Role of Recent MRI Technique (Double Inversion Recovery Sequence) in Diagnosis of Multiple Sclerosis Disease

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Abstract

Background: Multiple sclerosis causes neurological impairment in middle-aged and young people. The McDonald criteria help diagnose, whereas T2-weighted and FLAIR MRI are essential for monitoring. The Double Inversion Recovery (DIR) sequence reduces CSF fluid improving diagnostic contrast.

Objectives: To evaluate the role of DIR sequence in detecting brain lesions in MS patients compared to FLAIR and T2 sequences.

Patients and methods: This prospective research at Qena University Hospital examined 100 confirmed MS patients referred from the neurology department diagnostic criteria. The Radiology Department performed extensive assessments, medical history gathering, physical exams, and brain MRI scans with specified sequences (T1-weighted, T2-weighted, FLAIR, DIR). Anatomically classified lesions were utilized to examine MRI effectiveness for MS diagnosis and DIR sequence usefulness compared to FLAIR and T2 sequences.

Results: Patients, mean age 35±9.66years, with a mean sickness duration of 40.05±53.25months, were mostly women (91%). Remission occurred in 83%, secondary progression in 12%, and primary progressive in 5%. The mean EDSS score was 3.65, indicating moderate to severe impairment. DIR detected more lesions than T2, especially cortical lesions(9.37±8.9). Disease duration correlated positively with DIR and FLAIR. EDSS significantly correlated positively with lesions across all MRI.

Conclusion: DIR augments conventional MRI for early MS lesion detection, particularly in shorter illness durations. DIR detects overall and cortical lesions better than T2 and FLAIR. The remarkable correlation between EDSS scores and lesion counts across all MRI modalities shows their clinical relevance in disease severity assessment.

Keywords: Double Inversion Recovery sequence; Diagnosis, Multiple Sclerosis.

DOI: 10.21608/SVUIJM.2024.262335.1783

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Received: 14 January,2024.

Revised: 7 February ,2024.

Accepted: 24 February,2024.

Published: 7 January, 2025

Cite this article as: Ghada Mohamd. Abd Elrazik, Anfal Mohamed Taha, Mahmoud Mohamed Abd Elhamed Abo Elhafiz, Abdalraheem Huessin Ali.(2024). Role of Recent MRI Technique (Double Inversion Recovery Sequence) in Diagnosis of Multiple Sclerosis Disease. *SVU-International Journal of Medical Sciences*. Vol.7, Issue 2, pp: 995-1007.

Introduction

Multiple sclerosis (MS) is a prevalent chronic inflammatory demyelinating disease, often causing neurological disability in middle-aged and young adults. This ailment impacts various regions of the central nervous system, including the periventricular, juxtacortical areas, brainstem, optic nerves, and spinal cord. Notably, many patients exhibit substantial gray matter involvement **(Fymat et al., 2023).**

The principal diagnostic approach for MS relies on the McDonald criteria, emphasizing MRI findings that demonstrate widespread central nervous system damage over time and space. Another valuable marker is the presence of oligoclonal bands in spinal fluid. The diagnosis and monitoring of MS primarily involve MRI, utilizing a multisequence protocol encompassing T2-weighted, FLAIR, T1-weighted sequences. These pulse sequences vary in their sensitivity depending on the location of inflammatory brain lesions **(Absinta et al., 2016).** FLAIR imaging excels in detecting lesions near cerebrospinal fluid, such as juxtacortical and periventricular white matter, while T2-weighted sequences are better at identifying infratentorial lesions **(Mohamed et al., 2023).**

A novel pulse sequence, double inversion recovery (DIR), has been introduced to enhance MS diagnosis. This method employs two distinct inversion pulses to minimize cerebrospinal fluid and whole white matter signal, leading to superior gray-white matter contrast. This optimization arises from differences in T1 relaxation times between gray matter/cerebrospinal fluid and gray matter/white matter, further improving MS diagnosis and disease progression monitoring **(Govindarajan et al., 2020)**.

The aim of this study is to assess the role of DIR sequence in the detection of brain lesions in patients with MS compared to FLAIR and T2 sequences.

Patients and methods

A cross sectional study was implemented to thoroughly explore various aspects related to patients diagnosed with Multiple Sclerosis (MS).

The study was conducted within the diagnostic and interventional radiology department of Qena University Hospital. This choice of location provided a clinical environment suitable for conducting a comprehensive evaluation of the research objectives.

The study's participant selection process adhered to strict criteria. Individuals eligible for inclusion in the study were those who had been diagnosed with Multiple Sclerosis (MS) in accordance with the McDonald criteria 2017 **(Abidi et al., 2017).** This criterion ensured that the study focused exclusively on individuals with a confirmed MS diagnosis.

Conversely, individuals who had concurrent neurological disorders in addition to MS were excluded from participation. Additionally, patients with absolute contraindications to Magnetic Resonance Imaging (MRI), such as those with cardiac pacemakers or claustrophobia, were not included in the study to ensure their safety and the integrity of the MRI procedures.

A total of 100 MS patients who met the diagnostic criteria outlined in the McDonald criteria were selected as the study's subjects. These patients were referred from the Neurology Department to the Radiology Department for further assessment, ensuring a standardized cohort for analysis.

The study incorporated a comprehensive set of evaluation tools and components:

- A comprehensive medical history was gathered from all patients,

including information on age, gender, occupation, diagnosis, age at the onset of MS, and disease duration. This data collection helped establish a comprehensive patient profile.

- All study patients underwent thorough physical examinations. These examinations were essential to assess the patients' neurological status.

Magnetic Resonance Imaging (MRI)

- Scans of the brain were conducted using the Philips Achieva 1.5T MRI system located at Qena University Hospital. Patients were positioned supine and scanned with a standard quadrature head coil. The MRI protocol included the acquisition of various sequences, each with specific imaging parameters.
- Importantly, FLAIR, DIR, and T2-weighted sequences were acquired with identical anatomic parameters, ensuring consistency in image quality and analysis.

Image Sequences **(Abidi et al., 2017; Inglese & Petracca, 2018):**

a. T1-Weighted Images:

Plane: Axial, sagittal & coronal planes
Sequence: Fast-spin echo (T1 FSE) or gradient (T1 MPRAGE)

b. T2-Weighted Images:

Plane: Axial, sagittal & coronal planes
Sequence: T2 FSE

c. Fluid-Attenuated Inversion Recovery (FLAIR):

Plane: Axial, sagittal & coronal planes
Sequence: FLAIR

d. Double Inversion Recovery (DIR):

Plane: Axial, sagittal & coronal planes
Sequence: DIR

MS lesions were identified as hyper-intense spots measuring ≥3 mm. Additionally, distinctive high signal intensity artifacts, referred to as flow artifacts, were observed in a striped configuration, typically originating from sinuses or major vessels in extra-cortical regions.

Lesions were further categorized based on their anatomic locations into five distinct regions:

- Infratentorial lesions.
- Periventricular lesions, which were in close proximity to the lateral ventricles.
- Deep white matter lesions, located within the deep white matter.
- Juxtacortical lesions, situated in the white matter but in proximity to the cortex.
- Cortical lesions that did not exhibit visible involvement of the juxtacortical or subcortical cerebral white matter.

Ethical approval code: SVU-MED-RAD028-1-22-2-324.

Research Outcome Measures

a. Primary Outcome: The primary objective of this study was to evaluate the efficacy of MRI in diagnosing MS.

b. Secondary Outcomes: As a subsidiary goal, this research aimed to assess the utility of the DIR sequence in detecting brain lesions in MS patients, in comparison to FLAIR and T2 sequences.

Statistical analysis

The collected data will be coded, processed, and analyzed using SPSS program (Version 25) for windows. Descriptive statistics will be calculating to include means, standard deviations, medians, ranges, and percentages. For continuous variables, independent t-tests will be performing to compare the means, and chi-square test was used for categorical data. Pearson correlation: Used to find the correlation between variables. A p value below 0.05 considered statistically significant.

Results

The mean age of the patients was 35 ± 9.66 years. The average disease duration was 40.05 months, with a wide range indicated by the standard deviation of 53.25 months. Most of the patients were female (91%), with only a small proportion of males (9%). Of the patients, 38% showed motor symptoms, while a majority of 82% showed sensory symptoms. Additionally, 59% showed visual symptoms, and 38% showed cerebellar symptoms. (**Table .1; Fig.1).**

Table 1. Demographic data of included subjects

Variables	Value (N = 100)
Age (Years)	35 ± 9.66
Disease duration (Months)	40.05 ± 53.25
Gender	
• **Female**	91 (91%)
• **Male**	9 (9%)
Presenting symptoms	
• **Motor**	38 (38%)
• **Sensory**	82 (82%)
• **Visual**	59 (59%)
• **Cerebellar**	38 (38%)

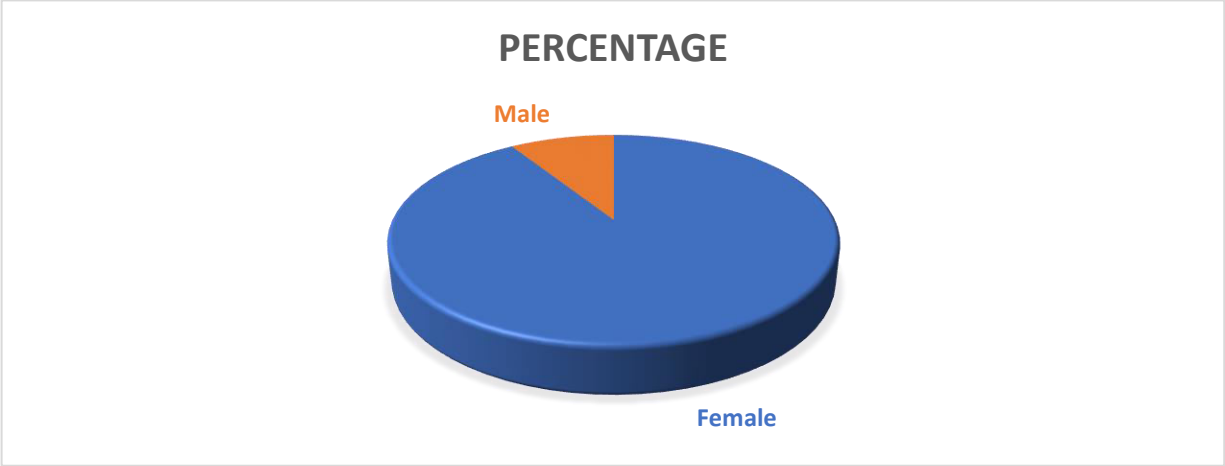

Fig.1. Gender distribution among included subjects

Of the patients, 83% had a Relapsing remittent course, while 12% had a secondary course. A minority of 5% had a primary progressive course of disease, **(Fig.2).** Lesions detected by DIR were significantly more than lesions detected by T2 hyperintensity except for infra tentorium lesions as lesions detected with T2 and FLAIR were more than those detected with DIR. Cortical lesions detected by DIR were significantly higher than those detected with T2 and FLAIR (**Table.2).** After applying enhancement techniques, the average number of lesions detected was 3.79, with a standard deviation (SD) of 4.91. The smallest lesions measured had an average size of 1.69 mm (SD = 1.02 mm), while the largest lesions measured averaged 10.81 mm in size (SD = 9.96 mm).

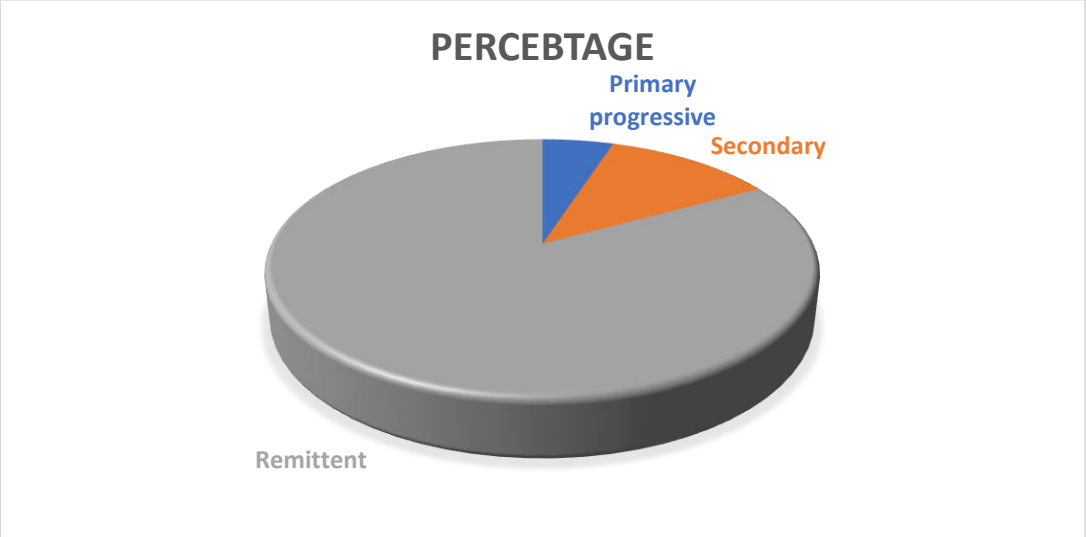

Fig. 2. Course of disease at time of MRI.

Table 2. Lesion Comparison between DIR, T2 hyperintensity and FLAIR among included 70 patients

Variables		DIR	T2 hyperintensity	FLAIR	$P_{(Post-Hoc)}$
Total number	Mean ± SD	70.19 ± 54.43	38.27 ± 23.63	56.46 ± 43.06	P1<0.0001*, P2=0.0493*
	Median (Range)	66 (3-218)	38 (2-83)	51.5 (3-177)	
Peri-ventricular	Mean ± SD	19.94 ± 18.15	8.38 ± 5.79	14.81 ± 13.31	P1<0.0001*, P2=0.06069
	Median (Range)	16 (1-83)	8 (1-22)	12 (1-57)	
Deep white matter	Mean ± SD	22.93 ± 22.96	11.95 ± 9.2	17.23 ± 17.45	P1=0.00041*, P2=0.10274
	Median (Range)	17 (1-136)	8 (1-33)	12.5 (1-109)	
Juxta-cortical	Mean ± SD	17.9 ± 16.35	9.16 ± 7.12	13.34 ± 12.2	P1=0.00011*, P2=0.0657
	Median (Range)	15 (1-82)	7 (1-24)	11 (1-65)	
Cortical lesions	Mean ± SD	9.37 ± 8.9	3.54 ± 3.53	6.87 ± 6.75	P1=0.00001*, P2=0.0418*
	Median (Range)	6 (1-42)	2 (0-14)	4.5 (1-31)	
Infra tentorium	Mean ± SD	3.95 ± 3.97	5.35 ± 5.36	5.83 ± 5.46	P1=0.0068*, P2=0.0404*
	Median (Range)	3 (0-21)	4 (0-30)	4 (0-31)	

P1(DIR/T2), P2 (DIR/FLAIR)

Patients' age showed a significant negative correlation with number of lesions detected by T2 Hyperintensity. Disease duration showed a significant positive correlation with number of lesions detected by both DIR and FLAIR and did not show any significant correlation with T2 Hyperintensity lesions. EDSS showed a highly significant correlation with number of lesions detected by DIR, FLAIR and T2 Hyperintensity, (**Table.3, Figs 3,4).**

Table 3. Correlation between age, disease duration and EDSS with lesions detected by different modalities

Variables	DIR		T2 Hyperintensity		FLAIR	
	r	P. value	r	P. value	R	P. value
Age	-0.01551	0.87826	-.136	0.1788	-0.01815	0.85776
Disease duration	.31**	0.0017	0.238*	0.017	.316**	0.0014
EDSS	.995**	<0.0001	.446**	<0.0001	.993**	<0.0001

R: Pearson Correlation

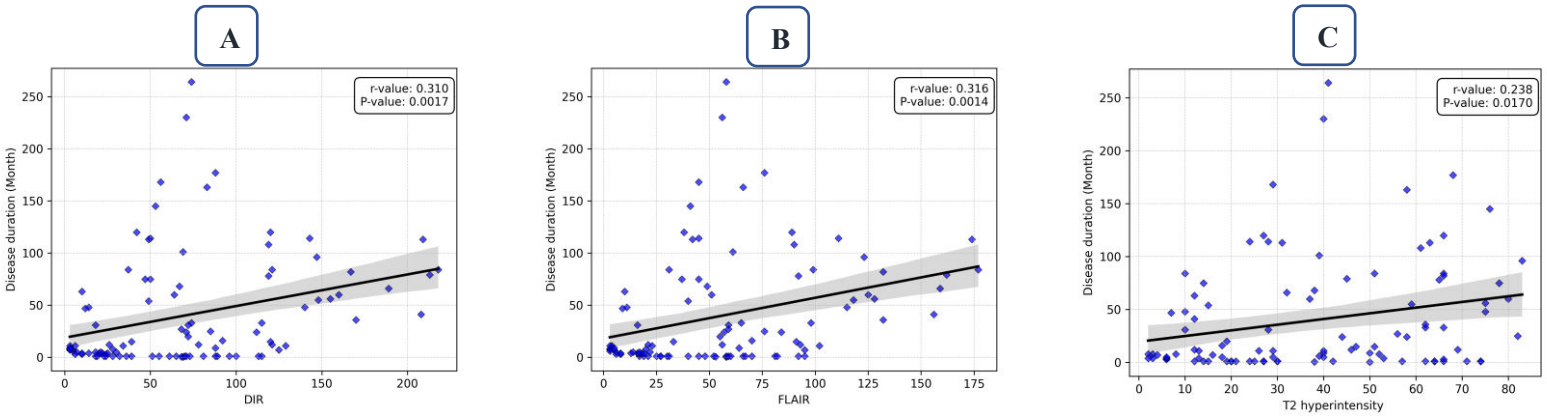

Fig.3. Correlation between Disease duration (Month) and lesions detected with different modalities. A: correlation with DIR, B: correlation with FLAIR, C: correlation with T2 Hyperintensity

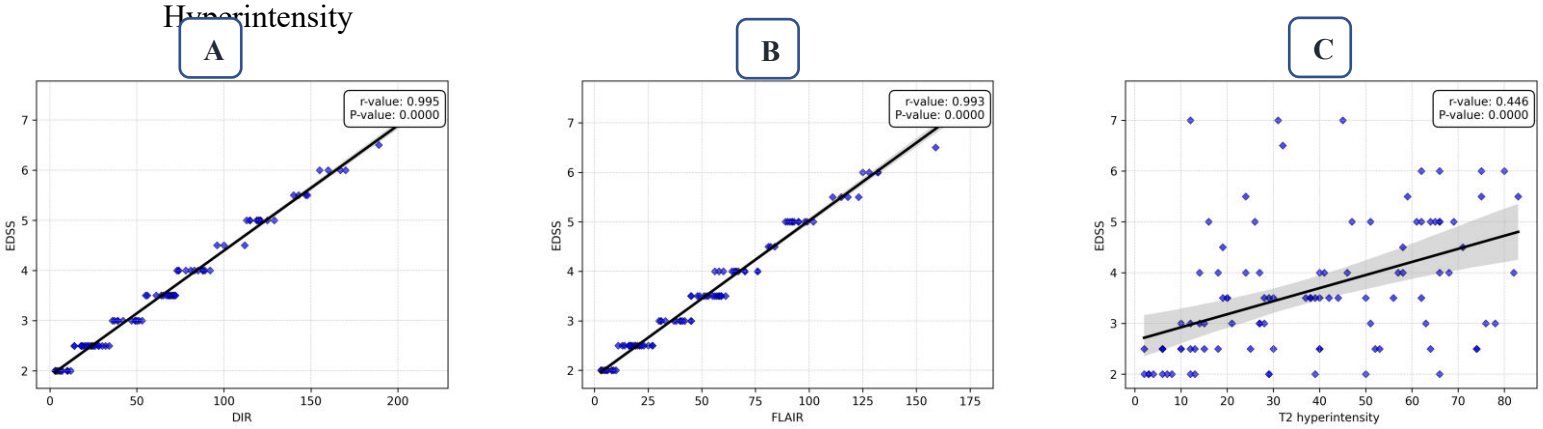

Fig.4. Correlation between EDSS and lesions detected with different modalities. A: correlation with DIR, B: correlation with FLAIR, C: correlation with T2 Hyperintensity

Case presentation

Case No. 1

A 45-year-old female patient known to have relapsing remitting MS of 3 years duration with multiple relapses of sensory symptoms. The patient now has no complain. Clinically, the patient has EDSS of 2, **(Fig5).**

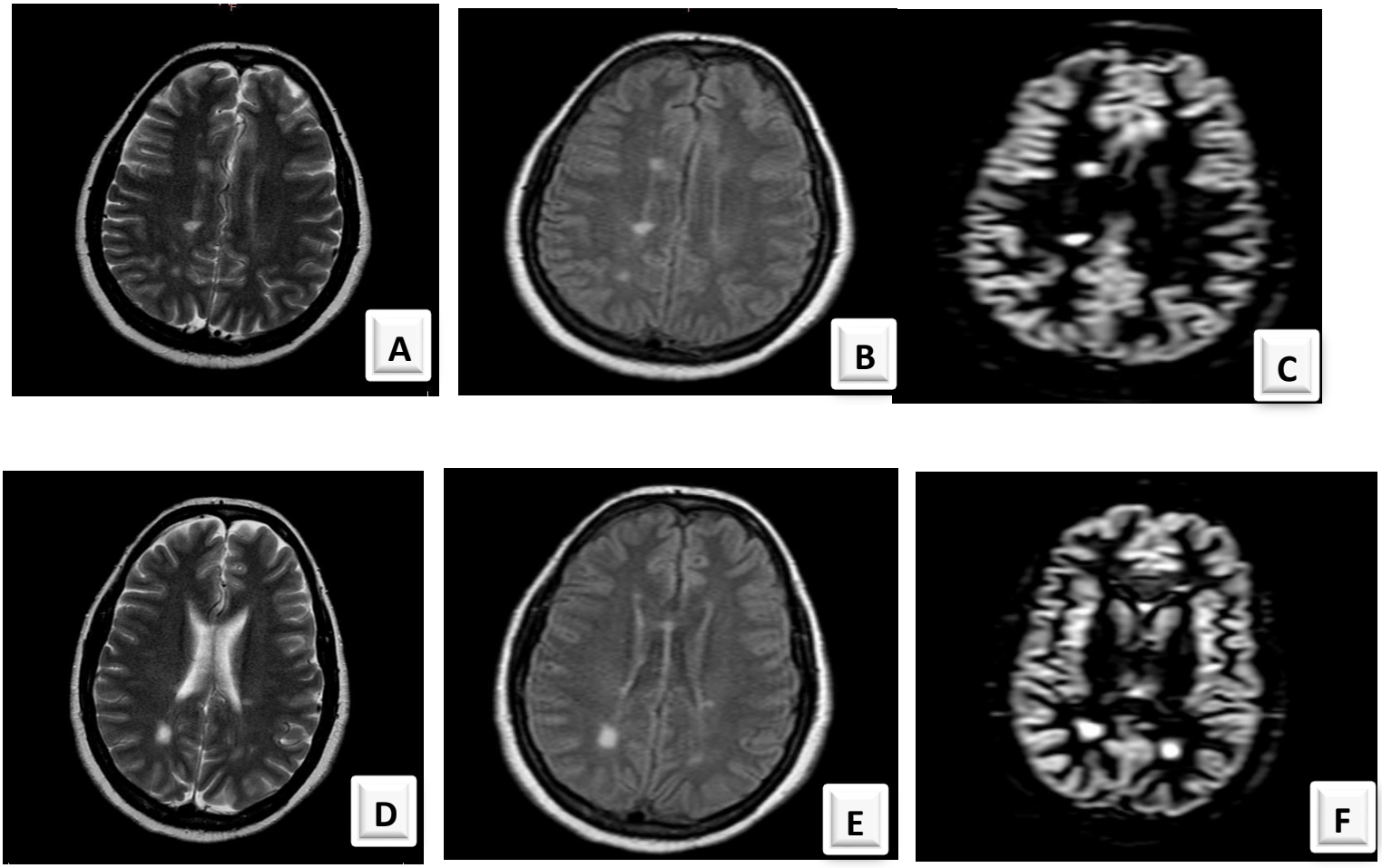

Fig.5. (A, D) T2, (B, E) FLAIR, and (C, F) DIR axial brain sections at multiple levels show multiple hyperintense lesions seen scattered at both cerebral hemisphere involving right parietal region, as well as both occipital periventricular regions with high contrast in case of DIR in comparison with T2WI and FLAIR.

Case No. 2

A 50-year-old female known to have relapsing remitting MS of 20 years duration. She is recently presented with blurring of vision of the left eye and left hemiparesis. Clinically, the patient's EDSS is 3. (**Fig.6).**

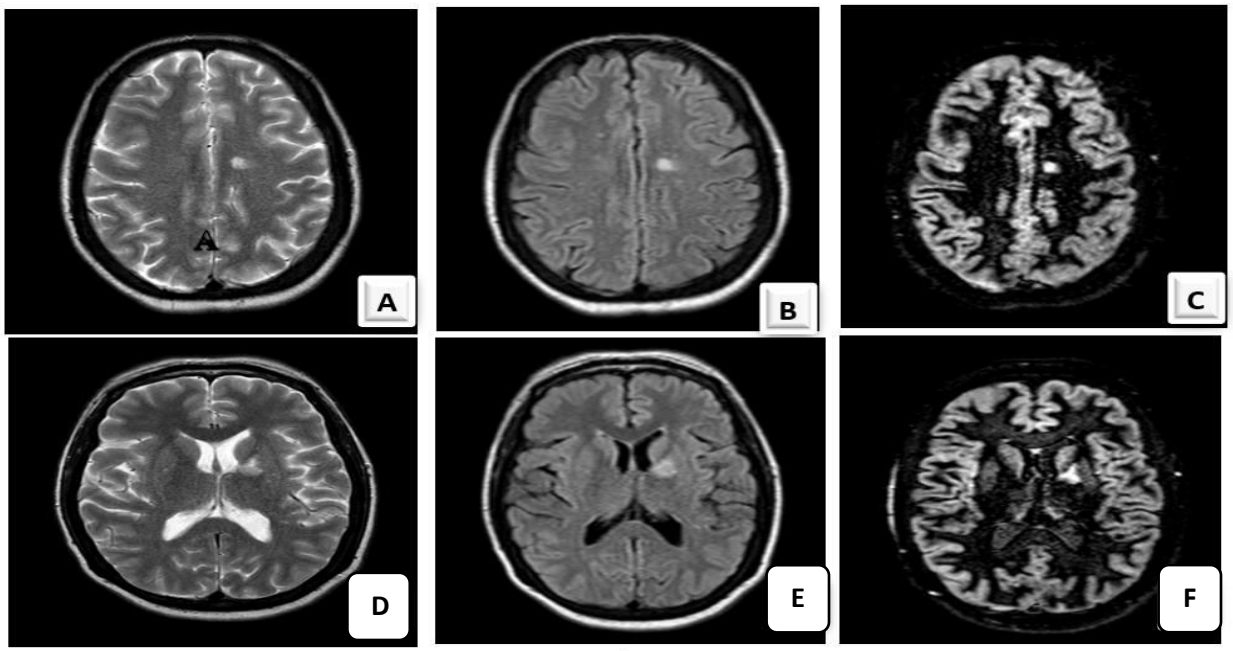

Fig.6. (A, D) T2, (B, E) FLAIR, and (C, F) DIR axial brain sections at multiple levels show two hyperintense lesions seen left parietal periventricular region, as well as anterior limb of left internal capsule.

Case No.3

A 40-year-old male patient diagnosed with secondary progressive MS for 6 years. The clinical condition includes motor and sensory symptoms. Now the patient is presented with right upper limb muscle weakness. Clinically, the patient has EDSS of 4.5. (**Fig.7).**

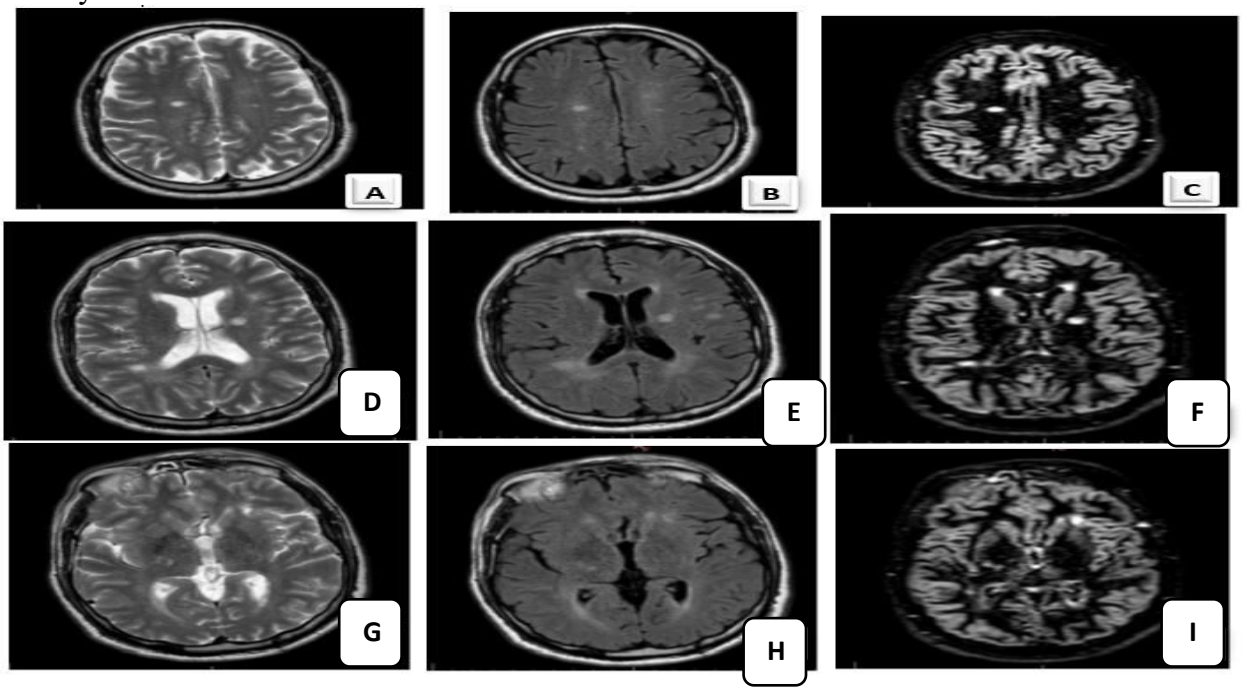

Fig.7. (A, D, G) T2, (B, E, H) FLAIR, and (C, F, I) DIR axial brain sections at multiple levels show multiple hyperintense lesions seen scattered at both cerebral hemispheres

involving right parietal, right occipital, left temporal periventricular regions and the anterior limb of left internal capsule with high contrast in case of DIR in comparison with T2WI and FLAIR

Discussion

Multiple Sclerosis (MS) is a chronic autoimmune disorder of the central nervous system characterized by inflammation, demyelination, and axonal damage. Timely and precise MS diagnosis is crucial for effective disease management. While conventional MRI sequences like T2-weighted and fluid-attenuated inversion recovery (FLAIR) are standard tools for MS diagnosis, they can lack sensitivity, especially in detecting cortical lesions **(Fymat et al., 2023).** This has led to growing interest in advanced imaging techniques, with the Double Inversion Recovery (DIR) sequence emerging as a valuable addition. DIR enhances lesion visibility, including cortical lesions, by nulling signals from cerebrospinal fluid and white matter, offering improved contrast compared to conventional sequences. Studies have shown DIR's superiority in detecting various MS lesions, making it a promising tool for early diagnosis and monitoring **(Govindarajan et al., 2020).**

Incorporating DIR into MS diagnostic imaging protocols can enhance early detection and lesion visualization, potentially leading to better treatment outcomes and quality of life for patients. Furthermore, it aids in distinguishing MS from other similar disorders, reducing misdiagnosis and unnecessary investigations. However, despite its advantages, challenges such as longer acquisition times and specialized post-processing have limited DIR's widespread clinical use. Nevertheless, ongoing advancements in MRI technology and post-processing techniques are addressing these challenges, making the routine integration of DIR into clinical protocols increasingly feasible **(Absinta et al., 2016).**

Our study patients had an average age of 35 years (SD ±9.66), with a disease duration of 40.05 months (SD ±53.25), predominantly female (91%). This demographic profile is similar to that in the study by **Ertan et al. (2018),** which analyzed the efficiency of 3D DIR and 3D FLAIR sequences in detecting cortical lesions among 24 MS patients (9 male, 15 female, average age 34.4±12.0 years). **Wattjes et al. (2007)** also explored this area but with a slightly different focus, examining 26 patients, including 17 with clinically isolated syndrome (CIS) and 9 with relapsing-remitting MS, noting smaller sample sizes in comparison to ours.

In terms of clinical manifestations, our cohort exhibited a range of symptoms: sensory (82%), visual (59%), motor (38%), and cerebellar (38%), with a majority experiencing a recurrent disease course (83%) and an average EDSS score indicating moderate disability (3.65). This is somewhat parallel to **Wattjes et al. (2007),** who reported milder disability levels in their participants, with 17 CIS patients having a median EDSS score of 1 and 9 relapsing-remitting MS patients a median score of 1.5. The variation in disability levels across studies may reflect differences in disease progression, duration, and participant selection criteria.

Our study has made significant strides in understanding the diagnostic capabilities of MRI sequences for Multiple Sclerosis (MS), particularly emphasizing the value of the Double Inversion Recovery

(DIR) sequence. We discovered that DIR identifies a significantly higher average number of lesions (70.19) when compared to traditional T2 hyperintensity (38.27) and FLAIR (56.46) sequences. Notably, while T2 hyperintensity and FLAIR excel in detecting lesions within specific regions such as the brain stem, DIR proves to be exceptionally adept at identifying cortical lesions. This distinction highlights DIR's unique ability to enhance visibility of lesions, especially those rich in water content indicative of edema and inflammation, thus facilitating a more nuanced approach to MS diagnosis and monitoring, particularly for subtle or early-stage lesions.

The efficacy of DIR in lesion detection aligns with findings from prior research, underscoring its enhanced sensitivity and diagnostic superiority. For instance, **Simon et al. (2010)** demonstrated DIR's effectiveness in revealing cortical and other white matter abnormalities, validating our observations regarding DIR's broad detection capabilities. Similarly, studies by **Vural et al. (2013)** confirmed DIR's superiority over FLAIR and T2 in detecting both white and grey matter lesions, mirroring our findings on DIR's effectiveness. This consensus is further supported by **Elnekeidy et al. (2014) and Abidi et al. (2017),** who noted DIR's proficiency in more distinctly highlighting cortical lesions compared to T2WI or FLAIR. **Ertan et al. (2018)** also observed DIR's superior detection of intracortical and grey matter lesions, reinforcing the sequence's value in MS research.

Contrasting perspectives, such as those presented by **De Santis et al. (2019),** highlight the ongoing need for advanced MRI techniques to more accurately capture the complexities of MS pathology. This reflects a broader discussion within the medical community about evolving diagnostic tools. Meanwhile, **Wang et al. (2018)** focused on the advantages of 3D FLAIR for identifying infratentorial lesions, showcasing the importance of utilizing advanced sequences in the nuanced diagnosis of MS. Despite these varied focal points, the consensus across studies underscores DIR's comprehensive sensitivity and diagnostic value, particularly for cortical and juxtacortical lesions.

Our study revealed an average of 3.79 lesions with a standard deviation (SD) of 4.91 following enhancement techniques. We observed a notable range in lesion sizes, from a minimum diameter of 1.69 mm (SD = 1.02) to a maximum of 10.81 mm (SD = 9.96), indicating significant variation. This variability underscores the impact of disease severity, lesion activity, and individual patient factors on lesion dimensions. Our findings align with additional research, such as that by **Abidi et al. (2017),** which highlighted the Double Inversion Recovery (DIR) sequence's superior ability in detecting Multiple Sclerosis (MS) lesions more accurately and sensitively compared to standard MRI sequences. The DIR sequence's enhanced sensitivity and precision in identifying lesions of varying sizes highlight its importance in the diagnosis and monitoring of MS and other neurological conditions.

In our analysis, we found a negative correlation between the presence of T2 hyperintensity lesions and patient age, whereas the duration of the disease showed a positive correlation with lesions detected by DIR and FLAIR sequences, but not with T2 hyperintensity lesions. Remarkably, the Expanded Disability Status Scale (EDSS)

score showed a strong correlation with the number of lesions identified by all three MRI modalities (DIR, FLAIR, and T2 hyperintensity), indicating the potential of MRI findings to reflect disease progression and severity.

Our results are consistent with those of **Mohsen et al. (2023),** who noted an increased detection of brain lesions with prolonged illness duration using DIR sequencing. This finding suggests that DIR's sensitivity to cortical lesions enhances with the chronicity of the disease, echoing the observations made by **Roosendaal et al. (2009)** regarding the accumulation of cortical lesions over time. Similarly, **Elkholy et al. (2020)** reported a positive association between patient age and the detection of cortical lesions with FLAIR and DIR sequences, further establishing the sequences' effectiveness in lesion identification across different brain regions. These sequences also demonstrated a positive correlation with disease duration and the prevalence of lesions in specific brain areas, though the EDSS score's correlation with lesion locations was not statistically significant in their study.

Furthermore, **Ertan et al. (2018)** found that patients with longer disease durations and more intracortical lesions tended to have higher EDSS scores, although they did not observe a significant correlation between overall lesion load and EDSS scores across all brain areas. This reinforces the complexity of MS pathology and the multifaceted nature of lesion impact on disability, supporting our findings and highlighting the nuanced role of MRI in understanding and managing MS.

Limitations: This study on DIR sequence use in MS diagnosis faces limitations: its single-center nature limits wider applicability, and its small sample size (100 patients) cautions against broad generalizations. Sole reliance on MRI sequences might not capture MS's complexity fully. Without a control group and long-term data, it's challenging to determine causality or track disease progression. Selection bias due to referral patterns may also skew population characteristics. Nonetheless, the study offers important insights and highlights the need for further, more comprehensive research.

Conclusion

Incorporating the Double Inversion Recovery (DIR) sequence as a complementary tool to conventional MRI can enhance the detection of lesions in patients with Multiple Sclerosis. DIR exhibited superior performance in overall lesion detection and particularly excelled in detecting cortical lesions compared to T2 hyperintensity and FLAIR sequences. Moreover, DIR's heightened sensitivity in patients with shorter disease durations and the robust correlation between EDSS scores and lesion counts across all MRI modalities underscore the clinical significance of these findings in gauging disease severity.

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