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# Synthetic T2 mapping is correlated with time from stroke onset: a future tool in wake-up stroke management?

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## Abstract

**Objectives** FLAIR-DWI mismatch is an effective method to select eligible wake-up stroke (WUS) patients for intravenous thrombolysis, but shows limitations in the case of subtle FLAIR hyperintensities. T2 mapping is a quantitative method, directly generated from synthetic MRI, which provides T2 relaxation times. We aimed to assess the correlation between T2 values and onset time in acute stroke patients.

**Methods** We prospectively included stroke patients in the 4.5-h window undergoing brain MRI including MAGnetic resonance Image Compilation (MAGiC) from March to October 2017. T2 relaxation times and FLAIR signal intensities were measured in ischemic and contralateral nonischemic regions to calculate FLAIR signal intensity ratio (rSI), difference, and ratio of T2 values. Correlation analysis with time from the onset was achieved using Pearson or Spearman correlation coefficient ($\rho$) test.

**Results** Forty-two patients were included. The strongest correlation with the time from onset was the difference in T2 relaxation times ($\rho = 0.71$; CI95% = [0.48; 0.85]), followed by the ratio ($\rho = 0.65$; CI95% = [0.37; 0.82]) and the absolute T2 relaxation time ($\rho = 0.4$; CI95% = [0.06; 0.66]), whereas the FLAIR rSI showed the weakest correlation ($\rho = 0.18$; CI95% = [− 0.16–0.51]).

**Conclusions** The difference and ratio in T2 relaxation times were correlated with the onset time in stroke patients in the 4.5-h window. T2 mapping generated from synthetic MRI may become a relevant tool to select WUS patients with subtle FLAIR hyperintensities. Given that no definitive statement can be made about its usefulness in the 4.5-h windows, further study including patients with an onset time > 4.5 h is required.

**Key Points**

- *The difference and ratio in T2 relaxation times are each individually correlated with the time from stroke onset in the 4.5-h window.*
- *FLAIR rSI showed a poor correlation with the time from stroke onset.*
- *T2 mapping, directly generated from synthetic MRI, may be a suitable quantitative marker to select safely WUS patients with subtle FLAIR hyperintensities for intravenous thrombolysis.*

**Keywords** Stroke · Acute stroke · Magnetic resonance imaging

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**Abbreviations**

| | |
|---|---|
| MAGiC | MAGnetic resonance Imaging Compilation |
| NIHSS | National Institutes of Health Stroke Scale |
| rSI | Signal intensity ratio |
| WUS | Wake-up stroke |

## Introduction

About 14–28% of stroke patients have neurological symptoms at awakening [1, 2]. These "wake-up" strokes (WUS) represent a major therapeutic challenge. Mechanical thrombectomy, respecting specific radiological and clinical criteria, can now be used for patients up to 24 h of last known normal, thus including WUS. However, the use of intravenous thrombolysis remains the only available alternative for patients with no large vessel occlusion and known time from the onset in a 4.5-h window [3–5].

Recently, a large multicenter trial has shown that in patients with acute stroke with an unknown time from onset, intravenous alteplase guided by a mismatch between DWI and FLAIR in the region of ischemia resulted in a significantly better functional outcome at 90 days [6]. Nonetheless, a major concern about the use of this mismatch as a selection method is the potentially subjective nature of the visual assessment of the ischemic stroke lesion with FLAIR. In this trial, the DWI-FLAIR mismatch was defined as the presence of an abnormal signal on DWI and no visible signal change on FLAIR in the region of the acute stroke. This dichotomous classification leaves unanswered doubts over subtle FLAIR hyperintensities in the acute stroke area. Thus, uncertainty remains about the course of action to be taken for patients with such FLAIR signal changes, who may benefit from intravenous thrombolysis, but are excluded from controlled trials. Several previous studies have focused on the direct assessment of FLAIR signal intensities in acute stroke for the prediction of time from symptom onset, but with contradictory results. Indeed, whereas Petkova et al found a significant correlation, two studies from Ebinger et al and Cheng et al showed an absence and a poor correlation, respectively [7–9]. Moreover, the latter, based on the MRI data from 399 patients included in the PRE-FLAIR multicenter study, showed that the quantitative measurements of FLAIR signal intensity ratio (rSI) confirmed the results of visual judgment but did not improve diagnostic accuracy in identifying patients, especially with subtle lesions, within a time window of 4.5 h of symptom onset [9].

T2 mapping is an MRI method that produces absolute T2 relaxation times, thus enabling quantification of minor signal changes visible on T2 contrasts, such as FLAIR imaging. It has been previously used in neuroimaging studies related to brain tumors, epilepsy, multiple sclerosis, and vascular diseases [10–19]. As a quantitative MRI technique, it might be an interesting tool for the assessment of subtle FLAIR changes in stroke, looking for a correlation between the T2 relaxation time in the ischemic region and the time to MRI in stroke patients with a known time of symptom onset. Synthetic MRI imaging, such as MAGnetic resonance Imaging Compilation (MAGiC) (General Electric healthcare) or NOVA + (Olea Medical), allows to reconstruct multiple contrasts from a single or two scans, respectively [20].

MAGiC is based on a multidynamic multiecho sequence that showed good intrascanner repeatability and interscanner reproducibility in the assessment of quantitative values for brain relaxometry [21]. Thus, it can provide essential contrasts for not only stroke evaluation (e.g., FLAIR) but also T2 mapping during the same acquisition.

Our objective was to evaluate the correlation between the quantitative T2 relaxation times within the acute stroke areas, obtained using MAGiC, the FLAIR rSI, and the time to MRI in patients with a known time of symptom onset in the 4.5-h window. T2 mapping could be a suitable marker to manage safely WUS patients with subtle FLAIR hyperintensities.

## Methods

### Population

From March to October 2017, we included in this prospective study all ischemic stroke patients, aged 18 or more, who were admitted to our Stroke Unit and underwent brain MRI within 4.5 h from symptom onset. Acute ischemic lesion was defined as a parenchymal hyperintensity on DWI explaining the clinical deficit.

Exclusion criteria were (i) unknown time from symptom onset, or time from symptom onset > 4.5 h; (ii) DWI hyperintensity area less than 1 $cm^2$ or with irregular shape not allowing correct ROI placement; (iii) DWI hyperintensity located within leukoaraiosis or with extensive contralateral leukoaraiosis (allowing assessment of the normal parenchyma with T2 mapping); (iv) contraindication for MRI; and (v) incomplete acquisition of the full MRI protocol or technical issues (e.g., motion artifacts).

For each subject, a complete record of relevant data was achieved, including time from symptom onset, severity of neurological deficit on admission assessed with the National Institutes of Health Stroke Scale (NIHSS) score, ongoing treatment, blood glucose level, and systolic blood pressure on admission [22].

The study was approved by our local Ethics Committee, the Institutional Review Board for Medical Research. Owing to the disability of stroke patients in the acute phase, the written informed consent was received in the subacute phase from the patient or the support person.

### MRI protocol

All MRI examinations were performed on a 3-T GE MR750W scanner (General Electric Healthcare) with a 24-channel phased-array head coil. The MRI protocol included DWI, 3D TOF, T2*, and MAGiC sequences. Main technical parameters used were:

– DWI: 30 slices, 6 diffusion-encoding directions, slice thickness = 4.2 mm, TE = 78.6 ms, TR = 7603 ms, FOV = 26 cm, matrix = 128 × 180, duration = 1 min 04 s

- 3D TOF: 130 slices, slice thickness = 1.4 mm, TE = 2.5 ms, TR = 22 ms, FOV = 22 cm, matrix = 320 × 224, duration = 1 min 57 s
- T2*: 26 slices, slice thickness = 5 mm, TE = 18 ms, TR = 660 ms, FOV = 24 cm, matrix = 448 × 224, duration = 1 min 55 s
- MAGiC: 368 slices, slice thickness = 5 mm, Multi TE and TR values, FOV = 26 cm, matrix = 416 × 288, flip angle = 90°, duration = 4 min 24 s. MAGiC allowed to generate automatically 2D T1, FLAIR, T2, and T1 quantitative maps. Thus, MAGiC was acquired instead of the 2D FLAIR sequence.

Total protocol duration was 9 min 20 s.

## Data processing

MAGiC sequences were processed directly on the main scanner console. The different contrasts were automatically generated by the MAGiC post-processing software (Fig. 1). One single radiologist, trained beforehand, assessed the whole data set during the same session.

For each patient, two 1-$cm^2$ 2D ROIs were placed in the same location on both the individual T2 quantitative map and the FLAIR imaging, respectively: one at the core of the acute ischemic lesion, in the same location as the area of the highest signal intensity on DWI, and one in the normal contralateral parenchyma, outside any potential leukoaraiosis lesion (Fig. 2).

Four different values were collected: the mean absolute T2 relaxation time and mean FLAIR rSI of the ischemic lesion and of the nonischemic contralateral parenchyma. The ratio and difference in T2 relaxation times between ischemic and nonischemic contralateral parenchyma, as well as FLAIR rSI, were then calculated.

## Statistical analysis

All statistical analyses were performed using R version 3.4.2. Qualitative variables are described by numbers and frequencies and quantitative variables by mean ± standard deviation and minimum-maximum. The Pearson or Spearman (for non-normal data) coefficient correlation ($\rho$) and its 95% confidence interval (CI) were calculated to evaluate the correlation

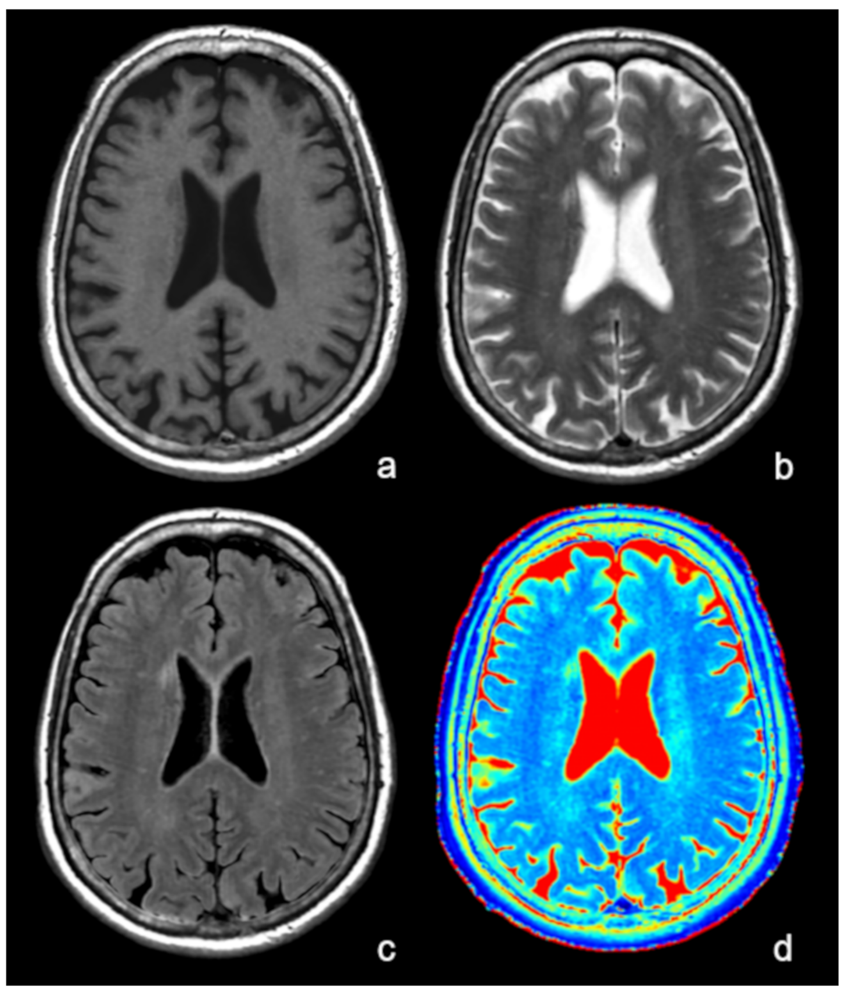


**Fig. 1** Examples of different contrasts automatically generated in the axial section by the MAGiC post-processing software. **a** T1-weighted image; **b** T2-weighted image; **c** FLAIR; **d** T2 map

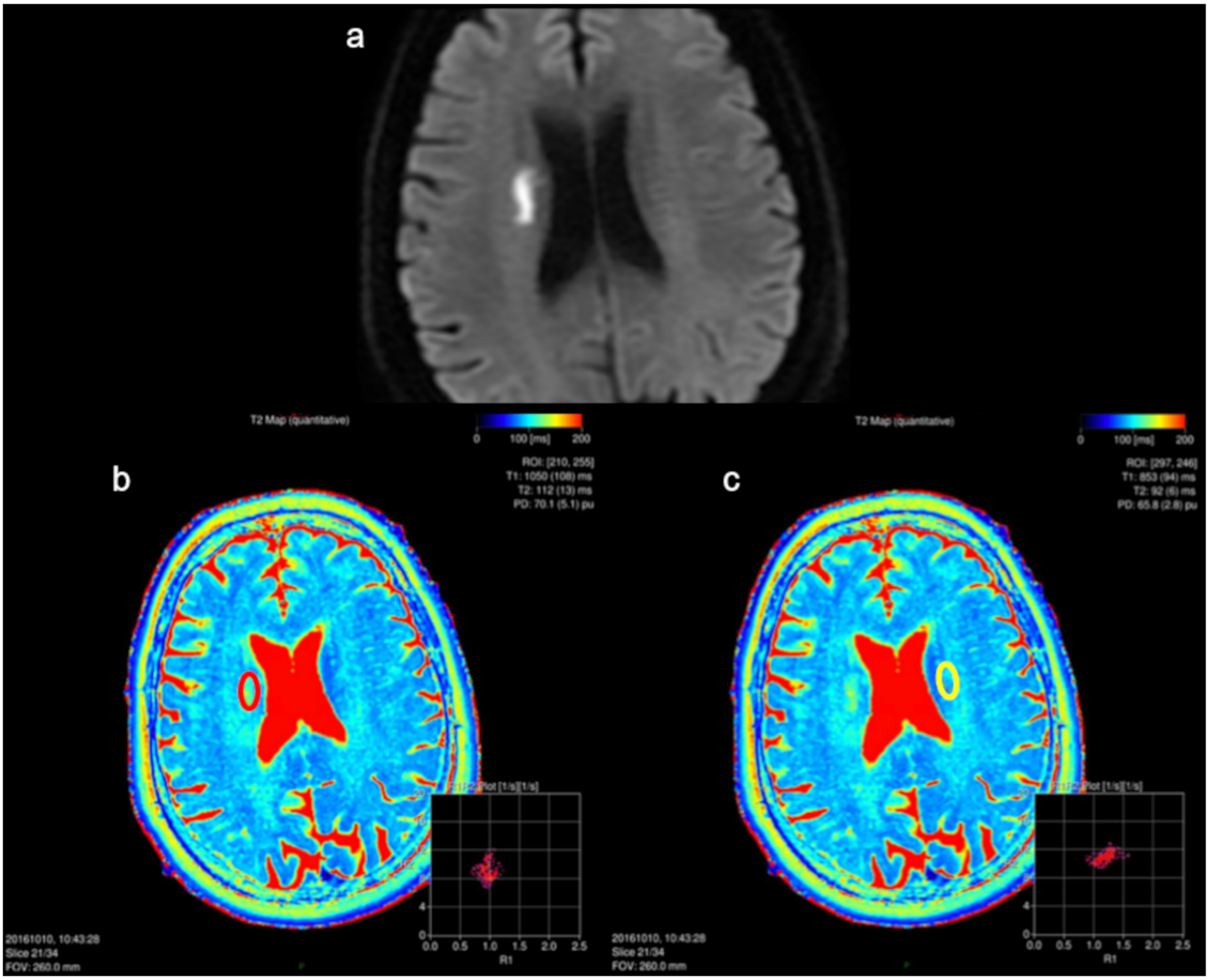


**Fig. 2** Example of the data processing of an acute ischemic stroke with the MAGiC software. The two ROI were placed respectively on the T2 map at the core of the ischemic stroke lesion (**b**) (bottom row, left picture, red ROI), at the same place as the DWI hyperintensity (**a**) (top row), and in the contralateral nonischemic parenchyma (**c**) (bottom row, right picture, yellow ROI)

between the T2 relaxation times, the FLAIR rSI, and the time to MRI. The correlation was considered very good if the absolute value of $\rho$ was greater than 0.8 strictly, good if it was between 0.61 and 0.8, moderate if it was between 0.6 and 0.41, and poor otherwise. The equation of the linear regression line between the T2 relaxation times and time from symptom onset to MRI was estimated to calculate the ratio and difference between T2 ischemic and nonischemic tissue for a time from onset of 4.5 h. Significance level was set at 5%.

## Results

### Population

Eighty-seven subjects were recruited and followed the specific MRI protocol as an emergency, including MAGiC. Forty-two patients were finally included after application of the inclusion criteria (see flowchart, Fig. 3).

Twenty-three patients were treated by intravenous thrombolysis, two by mechanical thrombectomy alone, and five by bridging therapy. The baseline characteristics are reported in Table 1.

### Quantitative analysis

Quantitative T2 relaxation times, differences, and ratios between ischemic and nonischemic ROI are detailed in Table 2.

### Correlation between time to MRI and T2 relaxation time

The correlation was good between the time to MRI and both the difference ($\rho = 0.71$; CI95% = [0.48; 0.85]) and the ratio

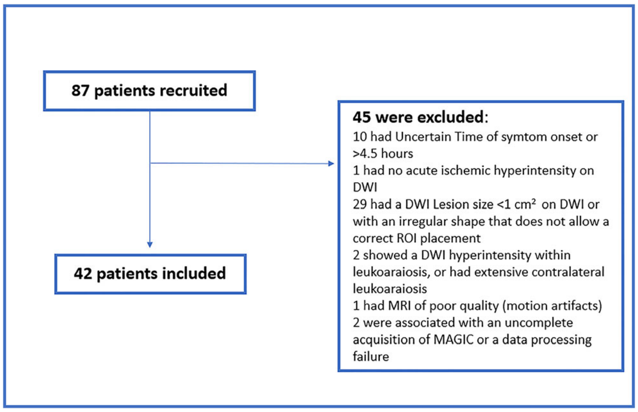


**Fig. 3** Study profile

($\rho = 0.65$; CI95% = [0.37; 0.82]) in T2 relaxation times. It was moderate for the absolute T2 relaxation time within the ischemic lesion ($\rho = 0.44$; CI95% = [0.16; 0.66]) and poor for the FLAIR rSI ($\rho = 0.18$; CI95% = % = [− 0.16–0.51]) (Fig. 4). The ratio and difference of T2 relaxation times between ischemic and nonischemic tissue were extrapolated from linear regression equations for a time from onset of 4.5 h, estimated at 1.28 and 24.9 ms, respectively.

## Discussion

Our results show a correlation between T2 relaxation time of acute ischemic stroke tissue and time from symptom onset. The difference between ischemic and nonischemic T2 values showed the best correlation (0.71), followed by the T2 relaxation time ratio (0.65), while the absolute T2 relaxation time showed a moderate correlation. By contrast, the correlation between FLAIR rSI and time from onset showed the weakest value (0.18). FLAIR rSI is a reflection of the amount of tissue water but it is also impacted by technical processes, such as the inversion recovery pulse applied before measuring the T2-weighted signal [9]. T2 values from T2 mapping are only and directly affected by local changes in water content, without technical issue. They reflect the acute ischemic changes and increase in proportion to the edema severity and thus to the time from onset [17, 23]. This could explain the better correlation of all the different T2 values with the time from onset compared with the FLAIR rSI. But quantitative T2 relaxation times are also influenced by the local tissue composition in the basal state, which depends on multiple factors (e.g., age, sex, anatomical region, and chronic vascular changes) [24]. The strongest correlations observed for the difference and ratio in T2 relaxation times suggest the need to weight the absolute T2 value in the stroke area by a contralateral T2 reference value representative of the baseline status prior to ischemia [16].

**Table 1** Baseline characteristics

| Sample size | $n$ = 42 |
|---|---|
| Mean age ± SD (years) | 72.9 ± 13.51 |
| Female (%) | 22 (52.4%) |
| Mean NIHSS Score on admission ± SD | 10.2 ± 8.04 |
| Mean NIHSS Score H+2 ± SD | 6.2 ± 6.7 |
| Treatment (%) | Intravenous alteplase, 30 (54.8%) |
| | Thrombectomy, 2 (4.8%) |
| | Bridging therapy, 5 (11.9%) |
| Time to MRI (min), IQR | 128.3, 83 |
| Volume of ischemic lesion (mL), IQR | 28.3, 31.1 |

*SD*, standard deviation; *NIHSS*, National Institutes of Health Stroke Scale, from 0 to 42; *MRI,* magnetic resonance imaging; *IQR*, interquartile range

**Table 2** Quantitative T2 values, including mean absolute T2 relaxation time within the acute ischemic region, mean difference, and ratio between ischemic and nonischemic ROI and FLAIR signal intensity ratio (rSI)

| | Mean ± SD | Min–max |
|---|---|---|
| T2 relaxation time in ischemic lesion (ms) | 93 ± 13 | 64–120 |
| Difference in T2 relaxation times (ms) | 9.9 ± 7.1 | 0–28 |
| Ratio of T2 relaxation times (ms) | 1.12 ± 0.09 | 1–1.34 |
| FLAIR rSI | 1.1 ± 0.16 | 0.82–1.92 |

We extrapolated the ratio and difference between T2 ischemic and nonischemic tissue for a time from onset of 4.5 h, estimated at 1.28 and 24.9 ms, respectively. These results suggest that T2 mapping could represent an objective marker for the assessment of time from stroke onset, especially in WUS, with quantitative thresholds for the 4.5-h limit criterion for intravenous thrombolysis.

T2 mapping has been assessed in acute stroke in a previous study focused on ischemic lesion with a known time of symptom onset [17]. However, results were focused on the 3-h window, and the MRI protocol required a supplementary multiecho T2 sequence in order to generate T2 mapping, with a specific post-processing leading to a significantly delayed analysis. Our study differed in several aspects. First, the analysis was conducted in the extended 4.5-h window. Second, our method can be easily and directly applied in routine clinical use. Indeed, MAGiC was acquired instead of FLAIR imaging, without adding any additional sequence. The data processing can be achieved immediately, without loss of time, which is consistent with a clinical use in the "time is brain" context.

The use of T2 mapping as a marker of time from stroke onset should be especially relevant for the selection of FLAIR-positive WUS patients eligible for intravenous thrombolysis. Indeed, the FLAIR-DWI mismatch remains a simple

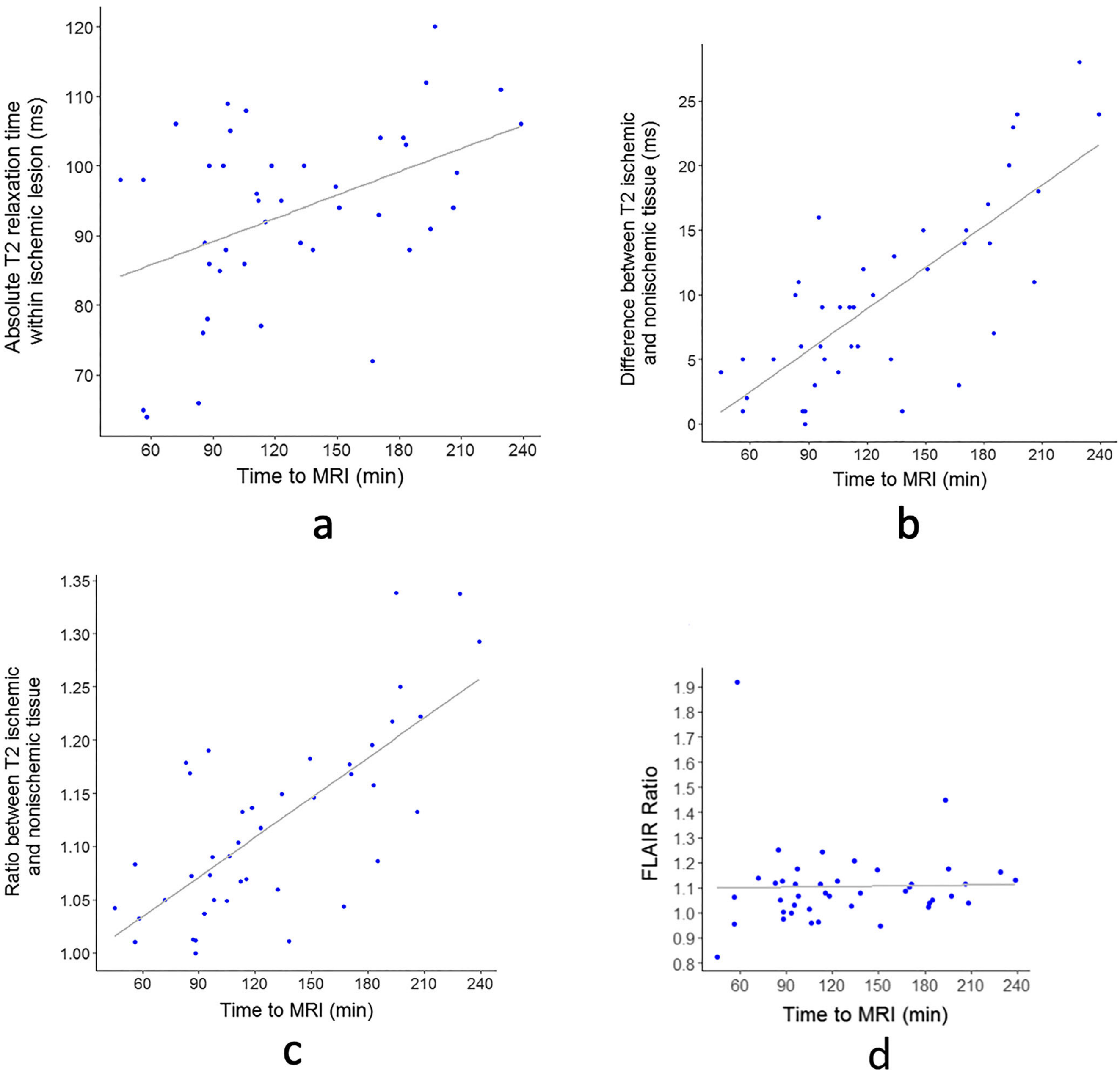


**Fig. 4** Absolute T2 relaxation time within the ischemic lesion (**a**), difference (**b**), and ratio (**c**) of T2 relaxation times and FLAIR rSI (**d**) between ischemic and nonischemic tissue, according to the time to MRI (min). The gray lines represent the regression lines

and efficient method when the FLAIR analysis is unambiguous, but can be affected by subjectivity bias in the case of subtle FLAIR lesions. In a previous multicenter study, the assessment of DWI-FLAIR mismatch in the identification of patients within 4.5 h of symptom onset showed 93.9% interobserver reproducibility for the visual analysis of DWI, but only 77.9% for FLAIR [25]. Moreover, even while the specificity and positive predictive value were good (respectively, 78% and 83%), sensitivity was low (62%) due to the high proportion of patients within the 4.5-h window with an acute ischemic lesion already visible on FLAIR imaging. Authors asked for further studies in order to assess quantitative markers for the evaluation of FLAIR-positive WUS patients. T2 mapping may help solve this issue by providing a quantitative and objective response for the triage of WUS patients with subtle hyperintensities on FLAIR imaging.

Our study presents several limits. Firstly, the sample was small. The 4.5-h threshold was extrapolated from linear regression equations. Indeed, our ethics committee agreement and the current recommendations for intravenous thrombolysis use in acute stroke did not allow to include patients beyond the 4.5-h limit in our preliminary study [3].

The recent recommendations about the selection of eligible subjects for mechanical thrombectomy up to 24 h from the last known normal allow to consider positively the inclusion of patients with an onset time of > 4.5 h in a further study with larger cohorts.

Secondly, the duration of MAGiC acquisition remains longer than that of a standard FLAIR sequence. Artifacts may occur in the interface between cerebrospinal fluid and brain parenchyma, leading to thin hyperintensities along the cortex. This issue had no consequence in our study, given that patients were in the 4.5-h window. Hence, unlike WUS, therapeutic management did not require a FLAIR analysis. However, this sequence still needs to be optimized in terms of duration and limitation of such artifacts.

Finally, the assessment of T2 relaxation times may be affected by the partial volume effect in the cortical areas. We did not include irregular cortical ischemic lesions in the study to prevent this risk.

In conclusion, our preliminary results showed that the difference and ratio in T2 relaxation times between ischemic and contralateral nonischemic regions were significantly correlated with the time from stroke onset in the 4.5-h window, whereas FLAIR rSI showed a poor correlation. Quantitative thresholds were calculated for a time from onset of 4.5 h. T2 mapping, directly generated from synthetic MRI, may become a suitable marker to select safely WUS patients with subtle FLAIR hyperintensities for intravenous thrombolysis. However, no definitive statement can be currently made about whether or not this marker is useful to identify stroke patients in the 4.5-h windows. Further study, including patients with an onset time beyond 4.5 h, is required to confirm our results.

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## Compliance with ethical standards

**Guarantor** The scientific guarantor of this publication is Pr Sebastien Verclytte.

**Conflict of interest** The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

**Statistics and biometry** One of the authors has significant statistical expertise.

**Informed consent** Written informed consent was waived by the Institutional Review Board.

**Ethical approval** Institutional Review Board approval was obtained.

**Methodology**
- Prospective
- Observational
- Performed at one institution

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