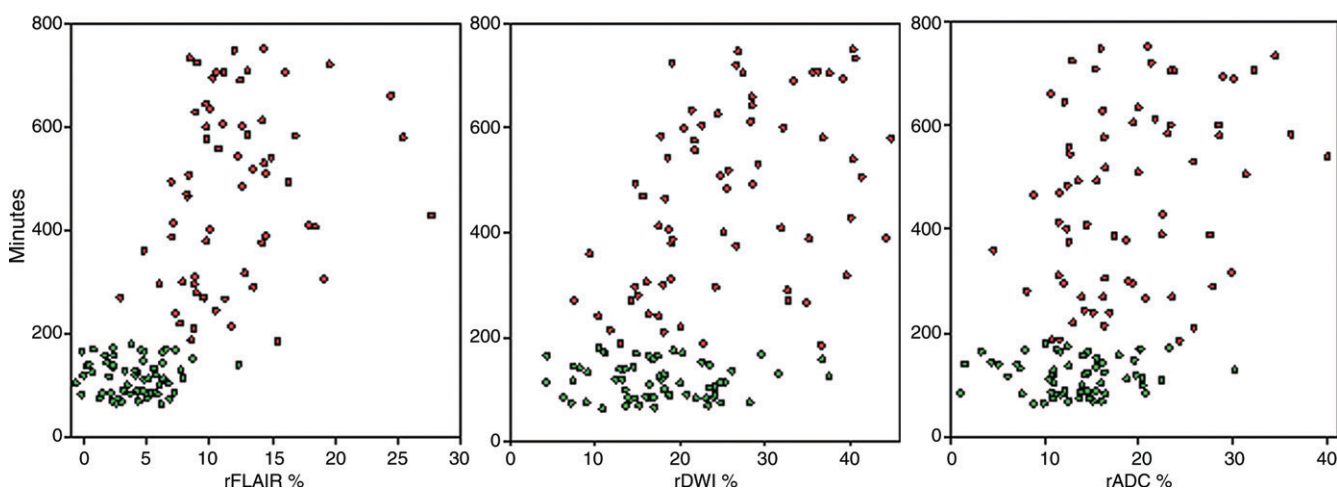


Figure 8: Scatterplots of imaging ratios and time from stroke onset (in minutes). Green symbols represent values for patients imaged 0–3 hours after stroke onset, and red symbols represent values for patients imaged more than 3 hours after stroke onset. *rADC* = ADC ratio, *rDWI* = DW imaging ratio, *rFLAIR* = FLAIR ratio.

analysis of FLAIR images was not fully automatic. Manual correction was required to avoid cerebrospinal fluid or chronic areas of high signal intensity on FLAIR images, limiting its use in an emergency. Third, we did not extend the time window up from 3.0 to 4.5 hours (37) given that only 10% of the population had been imaged in this time window. Fourth, our results cannot be extrapolated to images obtained at higher field strengths. Differences in coil systems or sequence parameters or the influence of the magnetic susceptibility effect likely affect FLAIR images differently at 1.5 and 3.0 T (38). This may help explain the low sensitivity

of negative FLAIR images obtained at 3.0 T in the allocation of patients to a time window of less than 4.5 hours (17). Finally, the results of our study, which was not designed to address the value of the perfusion-weighted imaging–DW imaging mismatch in the triage of patients with unknown stroke onset time for thrombolysis, do not imply that FLAIR alone can replace imaging of the penumbra for patient triage. If combined, both types of information may be useful for identifying patients with unknown stroke onset time who could be eligible for thrombolysis. Alternatively, CT, which was not performed in this series of

patients, may also help determine stroke age.

At 1.5 T, the use of quantitative signal intensity changes at FLAIR or the visual assessment of FLAIR and DW images as a surrogate marker of stroke age could help identify patients with unknown stroke onset time who may potentially be eligible for thrombolysis. Providing stroke neurologists with a reliable marker of stroke age may help ensure that patients with an unknown stroke onset time are treated as urgently as those with a known onset time, a necessary condition for extending trials on acute stroke treatment to patients with an unknown stroke onset time.

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