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Follow-up MRI in multiple sclerosis patients: automated co-registration and lesion color-coding improves diagnostic accuracy and reduces reading time

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Abstract

Objectives In multiple sclerosis (MS), the heterogeneous and numerous appearances of lesions may impair diagnostic accuracy. This study investigates if a combined automated co-registration and lesion color-coding method (AC) improves assessment of MS follow-up MRI compared with conventional reading (CR).

Methods We retrospectively assessed 70 follow-up MRI of 53 patients. Heterogeneous datasets of diverse scanners and institutions were used. Two readers determined presence of (a) progression, (b) regression, (c) mixed change, or (d) stable disease between the two examinations using corresponding FLAIR sequences in CR and AC-assisted reading. Consensus reference reading was provided by two blinded radiologists. Kappa statistics tested interrater agreement, McNemar's test dichotomous variables, and Wilcoxon's test continuous variables (statistical significance $p \leq 0.05$).

Results The cohort comprised 41 female and 12 male patients with a mean age of 40 (± 14) years. Average rating time was reduced from 78 (± 36) to 44 (±22) s with the AC approach ($p < 0.001$). The time needed to start and match datasets with AC was 14 (± 1) s. Compared with CR, AC improved interrater agreement, both between raters (0.52 vs. 0.67) and between raters and consensus reference reading (0.47/0.5 vs. 0.83/0.78). Compared with CR, the diagnostic accuracy increased from 67 to 90% (reader 1, $p < 0.01$) and from 70 to 87% (reader 2, $p < 0.05$) in the AC-assisted reading.

Conclusions Compared with CR, automated co-registration and lesion color-coding of MS-associated FLAIR-lesions in follow-up MRI increased diagnostic accuracy and reduced the time required for follow-up evaluation significantly. The AC algorithm therefore appears to be helpful to improve MS follow-up assessments in clinical routine.

Key Points

- *Automated co-registration and lesion color-coding increases diagnostic accuracy in the assessment of MRI follow-up examinations in patients with multiple sclerosis.*
- *Automated co-registration and lesion color-coding reduces reading time of MRI follow-up examinations in patients with multiple sclerosis.*
- *Automated co-registration and lesion color-coding improved interrater agreement in the assessment of MRI follow-up examinations in patients with multiple sclerosis.*

Keywords Multiple sclerosis · Magnetic resonance imaging · Disease progression · Brain · Image processing, computer-assisted

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Abbreviations

AC	Automated co-registration and lesion color-coding image reading approach
CR	Conventional reading
FLAIR	Fluid-attenuated inversion recovery
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
PACS	Picture archiving and communication system
RIS	Radiological information system
SD	Standard deviation.

Introduction

Multiple sclerosis (MS) is a chronic immune-mediated inflammatory disease of the central nervous system and characterized by demyelination as well as axonal damage [1]. Besides trauma, MS leads to the highest number of permanent disability in young adults [2]. Europe and the Northern United States rank among the regions with the highest incidence and prevalence [3, 4]. Women are affected more frequently than men and patients commonly present with relapsing-remitting disease [5]. Magnetic resonance imaging (MRI) is the method of choice to substantiate the clinically suspected diagnosis of MS [6, 7]. The McDonald diagnostic criteria, which are universally used in clinical routine, require a dissemination of lesions in space or time on MRI examinations [7, 8]. MS lesions are commonly found periventricular, in the corpus callosum and the centrum semiovale, and present hyperintense in T2-weighted and fluid inversion recovery (FLAIR) sequences [5]. Due to the frequent relapsing character of MS, patients receive repetitive MRI examinations on a regular basis to monitor disease activity and treatment response which is why these exams are common in daily radiological routine [9]. Comparing two consecutive MRI follow-up examinations is often burdensome and error prone, especially in patients with a high number of findings [10–12]. Additionally, a comparison of MRI examinations is impeded by different acquisition protocols and scanners [13, 14].

There are different approaches and tools available to facilitate detection of disease progression, such as subtraction or automated co-registration (AC) techniques [9, 11, 13, 15–17]. As differences in scan positions during the MRI examination seem to hamper the detection of new lesions, a voxel-based registration of pairs of images has been proven to be helpful to evade this problem [18]. Among others, subtraction of previously co-registered and intensity-normalized pairs of images is a well-investigated method, which supports the delineation of new lesions [9, 15, 19]. With the recent advent of artificial intelligence, several machine learning techniques have been proposed to improve automated delineation of pathologies [5, 20–22].

However, many of these techniques may not be suitable in clinical routine, as they either require special training or difficult implementation in the clinical workflow or are time consuming [11, 23]. Hence, no standard tool has been established in radiological routine [13]. Thus, investigations of accessible automated tools that assist radiological decision making are of high clinical interest [10, 24]. We hypothesized that an AC reading approach with lesion color-coding would improve the assessment of MRI examinations in patients with MS but may be too time consuming to implement in clinical praxis. Therefore, the purpose of this study was to compare an AC reading approach with a conventional reading approach (CR) in axial and sagittal FLAIR sequences in follow-up examinations of patients with MS, especially regarding diagnostic accuracy and required rating time.

Methods and materials

This retrospective study was performed after institutional review board approval with waved informed consent. It was conducted in accordance with the ethical regulations of the Declaration of Helsinki including its later amendments. All cerebral MRI exams were performed for clinical indications; no MRI was conducted solely for the purpose of this study.

Identification of potential study subjects was conducted based on a combined exploration of the picture archiving and communication system (PACS) and radiological information system (RIS) employing the following criteria:

1. Diagnosed MS
2. Age ≥ 18 years
3. At least two cerebral MRI examinations with axial and/or a FLAIR sequences between 1 January 2010 and 30 October 2017, either performed in our institution or provided from referring institutions.

Consecutively, 70 pairs of follow-up datasets from 53 patients were identified and included in the study. No patients were excluded from this study.

MRI datasets

MRI datasets were provided by our institution ($n = 131$) and by referring institutions ($n = 9$) consisting of different vendors, scanner generations, and field strengths (1.0 T/1.5 T/3 T). Detailed scan parameters are given in Table 1. In total, 37 pairs of axial and 33 pairs of sagittal FLAIR sequences were available.

Conventional and automated co-registration approach

Standard CR was carried out within the PACS software, which is routinely used in clinical practice in our institution (Impax EE

Table 1 Detailed MRI scan parameters

Parameter	Philips Ingenia 3.0 T		Philips Ingenia 1.5 T		Philips Achieva 3.0 T	
	Axial FLAIR	Sagittal FLAIR	Axial FLAIR	Sagittal FLAIR	Axial FLAIR	Sagittal FLAIR
Field of view (mm)	560 × 560	560 × 560	432 × 432	256 × 256	512 × 512	560 × 560
Matrix	280 × 211	280 × 189	256 × 160	256 × 177	256 × 201	280 × 209
Slice thickness (mm)	5.0	5.0	5.0	5.0	4.0	4.0
Repetition time (ms)	12,000	12,000	6000	6000	12,000	12,000
Echo time (ms)	140	140	140	120	140	140
Inversion time (ms)	2850	2850	2000	2000	2850	2850
Parameter	Philips Achieva 1.5 T		Philips Intera 1.5 T		Philips Panorama 1.0 T	
	Axial FLAIR	Sagittal FLAIR	Axial FLAIR	Sagittal FLAIR	Axial FLAIR	Sagittal FLAIR
Field of view (mm)	256 × 256	320 × 320	240 × 240	320 × 320	256 × 256	n/a
Matrix	256 × 172	300 × 150	232 × 174	312 × 219	256 × 158	n/a
Slice thickness (mm)	6.0	6.0	4.0	4.0	6.0	n/a
Repetition time (ms)	6000	6000	6000	5906	6000	n/a
Echo time (ms)	120	120	100	100	120	n/a
Inversion time (ms)	2000	2000	2000	2000	2000	n/a
Parameter	Range of scanner parameters of referring institutions (Siemens, Toshiba, Philips [1.5–3.0 T])					
	Sagittal FLAIR		Axial FLAIR			
Field of view (mm)	256 × 256–488 × 512		256 × 256–568 × 640			
Matrix	256 × 184–320 × 192		256 × 172–320 × 192			
Slice thickness (mm)	4.0–6.0		4.0–6.0			
Repetition time (ms)	5307–9000		6000–12,000			
Echo time (ms)	83–120		100–140			
Inversion time (ms)	2000–2500		2000–2850			

FLAIR fluid-attenuated inversion recovery, *n/a* not available

R20, XVII SU1, Agfa Healthcare). The corresponding FLAIR sequences were ordered side by side while adjustment of window settings was allowed. A manual linking of the sequences was possible, while scrolling through the images.

For the AC approach, a recently released CE-certified and FDA-approved AC algorithm (LoBI, Philips Healthcare) was applied. The AC approach is integrated into Intellispace Portal (ISP v.10, Philips Healthcare). After selecting the sequences to be compared, the AC application automatically co-registers and merges both sequences. The AC application performs a normalization on the intensity of the selected images. This normalization is executed on brain level and not separately for gray and white matter. The contrast ratio remains unchanged. Therefore, only sequences with similar contrast are comparable. Apart from FLAIR, the application is able to process other sequences, such as T2w (see Fig. 1). After co-registration, both sequences are linked and can be viewed on the same anatomic level. If needed, the co-registration can be corrected manually. Additionally, an color-coding approach (AC) as well as for axial and sagittal scan orientation. Diagnostic accuracy is given in percent (%)

Table 2 Contingence table for both readers. True positive (TP), false positive (FP), true negative (TN), and false negative (FN) are reported for conventional reading (CR) and for the automated co-registration with

Reader	MRI scan orientation	CR: change vs. stable					AC: change vs. stable				
		TP	FP	TN	FN	Accuracy (%)	TP	FP	TN	FN	Accuracy (%)
Reader 1	Axial	6	6	13	12	51	12	0	21	4	89
	Sagittal	13	3	15	2	84	13	3	17	0	91
	All	19	9	28	14	67	25	3	38	4	90
Reader 2	Axial	5	7	19	6	65	11	1	21	4	86
	Sagittal	11	5	14	3	76	13	3	16	1	88
	All	16	12	33	9	70	24	4	37	5	87

overlay map is created, which color-codes progressive or new lesions, respectively, as red, while regressive lesions are indicated blue. The overlay map is shown as a third screen in addition to both MRI sequences, whereby readers can check and confirm the highlighted lesions on the original sequences (see Fig. 2). The intensity of the color-coding can be adjusted using a seamless slider. All three sequences are linked and can be viewed simultaneously (Fig. 1).

Subjective rating

Two blinded radiologists (KRL, SP) with 4 years and 7 years of experience in neuroimaging independently rated pairs of MRI datasets in two sessions: a CR session and an AC session. Brain lesions were assessed for (a) progression (new lesions and/or increasing lesion size), (b) regression (diminished lesions and/or decreasing lesion size), (c) mixed changes (both diminishing/decreasing lesions and increasing/new lesions), or (d) stable disease of MS (no change in lesion amount or size).

An independent timekeeper recorded the time needed for decision-making. Further, the time required for the AC application to start, load, and match the patient data was recorded. Readers were blinded to clinical patient data and the readings were conducted at the same dedicated workstation in intervals of 4 weeks to avoid a recall bias. Before each reading, the patient order was randomized.

Consensus for ground truth was obtained by two radiologists, including a senior neuroradiologist (JB, DZ with 11 years and 4 years of experience), who did not participate in the subjective rating. Definitive determination of progression, regression, mixed changes, or stable disease was conducted by these two radiologists in consensus, taking all available imaging data from AC and CR as well as all radiological reports, follow-up investigations, clinical data such as laboratory data, findings of neurological examinations, and detailed medical history into account.

Statistical analysis

Statistical analyses were performed using JMP software (Version 13, SAS Institute). Continuous variables are written as mean ± standard deviation (SD). The interrater agreement was determined using kappa statistics, whereby kappa coefficient was interpreted as suggested in previous publications: excellent agreement ($\kappa \geq 0.8$), good agreement ($\kappa \geq 0.6$), moderate agreement ($\kappa \geq 0.4$), poor agreement ($\kappa \leq 0.4$). The difference between dichotomous variables was evaluated using McNemar's test and the difference between continuous variables using the Wilcoxon test. Statistical significance was set to $p \leq 0.05$.

Results

Study cohort

Of the 53 included patients, 41 were female and 12 were male. Mean patient age was 40 years (SD 14 years, range 18–71 years).

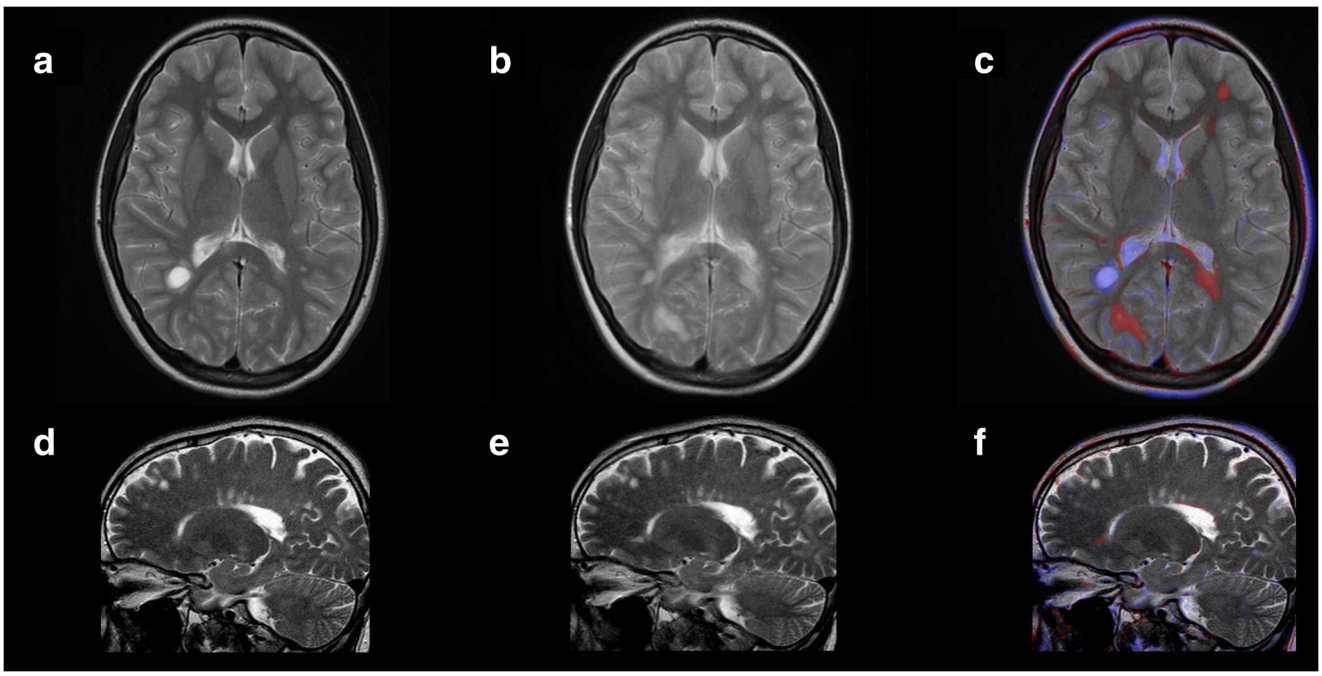

Fig. 1 Sagittal and axial T2w images of two patients. Baseline examinations (**a** and **d**, left) and corresponding follow-up exam (**b** and **e**, middle) and overlay map with color-coded lesions (**c** and **f**, right). Progressive lesions are marked in red and diminishing lesions in blue

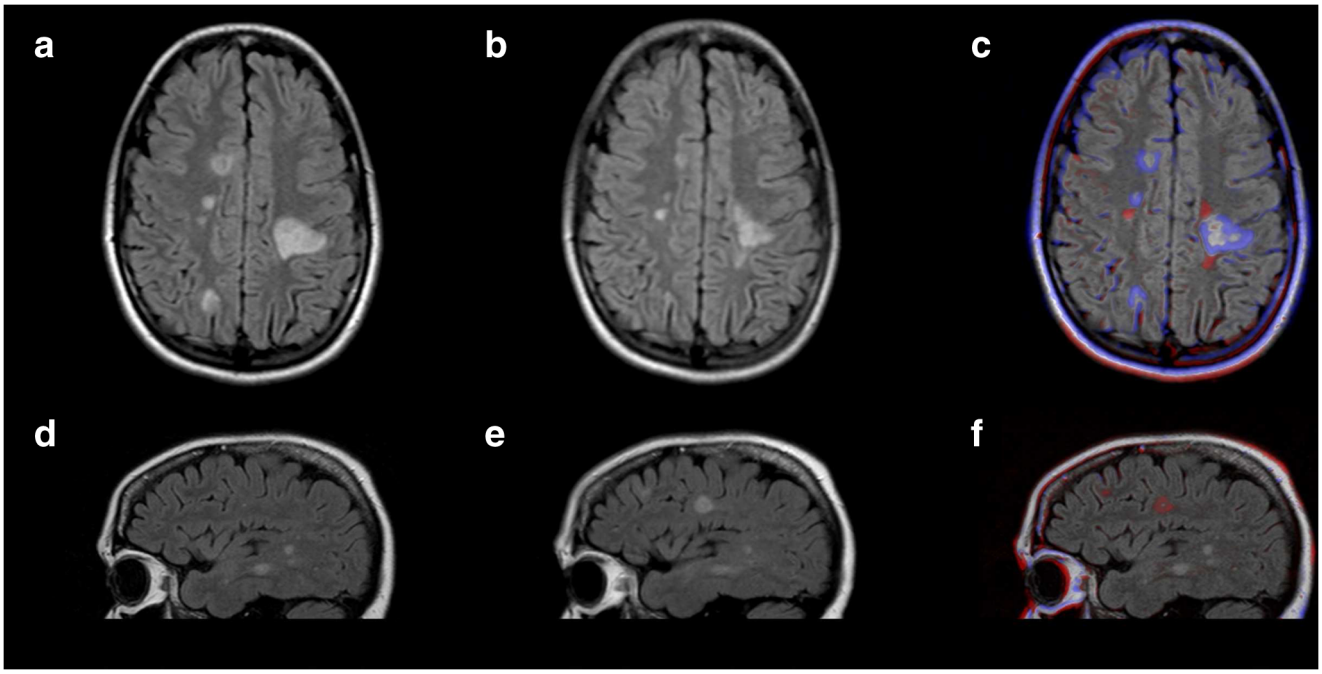

Fig. 2 Sagittal and axial FLAIR of two patients. Baseline examinations (**a** and **d**, left) and corresponding follow-up exam (**b** and **e**, middle) and overlay map with color-coded lesions (**c** and **f**, right). Progressive lesions are marked in red and diminishing lesions in blue

Rating time

The AC application took an average of 7 (± 0.05) s to start and 7 (± 0.07) s to load and co-register the MRI datasets. The mean time required for both readers to assess a pair of MRI datasets in CR was 78 (± 36) s and significantly decreased to 44 (± 22) s with AC ($p < 0.001$; see Fig. 3).

Interrater agreement

Interrater agreement between both readers increased from 0.52 in the CR approach to 0.67 in the AC approach. Between both raters and consensus, interrater agreement increased from 0.47 (reader 1) and 0.50 (reader 2) in the CR approach to 0.83 (reader 1) and 0.78 (reader 2) in the AC approach (see Fig. 4).

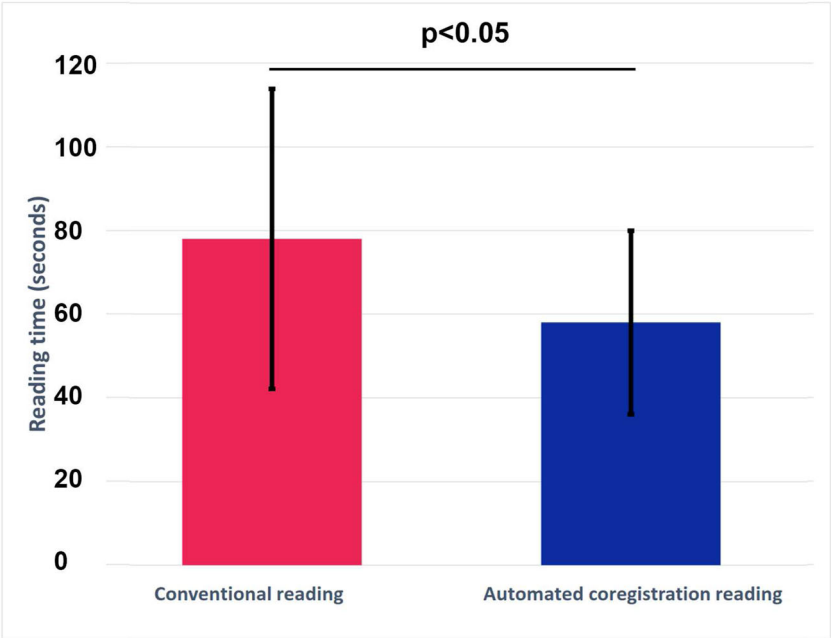

Fig. 3 Reading time (in seconds) is significantly reduced when using the automated co-registration and lesion color-coding image reading approach (AC) in comparison with conventional reading

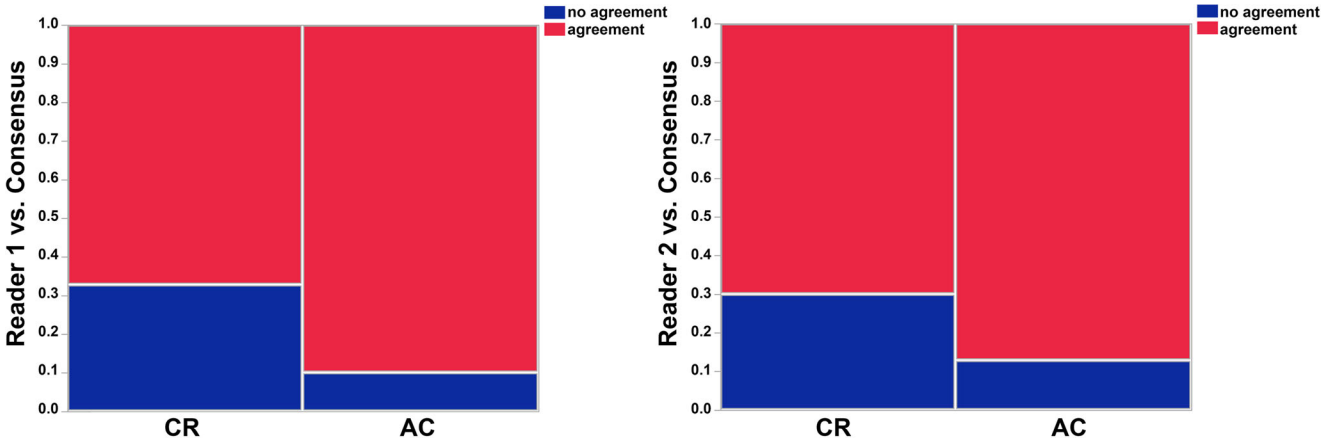

Fig. 4 Agreement between reader 1 (left) and consensus as well as agreement between reader 2 (right) and consensus was higher when using the automated co-registration and lesion color-coding image reading approach (AC) in comparison with the conventional reading (CR)

The diagnostic accuracy increased from 67 to 90% (reader 1, $p < 0.001$) and from 70 to 87% (reader 2, $p < 0.01$) in the AC approach in comparison with the CR approach (see Fig. 5 and Table 2).

Discussion

This study compared the assessment of MRI follow-up examinations in multiple sclerosis patients augmented by automated co-registration with color-coding (AC) with that by the commonly used reading technique (CR). The used AC algorithm automatically matches the corresponding MRI sequences, which then can be viewed at the exact same anatomical height and further color-codes regressive and progressive respectively new lesions by creating an overlay map.

Interrater agreement between both readers as well as between readers and consensus was significantly improved in the AC approach in comparison with the CR technique, from a moderate to a good respectively excellent agreement. These results are in line with previously published studies, which compared conventional reading performed by successively scrolling through images with different assisting techniques, such as subtraction procedures, automated segmentation, and co-registration-fusion methods, and found an improved detection of new lesions [9, 11, 15–17, 19, 25]. As follow-up examinations in patients with MS are frequent in daily radiological routine and an alteration of neurological treatment often depends on radiological findings [26, 27], an increased diagnostic accuracy may have a decisive impact on patient care. Especially general radiologists, who are not subspecialized in neuroradiological imaging, could benefit from assisting techniques, such as the evaluated AC application, as they often have a lower diagnostic accuracy [27]. However, many previous investigated tools are not implemented in the PACS, are time consuming to operate, or require specific training, which hampers their usage in clinical routine [9, 11, 23]. In contrast, the evaluated AC approach in this study is launched directly within the PACS, does not require specific training, and may therefore be more practical in a clinical environment. As it only took a few seconds to start and calculate the co-

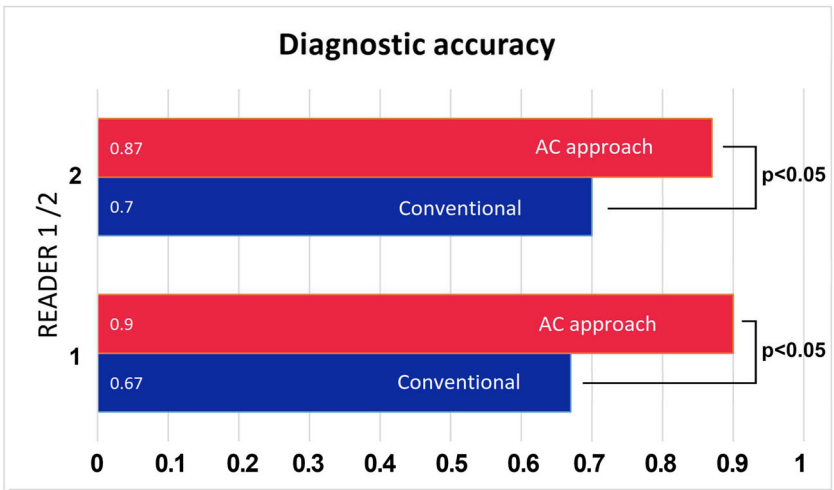

Fig. 5 Diagnostic accuracy of both readers was increased in comparison with the conventional reading (CR) when the automated co-registration and lesion color-coding image reading approach (AC) was employed

registered overlay maps, a delay in working routine seems unlikely. Regarding reading time itself, the AC approach in our study significantly reduced the required time to read and compare two MRI datasets and may therefore alleviate the radiological workload, which increases continually [28]. Further, other approaches used homogenous data from few scanners [11], whereas we included a wide variety of acquisition protocols, scanner types, and field strengths.

There are limitations to this study that need to be considered: First, apart from the retrospective study design, both readers could not be blinded to the reading method (CR vs. AC) they were using, which could cause a study bias. Second, we solely investigated FLAIR sequences, while T2w and contrast-enhanced T1w sequences are further and important means in the setting of MS [9, 17]. Third, although a latency period of 4 weeks was set between the CR and AC reading, a remaining influence by recall bias cannot be excluded entirely. Likewise, the readers had different levels of experience, which could cause a bias regarding both diagnostic accuracy and required reading time.

Conclusion

The tested automated co-registration reading approach of brain lesions in patients with multiple sclerosis significantly reduced the required time to evaluate MRI follow-up exams and increased diagnostic accuracy for lesion detection in comparison with the conventional reading. Hence, it could markedly accelerate this type of assessment when being applied in the clinical routine.

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Compliance with ethical standards

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Conflict of interest The authors of this manuscript declare relationships with the following companies:

Jan Borggrefe received speaker honoraria from Philips.

Statistics and biometry No complex statistical methods were necessary for this paper.

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

Ethical approval Institutional Review Board approval was obtained.

Methodology

- Retrospective
- Diagnostic or prognostic study
- Performed at one institution

References

1. Karussis D (2014) The diagnosis of multiple sclerosis and the various related demyelinating syndromes: a critical review. J Autoimmun 48-49:134–142
2. Ramagopalan SV, Sadovnick AD (2011) Epidemiology of multiple sclerosis. Neurol Clin 29(2):207–217
3. Dilokthornsakul P, Valuck RJ, Nair KV, Corboy JR, Allen RR, Campbell JD (2016) Multiple sclerosis prevalence in the United States commercially insured population. Neurology 86(11):1014–1021
4. Simpson S Jr, Blizzard L, Otahal P, van der Mei I, Taylor B (2011) Latitude is significantly associated with the prevalence of multiple sclerosis: a meta-analysis. J Neurol Neurosurg Psychiatry 82(10): 1132–1141
5. Danelakis A, Theoharis T, Verganelakis DA (2018) Survey of automated multiple sclerosis lesion segmentation techniques on magnetic resonance imaging. Comput Med Imaging Graph 70:83–100
6. Gramsch C, Nensa F, Kastrup O et al (2015) Diagnostic value of 3D fluid attenuated inversion recovery sequence in multiple sclerosis. Acta Radiol 56(5):622–627
7. Thompson AJ, Banwell BL, Barkhof F et al (2018) Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 17(2):162–173
8. Katz Sand IB, Lublin FD (2013) Diagnosis and differential diagnosis of multiple sclerosis. Continuum (Minneap Minn) 19(4 Multiple Sclerosis):922–943
9. Battaglini M, Rossi F, Grove RA et al (2014) Automated identification of brain new lesions in multiple sclerosis using subtraction images. J Magn Reson Imaging 39(6):1543–1549
10. Patel N, Horsfield MA, Banahan C et al (2017) Detection of focal longitudinal changes in the brain by subtraction of MR images. AJNR Am J Neuroradiol 38(5):923–927
11. Galletto Pregliasco A, Collin A, Guéguen A et al (2018) Improved detection of new MS lesions during follow-up using an automated MR coregistration-fusion method. AJNR Am J Neuroradiol 39(7): 1226–1232
12. Sweeney EM, Shinohara RT, Shea CD, Reich DS, Crainiceanu CM (2013) Automatic lesion incidence estimation and detection in multiple sclerosis using multisequence longitudinal MRI. AJNR Am J Neuroradiol 34(1):68–73
13. Roura E, Oliver A, Cabezas M et al (2015) A toolbox for multiple sclerosis lesion segmentation. Neuroradiology 57(10):1031–1043
14. García-Lorenzo D, Francis S, Narayanan S, Arnold DL, Collins DL (2013) Review of automatic segmentation methods of multiple sclerosis white matter lesions on conventional magnetic resonance imaging. Med Image Anal 17(1):1–18
15. Horsfield MA, Rocca MA, Pagani E et al (2016) Estimating brain lesion volume change in multiple sclerosis by subtraction of magnetic resonance images. J Neuroimaging 26(4):395–402
16. Cabezas M, Corral JF, Oliver A et al (2016) Improved automatic detection of new T2 lesions in multiple sclerosis using deformation fields. AJNR Am J Neuroradiol. https://doi.org/10.3174/ajnr.A4829
17. Jain S, Sima DM, Ribbens A et al (2015) Automatic segmentation and volumetry of multiple sclerosis brain lesions from MR images. Neuroimage Clin 8:367–375
18. Tan IL, van Schijndel RA, Fazekas F et al (2002) Image registration and subtraction to detect active T(2) lesions in MS: an interobserver study. J Neurol 249(6):767–773
19. Ganiler O, Oliver A, Diez Y et al (2014) A subtraction pipeline for automatic detection of new appearing multiple sclerosis lesions in longitudinal studies. Neuroradiology 56(5):363–374
20. Laukamp KR, Thiele F, Shakirin G et al (2018) Fully automated detection and segmentation of meningiomas using deep learning on routine multiparametric MRI. Eur Radiol. https://doi.org/10.1007/s00330-018-5595-8

21. Salem M, Cabezas M, Valverde S et al (2018) A supervised framework with intensity subtraction and deformation field features for the detection of new T2-w lesions in multiple sclerosis. Neuroimage Clin 17:607–615
22. Nguyen TD, Zhang S, Gupta A, Zhao Y, Gauthier SA, Wang Y (2018) Fast and robust unsupervised identification of MS lesion change using the statistical detection of changes algorithm. AJNR Am J Neuroradiol 39(5):830–833
23. van Heerden J, Rawlinson D, Zhang AM et al (2015) Improving multiple sclerosis plaque detection using a semiautomated assistive approach. AJNR Am J Neuroradiol 36(8):1465–1471
24. Castellino RA (2005) Computer aided detection (CAD): an overview. Cancer Imaging 5:17–19
25. Bilello M, Arkuszewski M, Nasrallah I, Wu X, Erus G, Krejza J (2012) Multiple sclerosis lesions in the brain: computer-assisted assessment of lesion load dynamics on 3D FLAIR MR images. Neuroradiol J 25(1):17–21
26. Krauss W, Gunnarsson M, Nilsson M, Thunberg P (2017) Conventional and synthetic MRI in multiple sclerosis: a comparative study. Eur Radiol 28(4):1692–1700
27. Wang W, van Heerden J, Tacey MA, Gaillard F (2017) Neuroradiologists compared with non-neuroradiologists in the detection of new multiple sclerosis plaques. AJNR Am J Neuroradiol 38(7):1323–1327
28. Chokshi FH, Hughes DR, Wang JM, Mullins ME, Hawkins CM, Duszak R Jr (2015) Diagnostic radiology resident and fellow workloads: a 12-year longitudinal trend analysis using national Medicare aggregate claims data. J Am Coll Radiol 12(7):664–669