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The added value of double inversion recovery (DIR) sequence compared to fluid attenuation inversion recovery (FLAIR) in identifying multiple sclerosis lesions and different cortical subtypes

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ABSTRACT

Background. There is a rising concern about multiple sclerosis (MS) lesions that occur in the cortical gray matter (GM), owing to its direct relationship with the disability and cognition dysfunction that occur during the MS course. Two magnetic resonance imaging (MRI) sequences that aid in the precise identification of these lesions are the Double Inversion Recovery (DIR) and Fluid Attenuation Inversion Recovery (FLAIR) sequences.

Objective. To study the importance of the DIR for brain lesion detection and the various cortical subtypes distinction in MS-diagnosed patients and its correlations to the level of patient disability by comparing it to FLAIR.

Patients and Methods: Thirty MS patients participated in this retrospective cross-sectional study, who had been previously diagnosed with MS and were routinely followed up at the Radiology Department at Ain-Shams University.

Results. Comparing the DIR sequence to FLAIR, the overall MS lesion detection enhanced by 8% ($p<0.001$). Regarding the detection of cortical lesion subtypes (I–IV), it was discovered that the DIR sequence revealed significantly more lesions than FLAIR ($p<0.001$). The cortical lesions detected by DIR or FLAIR were found to have positive, highly significant correlations with both patients' disability and the MS duration.

Conclusion. For lesion identification, DIR is more effective than FLAIR, particularly for cortical and juxtacortical lesions in MS patients.

Keywords: multiple sclerosis, FLAIR, DIR, cortical lesions

List of abbreviations

CL – Cortical lesions
CSF – Cerebrospinal fluid
DIR – Double inversion recovery
EDSS – Expanded Disability Status Scale
FLAIR – Fluid attenuation inversion recovery
GM – Grey matter
MS – Multiple sclerosis
RRMS – Relapsing remittent multiple sclerosis
PPMS – primary-progressive multiple sclerosis
WM – White matter

INTRODUCTION

One of many conditions that can lead to physical and mental impairment is multiple sclerosis (MS) disease, in which plaques with inflammatory, demyelinating, and neurodegenerative nature evolved in any central nervous system (CNS) region [1]. On magnetic imaging resonance (MRI), the diagnostic scan of choice, white matter (WM) MS plaques are mostly conspicuous. Nevertheless, there is a rising concern about MS lesions that occur in the cortical gray matter (GM), owing to its direct relationship with the dis-

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ability and cognition dysfunction that occurs during the MS course [2].

Currently, the MS diagnostic criteria encompass cortical as well as juxtacortical lesions instead of solely juxtacortical lesions. This is due to the discovery that cortical GM lesions, which can be seen on MRIs, are a pathologic marker for the disease [3].

It has been determined that cortical lesions fall into four categories: type I lesions impact the WM and GM; type II lesions are small, perivascular, and completely integrated into the cerebral cortex; type III lesions are subpial demyelinated areas that with or without involving the cortex's layers; and lesions that affect the whole cortex width without penetrating the subcortical WM, known as type IV lesions [4].

Using conventional MRI, including the Fluid Attenuation Inversion Recovery (FLAIR) sequence, GM cortical lesions may not be noticeable because of their tiny size and low contrast in comparison to normal appearance [5].

Advances in MRI have improved the visualization of cortical plaques, particularly by using the double inversion recovery (DIR) sequence. Whereas a single inversion pulse is used in FLAIR, the DIR sequence uses two separate inversion pulses to attenuate not only CSF but also the entire WM, resulting in a better demarcation of the WM and GM. However, because DIR requires longer acquisition periods (10–15 minutes), it is generally not included in the standard protocol of diagnostic and clinical trial evaluation [6].

Our objective was to compare the efficacy of the DIR and FLAIR in identifying brain lesions and differentiating cortical subtypes in MS patients, as well as its influence on determining the patient's degree of disability.

PATIENTS AND METHODS

In this cross-sectional retrospective analysis, 30 MS patients, ranging in age from 18 to 60, were on routine follow-up at the Ain-Shams Radiology Department's MRI unit. All patients were previously diagnosed with MS based on the 2017 revised McDonald criteria [3].

After obtaining approval from our Institutional Ethical Committee, the whole procedure was explained in detail to the patients, and informed consent was obtained from each patient.

Patients with poor general health, those with insufficient clinical data, or those without an expanded disability status scale score (EDSS)were not included. Additionally, patients with recognized contraindications for MRI, such as pacemakers, implanted magnetic devices, or claustrophobia, were denied access.

Philips Ingenia was used to scan every single patient. A head coil (quadrature detection, Transmit/Receive coil solution) brain MRI was applied for each patient while lying supine. MRI sequences were as follows: Axial T1 weighted images; T1WI (Repetition Time (TR) = 581, Time to Echo (TE) = 15), Sagittal T1WI (TR = 142, TE = 2.2), Axial T2 weighted images; T2WI (TR = 4846, TE = 110), Coronal T2WI (TR = 4811, TE = 120), Axial FLAIR (TR = 11000, TE = 130), Sagittal FLAIR (TR = 10000, TE = 140), Axial Diffusion weighted images (DWI) and Apparent diffusion coefficient; ADC maps (TR = 3935, TE = 114), and finally 3D-DIR (TR = 5500, TE = 317).

Two radiologists examined and evaluated every scan. On axial T2WI, comprehensive brain analysis was carried out in addition to FLAIR and DIR sequences. The following criteria were used to evaluate hyperintense demyelinating lesions in axial FLAIR and DIR sequences: 1) Lesion load, which supplies the total Lesion number per patient in DIR and FLAIR sequences separately; and 2) Lesions Site. The cortical lesions were categorized into 4 subtypes (I - VI) [4].

The expanded disability status scale (EDSS), which had a score range from 0 (no impairment) to 10 (patient death due to MS), is measured to find its correlation with cortical lesion load.

Statistical analysis:

The collected data were examined using SPSS Inc.'s statistical program for social sciences, version 23.0 (Chicago, Illinois, USA). The ranges and mean ± standard deviation were used to present the quantitative data. Additionally, percentages and figures were used to represent qualitative characteristics. When comparing two sets of non-parametric data, the Mann-Whitney U test was employed. In the event that one or both of the variable sets were skewed, Spearman's rank correlation coefficient (rs) was utilized to find the associated degree between different variables. Significance was distinct when a p-value of less than 0.05.

RESULTS

Patient ages ranged from 21 to 54 years old, with a mean ± SD of 31.20 ± 7.81 years. The female-to-male ratio was 1.7:1, with 63.3% of the population being female and 36.7% being male. When the patients were diagnosed with MS, their ages ranged from 18 to 44 years old, with a mean ± SD of 26.07 ± 6.31 years. The duration of MS ranged from 2 to 11 years, with a mean ± SD of 4.80 ± 2.17 years. The EDSS had a mean of 2.30 ± 1.33 and ranged from 0 to 6.5. Relapsing-remitting MS (RRMS) accounted for 96.7 percent of MS-diagnosed patients, while only one patient (3.3%) had primary-progressive MS (PPMS) (Table 1).

DIR significantly improved the detection of juxtacortical lesions by 53% ($p<0.001$) (Figure 1), cortical lesions by 72% ($p<0.001$) (Figure 1), and infratentorial

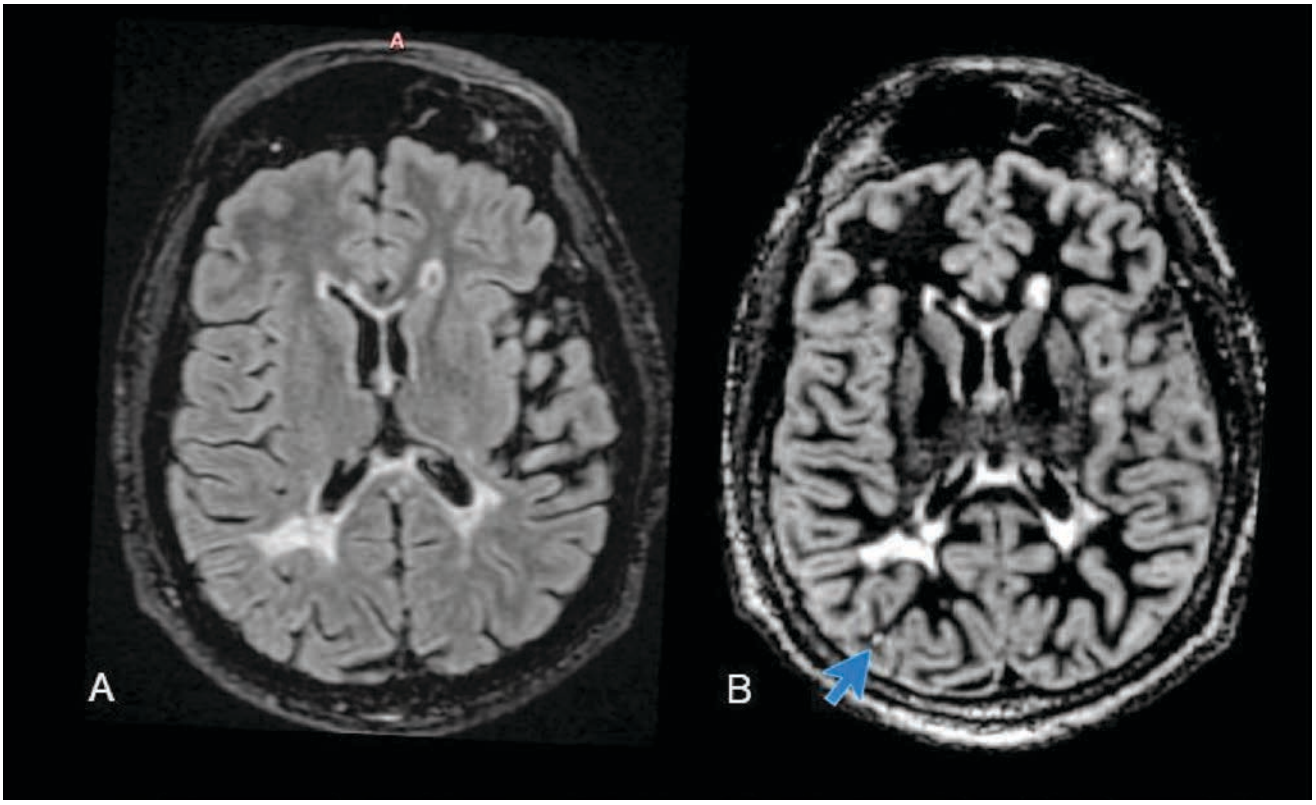

FIGURE 1. A female patient, 34 years old, with RRMS with an EDSS score of 2.0. At the same level, axial FLAIR (A) and axial DIR (B) revealed a few cortical, periventricular plaques not found in the FALIR sequence, but on DIR (cortical/juxtacortical lesions (blue arrow)

TABLE 1. Clinical information and demographics of MS diagnosed patients

Demographic and clinical data	Total (n=30)
Gender	
Female	19 (63.3%)
Male	11 (36.7%)
Age "years"	
Range	21-54
Mean±SD	31.20±7.81
Age at diagnosis (years)	
Range	18-44
Mean±SD	26.07±6.31
The disease of duration "years"	
Range	2-11
Mean±SD	4.80±2.17
EDSS	
Range	0-6.5
Mean±SD	2.30±1.33
MS TYPE	
PPMS	1 (3.3%)
RRMS	29 (96.7%)

involved lesions by 66% (p= 0.012) compared to FLAIR. Whereas FLAIR significantly improved the detection of periventricular lesions by 33% (p= 0.004) and corpus callosum lesions by 45% (p<0.001) than the DIR. Both the DIR and FLAIR sequences demonstrated similar levels of identification of craniocervical junction lesions and deep WM-involved ones. Overall, the DIR sequence enhanced the detection of MS lesions by 8% and outperformed FLAIR in the detection of all MS. (p<0.001) (Table 2).

Regarding the identification of cortical lesions of types I, II, III, and IV, we found that the DIR sequence detected considerably more lesions than FLAIR. (p<0.001) (Table 3) (Figures 2, 3, and 4).

The identified cortical lesions number by DIR showed highly significant positive relationships with the EDSS (r=0.579; p <0.001) and the MS duration (r=0.670; p <0.001). The quantified periventricular (r=0.428; p=0.018), deep WM (r=0.471; p=0.009), infratentorial-involved (r=0.395; p=0.031), and corpus callosum-involved lesions count (r=0.468; p=0.009) determined by DIR also showed a significant positive correlation with the EDSS (Table 4).

Additionally, the count of cortical involved lesions detected by FLAIR showed highly positive significant relationships with the (EDSS) (r= 0.466; p= 0.009) and the MS duration (r= 0.665; p <0.001). The count of periventricular (r=0.417; p=0.022), deep WM (r=0.404; p=0.027), juxtacortical (r=0.388; p=0.034), infratentorial (r=0.407; p=0.026), and corpus callosum (r=0.436; p=0.016) involved lesions that were identified by FLAIR also displayed a significantly positive correlation with the EDSS (Table 5).

TABLE 2. Comparison between DIR and FLAIR according to lesions involved regions

Lesions regions	DIR		FLAIR		% improvement	Test value	p-value	Sig.
	Mean±SD	No	Mean±SD	No				
Periventricular	8.90±3.19	267	11.8 ± 4.3	355	33	2.967	0.004	HS
Deep white matter	8.17±3.28	245	8.00±3.39	240	2	0.193	0.847	NS
Juxtacortical	10.03±3.12	301	6.53±2.10	196	53	5.096	0.000	HS
Cortical	13.17±4.56	395	7.67±3.42	230	72	5.289	0.001	HS
Infratentorial	2.93±1.98	88	1.77±1.48	53	66	2.585	0.012	S
Cranio-cervical junction	1.07±0.98	32	0.67±0.88	20	60	1.660	0.102	NS
Corpus callosum	8.00±2.70	240	11.60±3.62	348	45	4.367	0.000	HS
Overall of lesions		1568		1442	8		0.000	HS

TABLE 3. Comparison between DIR and FLAIR according to cortical subtypes

Cortical subtypes	DIR		FLAIR		% improvement	Test value	p-value	Sig.
	Mean±SD	No	Mean±SD	No				
TYPE I	5.03±1.94	151	3.50±1.59	105	44	3.348	0.001	HS
TYPE II	6.20±2.16	186	3.37±1.77	101	84	5.562	0.000	HS
TYPE III	0.57±0.57	17	0.10±0.31	3	67	3.963	0.000	HS
TYPE IV	1.37±0.76	41	0.70±0.53	21	95	3.912	0.000	HS
Overall lesions of Cortical		395		230	72	5.289	0.000	HS

TABLE 4. Correlation between clinical data with regions of lesions in DIR

DIR	Disease of duration «years»		EDSS	
	Rs	p-value	Rs	p-value
Number of Periventricular lesions	0.059	0.760	0.428	0.018*
Number of Deep WM lesions	0.105	0.581	0.471	0.009*
Number of Juxtacortical lesions	0.195	0.303	0.325	0.079
Number of Cortical lesions	0.670	<0.001**	0.579	<0.001**
Infratentorial lesions	0.070	0.713	0.395	0.031*
Cranio-cervical junction lesions	-0.191	0.312	0.087	0.646
Corpus callosum lesions	0.367	0.046	0.468	0.009*

TABLE 5. Correlation between clinical data with regions of lesions in FLAIR

FLAIR	Disease of duration «years»		EDSS	
	Rs	p-value	Rs	p-value
Number of Periventricular lesions	0.149	0.432	0.417	0.022*
Number of Deep WM lesions	0.190	0.322	0.404	0.027*
Number of Juxtacortical lesions	0.224	0.243	0.388	0.034*
Number of Cortical lesions	0.665	<0.001**	0.466	0.009*
Infratentorial lesions	0.153	0.428	0.407	0.026*
Cranio-cervical junction lesions	-0.152	0.431	-0.065	0.732
Corpus callosum lesions	0.304	0.109	0.436	0.016*

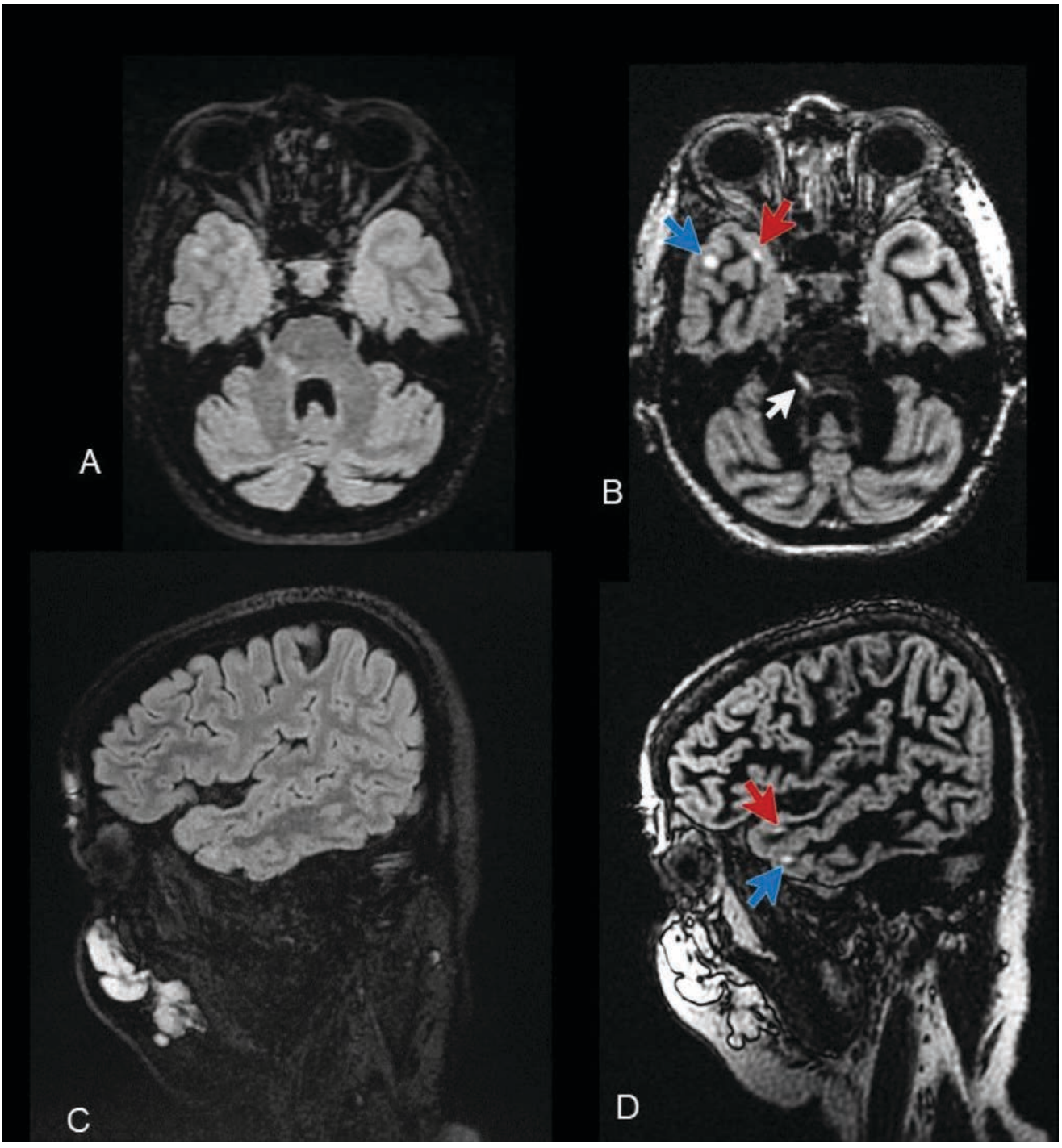

FIGURE 2. A female patient, age 29, has an EDSS score of 3 and RRMS. At the same level, A. Axial FLAIR and B. Axial DIR showed in contrast to the FLAIR Sequence, the DIR sequences clearly showed the right middle cerebellar peduncle plaque (white arrow), with few cortical, infratentorial involved lesions. Cortical type I (blue arrow) and cortical type II (red arrow) were not present in the FALIR sequence, while be indicated in the axial DIR. C. Sagittal FLAIR. D. Sagittal DIR at the same altitude demonstrated Axial DIR revealed two cortical types that were not discovered in the FALIR sequence: cortical type I (indicated by blue arrow) and cortical type II (indicated by red arrow)

DISCUSSION

Recently, significant attempts have been made to overcome the limits of conventional MRI by using non-traditional MR metrics to offer precise pathology information about the mechanisms underlying MS using various imaging modalities in an effort to halt the neurodegenerative processes. Among these novel techniques is the DIR sequence [2].

In our work, DIR significantly improved the detection of cortical lesions by 72% ($p<0.001$) compared to FLAIR. Similarly, several studies found that DIR significantly outperforms T2WI and FLAIR in identifying cortical lesions in MS-diagnosed patients. Higazi et al. [7] reported a greater diagnostic performance in detecting the cortical MS plaques with DIR than the FLAIR and T2WI. Furthermore, they noted that

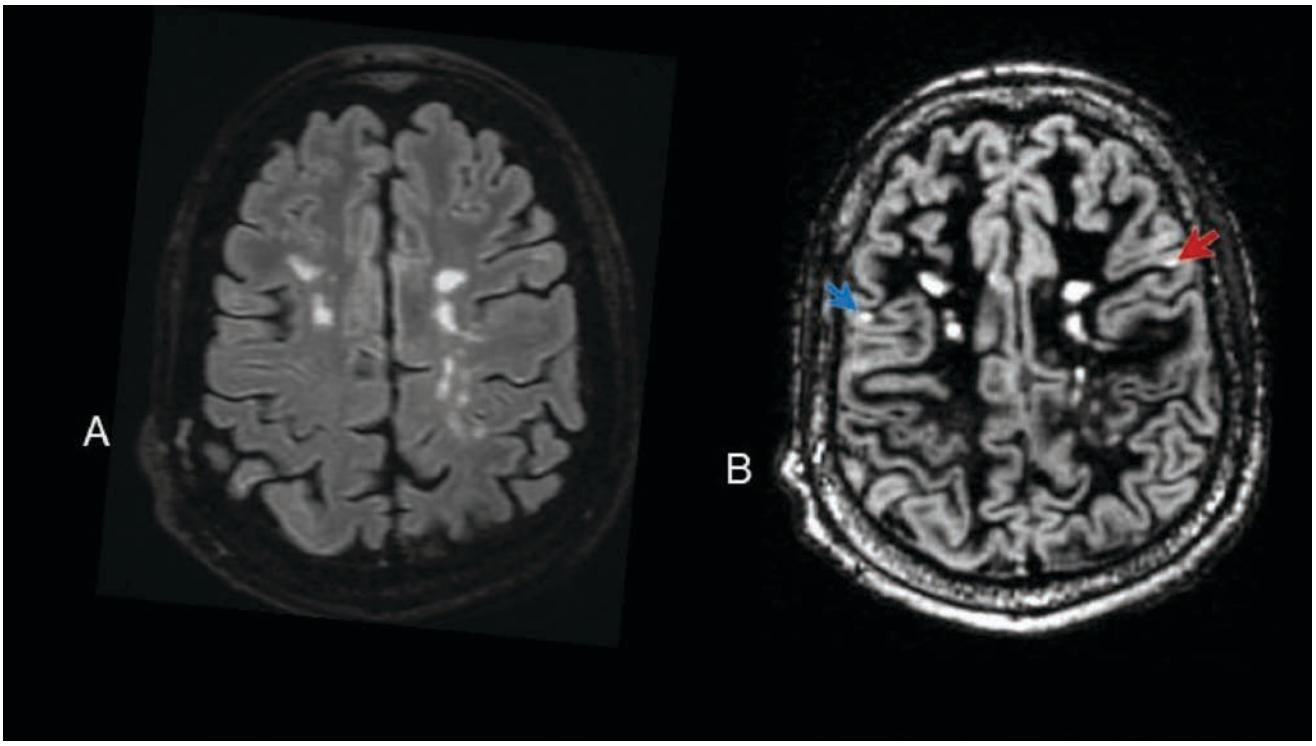

FIGURE 3. A 23-year-old male patient with RRMS has an EDSS score of 2.5. At the same level, Cortical types II (blue arrow) and III (red arrow), which were absent from the FALIR sequence, were found by axial DIR analysis of a few cortical, deep WM plaques, as demonstrated by A. axial FLAIR and B. Axial DIR

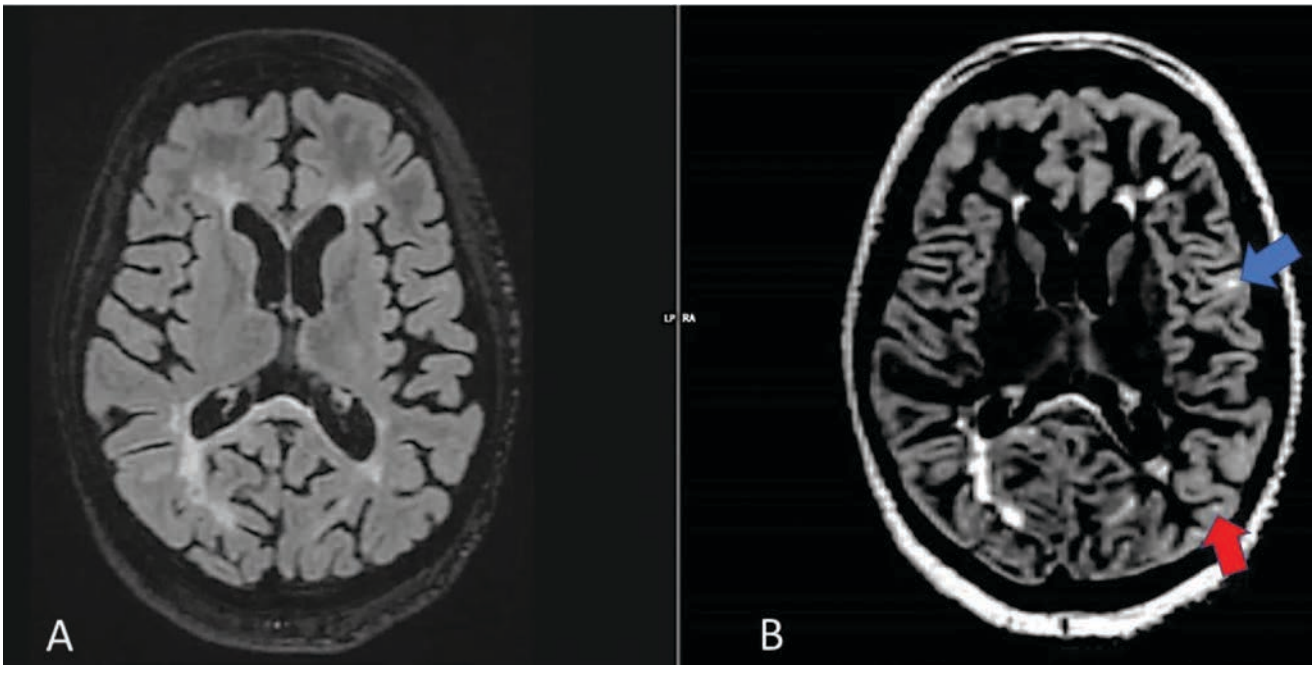

FIGURE 4. A female patient, age 26 with RRMS, and an EDSS score of 2.5. A. Axial FLAIR and B. Axial DIR both identified many cortical and subcortical periventricular plaques at the same level. Additionally, cortical plaque types II (indicated by the red arrow) and I (indicated by the blue arrow) that were absent from the FALIR sequence were revealed by the axial DIR

DIR and FLAIR had a high agreement in identifying cortical MS lesions, indicating that the two sequences are complementary in the MS diagnosis. El-Hussein et al. [8] stated that the cortical MS-involved lesions were considerably larger than MS lesions in FLAIR, which is consistent with our results. ($p < 0.05$). Also, these findings were in line with those of Abdelrahman et al.[9] who demonstrated that DIR identified cortical lesions in MS patients 204% ($p < 0.001$) more accurately than FLAIR.

We also found that, with regard to the cortical lesions classes (I–IV), there were noticeably more lesions apparent in the DIR sequence than in the FLAIR. ($p<0.001$). Our findings support the results of Abdel-

rahman et al. [9] who evaluated the 3D-DIR role in detecting the MS lesions emphasizing the cortical subtypes. According to the authors, the 3D DIR sequence identified considerably more cortical plaques of all types than the FLAIR sequence did. ($p < 0.001$). Earlier, Calabrese et al. [10] revealed that the DIR sequence, especially at later MS stages compared to early stages, has greatly boosted the cortical lesion types detection, involving both intra-cortical lesions and leukocortical lesions.

As regards juxtacortical lesions, following our results in which DIR significantly improved the detection of juxtacortical lesions by 53% ($p<0.001$). Similarly to Geurts et al, juxtacortical lesions were more common on DIR than on FLAIR, according to [11] Elhussein et al. [8] and Abdelrahman et al. [9]. In contrast to our findings, Ertan et al. [16] found that DIR detected 1.76 times more juxtacortical lesions than FLAIR, which were not significant statistically; however, Moraal et al. [13] and Vural et al. [14] observed a greater juxtacortical lesions number using FLAIR than the DIR, even though neither study found a difference with statistical significance.

The ability of DIR to identify infra-tentorial lesions was a significant additional benefit in our study. Comparing DIR to FLAIR, a substantial improvement in lesion detection was found ($p = 0.012$, improvement = 66%). This was consistent with the obtained results by Abdelrahman et al.[9], Elhussein et al. [8], Elnekeidy et al. [15], and Hamed et al. [16]. In contrast, a similar infra-tentorial involvement lesions count identified by DIR, FLAIR, and T2 imaging were detected by Moraal et al. [13].

Conversely, we found FLAIR significantly improved the detection of the periventricular lesions by 33% ($p= 0.004$) compared to the DIR. El-Hussein et al.[8] agreed with our findings, declaring that compared to DIR, FLAIR displayed a noticeably greater occurrence of periventricular lesions. Nevertheless, Abdelrahman et al.[9] reported that DIR was also much better than FLAIR in detecting MS lesions in the periventricular WM, which runs counter to our findings.

The deep WM lesions and craniocervical junction lesions detection in our work were comparable in both DIR and FLAIR sequences. This was consistent with Abdelrahman et al. [9] and Haider et al. [17] studies, however, Elhussein et al.[8] and Elnekeidy et al. [15] revealed deeper WM-involved lesions in the case of DIR [9]. Whereas, Geurts et al. [11] and Vural et al. [14] discovered that, when it came to identifying MS plaques in the deep WM, FLAIR was noticeably more accurate than DIR. For deep WM plaques, the detection rates of the DIR and FLAIR are remarkably comparable, even though the results of the previously mentioned studies indicate different results. This observation may be explained by the plaques' remote placement from the cortical and periventricular areas.

Matching with Elkholy et al. [18], who reported that corpus callosum lesions were significantly higher on FLAIR to DIR imaging ($p = 0.025$), we observed that the corpus callosum lesion detection improved by 45% ($p<0.001$) compared to the DIR.

Overall, in accordance with Elhussein et al.[8], Abidi et al. [19], Almutairi et al. [20], and Abdelrahman et al. [9] studies, our results showed that the DIR sequence enhanced the detection of MS lesions by 8% and outperformed FLAIR in all MS detection. ($p<0.001$).

Previous research found a link between cortical lesions and the cognitive impairment degree that develops in MS-suffering patients, as well as physical disability [7,14,16]. Even, the cortical lesions count can be considered as a potential biomarker of cognitive and neurologic status in MS patients [21].

Similarly, we discovered significant positive correlations between the number of cortical lesions identified by FLAIR or DIR and the EDSS as well as the MS duration. This finding is seen to be a crucial benefit of FLAIR and DIR sequences in resolving the clinical-radiological dispute in multiple sclerosis. Additionally, there were notable positive relationships between the lesions count identified by FLAIR and DIR and the EDSS, namely the corpus callosum, infratentorial, periventricular, and deep WM-involved lesions. However, EDSS was significantly correlated to the juxtacortical lesions detected by FLAIR, not DIR. In addition, craniocervical junction lesions were not correlated to the disease duration or the clinical outcomes.

Relatively matching our results, Abdelrahman et al. [9] exhibited a significant correlation among the total cortical MS count of lesions, juxtacortical lesions, periventricular WM lesions, and the MS disease duration, as well as EDSS. Contrary to our findings, they found no evidence of a significant relationship between the EDSS and the MS disease duration in patients diagnosed with deep WM and infratentorial-related MS plaques.

According to Elkholy et al. [18], the periventricular, deep WM and infratentorial lesion numbers counted by both FLAIR and DIR show a positive association with EDSS. However, this link is not significant statistically.

Using FLAIR and especially DIR to visualize and quantify the cortical lesions in MS patients is a top priority due to the GM-involved damage significance and its impact on the disability of diagnosed patients. It is also encouraged to introduce DIR as a supplementary tool to standard FLAIR and T2 sequences in routine scans.

Our study's cross-sectional retrospective design and limited sample size are its primary limitations.

Furthermore, because measuring the lesions' volume is more challenging technically than counting the number of lesions, we rely on estimating the number of MS lesions rather than their volume in our work.

CONCLUSION

Most MS lesions may be seen by using both FLAIR and DIR imaging, which can cover a gap in neuroimaging. Our findings show that DIR is more supreme than FLAIR in noticing MS plaques, particularly cortical and juxtacortical-involved lesions. Incorporating DIR as an additional tool to FLAIR and T2 sequences during routine scans is critical to observing and quantifying cortical lesions in MS patients, given the significance of Grey Matter damage and its impact on the patient's ability.

Authors' contributions: M.M.A. put the study design, editor of the manuscript, and performed the MRI assessment. K.A.S participated in the MRI assessment and data collection and performed statistical analysis. K.S.A data collection and clinical assessment of the patients. A.M.M. put the idea of the study, participated in the study design, and did an MRI assessment. All authors read and approved the final manuscript.

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Consent for publication: All patients included in this research gave written informed consent to publish the data contained within this study.

Competing interests: The authors declare that they have no competing interests.

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