



## Added Value of Double Inversion Recovery (DIR) Magnetic Resonance Sequence in Diagnosis of Cerebral Multiple Sclerosis Compared to Fluid Attenuation Inversion Recovery (FLAIR) Sequence

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### Abstract

**Background:** Multiple sclerosis (MS) is the most common young adults' central nervous system (CNS) chronic inflammatory disease. In addition to white matter (WM) involvement, gray matter (GM) involvement is important to be detected in many patients. Double-inversion recovery (DIR) pulse sequence has recently been added to conventional MRI protocol to improve the visibility of GM lesions as well as cortical lesions. Our study aimed to evaluate the value of double inversion MRI sequence in the detection of multiple sclerosis, compared mainly with FLAIR sequencing.

**Results:** Fifty patients with clinically proven MS were included in this study. 32 female (64%) and 18 male (36%) were included with female to male ratio 1.7:1. The patients mean age was  $31.34 \pm 5.61$  years (range 19 - 45 years). Imaging was performed using a Philips Intera 1.5 Tesla machine. DIR and FLAIR were the main sequences performed and compared in between, in addition to T2 and T1 weighted images. DIR showed significantly higher total number of MS lesions compared to both FLAIR sequence with  $P < 0.003$ . DIR was more sensitive for cortical and mixed W/GM lesions compared to FLAIR sequence  $P < 0.001$  &  $P < 0.05$  respectively. As well as, we found a positive correlation between patients with cortical lesions and higher EDSS scores.

**Conclusion:** DIR is a powerful MRI sequence for visualizing brain lesions in patients with multiple sclerosis, surpassing FLAIR sequence as well as other MRI sequences in detecting lesions in CNS multiple sclerosis. DIR should combine conventional MRI imaging protocol of MS patients.

**Key words:** Double inversion recovery, Multiple sclerosis, Cortical lesions, Mixed gray/ white matter lesions.

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### 1. Background

Multiple sclerosis (MS) is a central nervous system (CNS) chronic inflammatory demyelinating disease. It is believed to be the most common cause of neurological disease affects both the brain and spinal cord, primarily in middle-aged and young adults. MS is considered an autoimmune disorder because it is somewhat similar to other autoimmune disorders such as systemic lupus erythematosus(1).



MS early symptoms include muscle weakness, loss of sensation, numbness, diplopia, and coordination troubling. MS is considered a complex disease that combines multiple environmental and genetic factors to cause the disease(2).

Understanding MS inflammatory mechanisms help in its diagnosis as they are considered the pathological features of the disease. The hallmark demyelinating lesions form focal confluent perivenous lesions observed throughout the CNS in both white and/ or gray matter regions with various axonal loss and reactive glial disease. The spatial distribution of MS lesions is in particular noted in periventricular, deep white matter and infratentorial regions such as the cerebellum and pons, as well ascervical and thoracic spinal cord (3).

In MS, demyelination occurs in identifiable lesions called plaques that consists of localized demyelination, inflammation, gliosis, and varying degrees of axonal loss. The size of these plaques ranges from a few millimeters to a few centimeters and is usually perivenous. Inflammation and demyelination are abundant in the early stages of the plaque formation, but axonal damage and neuronal loss predominate in the later stages (4).

Nowadays, more attention is paid to gray matter function in spite of the disease being clearly affecting the periventricular, the corpus callosum regions, the cerebellum, the brainstem and the basal ganglia (5).

Conventional MRI imaging performs a crucial function in MS early diagnosis, yet it has a limited capacity to show intracortical lesions (ICLs) apparently, properly due to their small size. Currently, several attempts have been given to increase the sensitivity of detecting more multiple sclerosis lesions in specific anatomical regions (6). FLAIR imaging is much less sensitive for detecting lesions of the inferior cranial fossa, but has the highest sensitivity near the cerebrospinal fluid and periventricular white matter. Regarding T2 sequence and in spite of its better sensitivity in the infratentorial lesions, yet juxtacortical lesions were considered a challenge in their detection (7).

Double Inversion Recovery (DIR) images show good delineation of gray matter lesions. The priority and optimized contrast of DIR is due to the difference in T1 relaxation time between the gray matter and CSF as well as the white matter providing two different inversion pulses that attenuate both CSF and white matter resulting a superior differentiation in between them (8).

Our study main aim was to estimate the role of DIR sequence in the detection of more brain lesions in patients with clinically proven MS, compared to other conventional MRI sequences, in particular FLAIR images.

## 2. Methods

### 2.1 | Study population

This cross-sectional study, hospital based, study included fifty patients who were clinically diagnosed as MS patients according to 2017 revised MacDonald criteria. From January 2019 to December 2021, our cases were transmitted from Mansoura University Hospital neurological department to the radiological department MRI unit. We excluded patients with cardiac pace maker or metallic objects in eye or near spinal cord or even cochlear implants.

Each patient was evaluated clinically during MRI examination using the Expanded Disability Status Scale (EDSS). EDSS scale characterizes the patient's ability to work regarding a scale ranging from 0 point (zero



disability) to 10 points (death of the patient due to multiple sclerosis). Based on patient's clinical data, we classified them to having no or minimal disability (EDSS score 0 - 2), mild to moderate disability (EDSS score 2 - <4) or clinically significant disability (EDSS score  $\geq 4$ ). As well as on the basis of established diagnostic and clinical criteria, patients were classified into the following disease groups: Relapsing-remitting MS (RRMS; n = 32), secondary progressive MS (SPMS; n = 13), and primary progressive MS (PPMS; n = 5).

## 2.2 | MRI

Imaging was carried out using 1.5T MRI machine (Philips Intera) while the patient was in the supine position using a head coil, as well as neck coil for patients performed cervical spine imaging. A standardized protocol for MRI in MS or suspicious MS is recommended: axial T2 weighted and fluid attenuated inversion recovery (FLAIR). Axial T1-weighted sequence prior to contrast administration. Post-contrast T1 sequences were not performed in all cases included in the study because disease activity was not our primary study objective. For each sequence, we recommend continuous 3 mm thick slices with no gaps.

In addition, double-inversion-recovery (DIR) sequence was proceeded for cortical lesions that couldn't be detected on conventional MRI. Then, through using MRI imaging standards such as field of view (FOV), voxel size, matrix, slice thickness and number mean signal quality (NSA), we compare between the three sequences (DIR, FLAIR and T2) in the axial plane with congruent anatomical positions. The parameters mentioned in **(Table 1)**.

Sagittal sequences are preferred in the detection of MS lesions on the regions of the calloso-septal interface and the corpus callosum. On the other hand, cortical MS plaques and that are seen in the parietal regions are best detected in the axial planes. As well as the cervical spine imaging is preferred in both sagittal and axial sections.

## 2.3 | MRI Image Analysis

The images were imported from a DICOM format file. MS plaques appear in the form of high signal lesions with average 2 mm or more in size. We counted the number of MS lesions individually for each sequence, and regarding the brain anatomical region, the lesions were classified into (i) Infratentorial plaques (ii) White matter (WM) plaques (iii) Intracortical plaques (ICLs). Regarding white matter lesions, they are classified to: (a) Periventricular plaques that are in touch to the lateral ventricle. (b) Deep white matter (DWM) plaques and (c) Juxtacortical plaques which are located in contact with cortex. Finally, the MS lesions total number, in each sequence, were also determined individually. Regarding the spinal cord lesions, they were classified as "existing" or "absent" rather than lesion numbers.

**Table (1) shows MRI imaging sequences for brain.**

Parameter	T2W-TSE	FLAIR	DIR
Slice direction	Axial	Axial	Axial
Field of view (mm)	230	230	230
Matrix	256	256	256
Thickness of Slice (mm)	5	5	5



<b>Voxel size</b>	<b>0.9</b>	<b>0.9</b>	<b>0.9</b>
<b>Repetition time (ms)</b>	<b>4500</b>	<b>10000</b>	<b>9600</b>
<b>Echo time (ms)</b>	<b>100</b>	<b>140</b>	<b>25</b>
<b>Inversion time (ms)</b>	<b>-</b>	<b>2800</b>	<b>3400/325</b>
<b>Acquisition Time (min:sec)</b>	<b>3</b>	<b>3:20</b>	<b>2:14</b>

**Millimeters (mm), Millisecond (ms), Minute (min), Double Inversion Recovery (DIR), Fluid Attenuation Inversion Recovery (FLAIR).**

## 2.4 | Statical analysis

The acquired data were transferred to a computer and analyzed by using IBM SPSS Corp, that is published in 2013. IBM SPSS Statistics for Windows, version 22.0. Armonk, NY: IBM Corp. Qualitative data are described by numbers and percentages using the mean (minimum and maximum) for the non-parametric data and the standard deviation for the parametric data after testing for normality by try Kolmogrov-Smirnov test. The significance of the obtained results is assessed at the (0.05) level.

### Data Analysis

#### Qualitative Data:

- The Monte Carlo test as a modification to the ChiSquare test when more than 25% of cells in tables have a count fewer than 5 ( $>2*2$ ).

#### Non-Parametric Test:

- We used MannWhitney's U-test to compare two independent groups.

## 3. Results

In our study, among the fifty patients, 32 female (64%) and 18 male (36%) were included with female to male ratio 1.7:1. The patients mean age was  $31.34 \pm 5.61$  years (range 19 - 45 years). The disease onset average age was  $25.04 \pm 2.98$  years (range 18 - 31 years) with a mean average 6 years (range 1 - 16 years) as disease duration. On DIR imaging, we detected about 1749 MS total number of lesions, compared to FLAIR imaging that showed 1352 lesions MS total number of lesions. According to these results we discovered that DIR images had displayed a statistically significantly higher total number of lesions ( $P < 0.003$  with a relative ratio of 1.2) in comparison to FLAIR imaging. Regarding the infratentorial region, MS lesions are described as significantly higher on DIR imaging compared with FLAIR ( $P$  value  $< 0.001$  with relative ratio 1.9). DIR had significantly demonstrated more cortical plaques in comparison to FLAIR sequence ( $P$  value  $< 0.001$  with 2.1 as relative ratio).

In supratentorial juxtacortical lesions, no considerable difference detected between DIR and FLAIR sequences with relative ratio 0.9. As well as deep white matter lesions, no statically significant regarding DIR and FLAIR sequences ( $P = 0.159$ , relative ratio 1). As well as slightly higher numbers of periventricular lesions were found on DIR imaging compared to FLAIR imaging ( $P$  value = 0.001, relative ratio 0.8) (**Table 2**



**& Figure 1).** Contrariwise, DIR is statically significant in detecting mixed W/GM lesions compared to FLAIR (P value< 0.05 with relative ratio 1.3).

**Table (2): Shows the comparison between DIR & FLAIR sequences regarding the number of MS lesions and their relative ratio among the 50 patients**

Region	DIR (Total No. of lesions= 1749)	FLAIR (Total No. of lesions= 1352)	DIR/FLAR	
			Relative ratio	P value
Peri-ventricular	8.13±3.58 8 (1-16)	7.52±3.27 8(1-15)	0.8	P=0.001*
Cortical	9.34±2.01 9 (4-13)	3.54±1.01 3.0 (1.0-5.0)	2.1	P<0.001*
Juxta-cortical	3.93±1.15 4 (1-5)	4.71±1.3 4.0 (1-6)	0.9	P=0.101
DWM	11.48±3.39 10.0 (6-18)	11.52±3.3 11 (6-18)	1.0	P=0.159
Infratentorial	3.61±0.99 4 (2-5)	1.24±0.44 1.0 (1.0-2.0)	1.95	P<0.001*
Mixed W/GM	3.92±1.43 5 (1-8)	2.91±1.0 3.0 (1-5)	1.3	P<0.05*
Total	42.38±12.5 39.5 (5 - 85)	35.40±8 30 (4- 50)	1.2	P<0.003*

\*Statistically significant if p vlaue<0.05. Highly significant if p value < 0.001. Relative ratio is calculated by dividing number of lesions detected by DIR/ number detected by FLAIR sequence. Double Inversion Recovery (DIR), Fluid Attenuated Inversion Recovery (FLAIR), White/ Grey Matter (W/GM), Deep White Matter (DWM).

There was a statistically significant positive correlation between the duration of the patient's illness and the number of cortical lesions, longer disease duration being associated with more cortical lesions. We found that 100% of cases of cortical disorders were associated with disease duration of more than 10 years. Regarding MS subtype and duration, 60% of patients with disease lasting more than 10 years had SPMS subtype (**Figure 2**). As well as EDSS, the longer the duration of the disease, the higher the EDSS score. 70% of patients with EDSS score ≥ 4 had disease duration of more than 5 years.



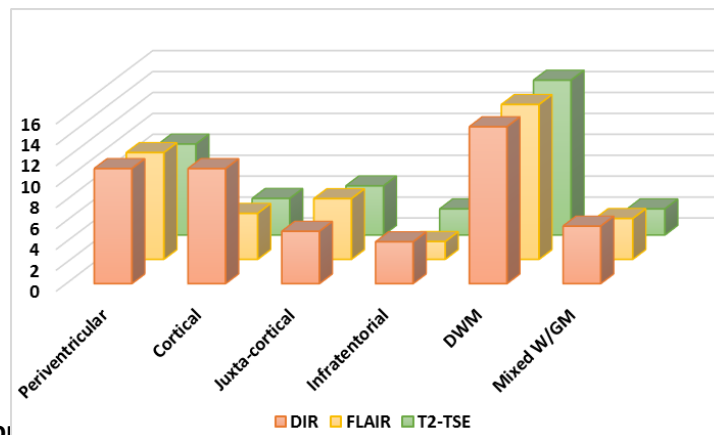


Figure (1): Comparison of DIR, FLAIR, and T2-TSE sequences across lesion types: Periventricular, Cortical, Juxta-cortical, Infratentorial, DWM, and Mixed W/GM.

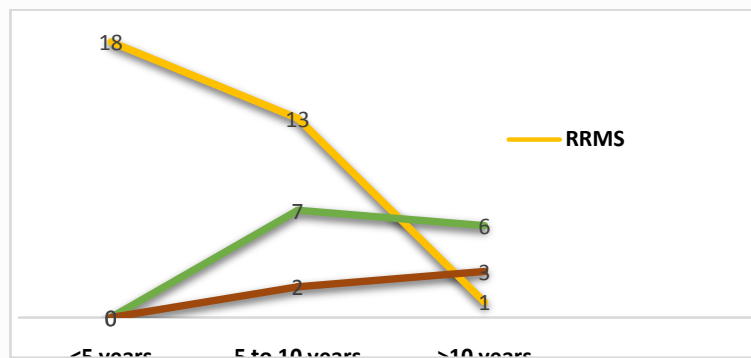


Figure (2): shows correlation between different MS subtypes and disease duration.

Approximately 70% of our patients had cortical lesions. Only 44% of the patients had spinal involvement. There was static significance between higher EDSS scores and cortical and spinal involvement. More cortical lesions were found in patients with EDSS  $\geq 4$ , with  $P=0.003$ , as well as spinal disease, 17 out of 22 patients (85%) with a positive spinal cord lesion had EDSS score  $\geq 4$ .

From a clinical point of view, we found that visual and sensory disturbances were the most frequent symptoms in our patients. We reported that fatigue is the least symptomatic in these patients with 16% percentage. Movement disorders were reported in about 100% of patients with PPMS

#### 4. Discussion

Multiple sclerosis (MS) is a central nervous system autoimmune inflammatory disease that causes worldwide neuropathy in both adolescents and the elderly. The disease hallmark was the existence of scattered lesions (plaques) of the axonal myelin sheath that are disseminated in space and/ or in time(9). In spite of multiple sclerosis being mainly affecting the brain white matter in the regions of periventricular, the corpus callosum interface, the cerebellum, the brainstem, & basal ganglia, yet more concern has been directed to gray matter function as abnormalities in cortical gray matter correlate with physical and neurobehavioral disorders in patients with multiple sclerosis(8).

Magnetic resonance imaging (MRI) is sensitive and reveals tissue macroscopic abnormalities in MS patients. Conventional MRI sequences such as FLAIR (Fluid Attenuated Inversion Recovery), T2 and T1-weighted imaging, with or without gadolinium-based contrast, all are used for MS diagnosis, as well as understand its natural history, and to evaluate treatment (10). However, conventional MRI is not sufficient for detecting cortical or juxtacortical lesions. Through adding DIR sequence to traditional MRI



imaging protocol, it is possible to simultaneously suppress white matter and cerebrospinal fluid signals to obtain images with excellent delineation of gray matter lesions(6).

Our study aim was to evaluate the value of adding DIR imaging sequence to MRI protocol of multiple sclerosis imaging and compare it mainly with FLAIR sequence in detecting cortical, juxtacortical or mixed W/GM MS plaques.

Thirty-two patients in this study were classified, according to their clinical assessment, as relapsing remitting subtype of MS (RRMS), about 64% percentage, and thirteen cases (26%) were classified as secondary progressive subtype (SPMS), and 5 cases (10%) were classified as primary progressive MS (PPMS).

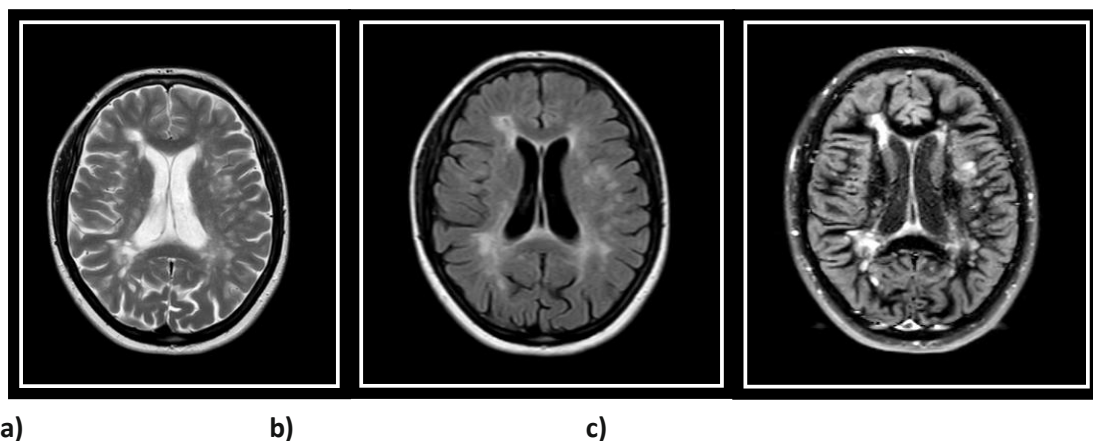
DIR had a significant increased intracortical lesions (ICLs) detection rate with total number of 327 lesions, average  $9.34 \pm 2.01$  compared to FLAIR which counted about 124 as ICLs total number (P value < 0.001). This was in agreement with **Abidi et al., 2017(8)** who detected more ICLs in DIR imaging than both FLAIR and T2 sequences, with a relative ratio of 2.53 and 8.87 respectively. **Ghonim et al., 2021(12)** reported equal results.

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In addition to increasing the sensitivity of DIR to ICL detection, DIR was also found to improve the capability of differentiation between white/ gray matter and juxtacortical lesions (**Figure 3**). The contrast difference between white and gray matter is so minimal that it is often difficult to distinguish mixed gray and white matter lesions from pure intra or juxtacortical lesions, yet DIR can distinguish them and **in agreement with Hamed et al, 2019 (16), we found that** the mean number of lesions detected with DIR in mixed gray/ white matter was significantly more than the lesions detected FLAIR sequence (P value < 0.05).

No statistically significant difference between DIR and FLAIR sequences in juxta-cortical lesions detection, they were hardly equal, even FLAIR sequence detected little more lesions with P value=0.101 and relative ratio 0.9.

The clarification of this difference is that the lesions that were initially of all recognized as juxtacortical lesions at FLAIR images are classified as mixed W/GM lesions in the DIR sequence, resulting in DIR less juxtacortical lesion and much more mixed white/grey matter lesions compared to other sequences. **This was equivalent to Hamed et al, 2019 (16) and Elkholy et al., 2020 (9) studies. Contrariwise to Abidi et al, 2017 (8),** who found that DIR showed more juxtacortical WM lesions compared with FLAIR and T2W images (P value=0.000 with a relative ratio of 8) (P value=0.000 with a relative ratio of 18). **The same was as Almutairi et al., 2020(11)** who also detected the superiority of DIR in detecting juxtacortical lesions.



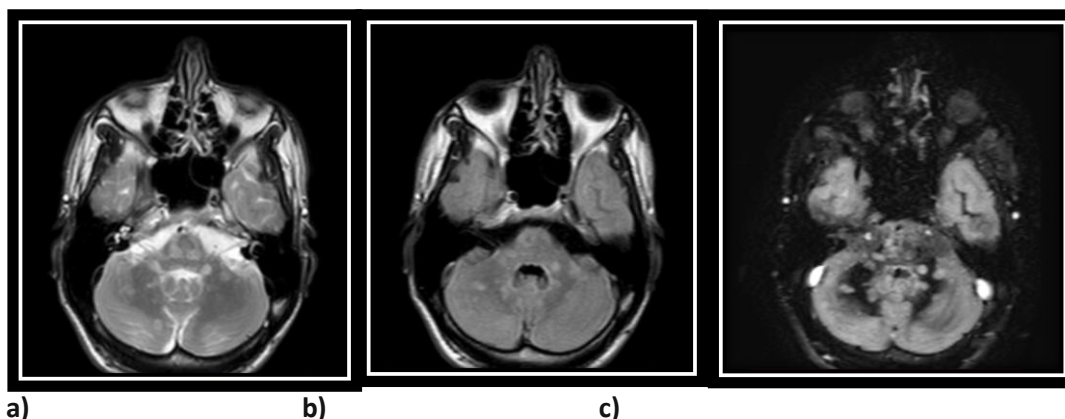
**Figure (3):** Axial MRI brain images at the same level in a 29 years old female patient with MS a) T2-TSE, b) FLAIR & c) DIR, show better delineation of peri-ventricular and juxta cortical lesions. Note lesions in occipital region considered juxta cortical in both T2 & FLAIR sequences, in DIR appear to be mixed W/GM lesions.

Regarding periventricular MS lesion, we revealed that DIR had slightly higher difference (P value= 0.001, Relative ratio 0.8) in comparison to FLAIR images, yet DIR was superior to FLAIR images not only in periventricular lesions detection, but it added better morphological characterization of MS lesions and their description becomes easier to be counted than confluent configuration in FLAIR sequence. This was **in agreement with Abidi et al., 2017(8)**. Similar detection rates were reported for all sequences of deep white matter lesions (DWM) with no statistically significant differences.

However, **Filippi et al, 2019(13)** had reported that T2-WI is considered a gold standard sequence for periventricular lesion assessment. **According to Hemond and Bakshi, 2018 (10)**, periventricular lesions in multiple sclerosis are best detected in fluid-attenuated inversion recovery (FLAIR) sequence that inhibits signal from the cerebrospinal fluid and improves the detection sensitivity of periventricular hyperintensity lesions

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It is important to diagnose infratentorial lesions in MS imaging, as it considered a valuable indicator in determining disease related long-term disability. Damage to the structure of the infratentorial compartment can have a significant impact on clinical disability, and its presence can also be an indicator of spinal cord disease, which may correlate well with disability. Adding DIR sequence to the MRI imaging protocol is an advantageous method as DIR has identified significantly more inflammatory lesions in the infratentorial brain region than other MRI sequences (**Figure 4**), even more than T2 sequence which is regarded the “gold standard” in the infratentorial lesions diagnosis at high magnetic field strength.



**Figure (4):** 31 years old female MS patient a) T2-TSE, b) FLAIR & c) DIR images at the same axial level show bilateral cerebellar lesions are ill defined in FLAIR imaging with better delineation and being more counted in the DIR sequence.

**In our study**, DIR had a high statically significance for infratentorial lesions detection in comparison to both FLAIR & T2 with relative ratio 1.95 & 1.4 respectively. This was in contrast to the result obtained by **Vural et al., 2013(17) that was almost the only study that has been found that** no significant difference between DIR or FLAIR regarding the mean number of lesions detected in the this area, as well as this study detected that the mean number of T2 detectable lesions in the infratentorial region was significantly higher than the mean number of lesions detected by DIR.

Among the CNS inflammatory diseases, spinal cord (SC) lesions are most commonly seen in multiple sclerosis, although they are very rare in other neurological diseases. SC is considered one of the four CNS domains that required to record MS dissemination in space (DIS) and dissemination in time (DIT) as specified in McDonald's criteria for diagnosis of MS. SC MRI is simpler than brain MRI to meet McDonald's criteria for distinguishing MS from MS mimics (14). Therefore, it was important to assess the cervical spine, in particular with DIR if available.

For cervical cord imaging, the MRI imaging protocol mainly included T1WI and T2WI. One limitation of our study is that DIR is more susceptible to motion artifacts such as swallowing. The image quality of the DIR sequence was limited due to aliasing artifacts. Therefore, in these patients, we mainly relied on the T2 sequence for enumeration and documentation of spinal cord lesions

Twenty-two patients (44%) with spinal lesions were observed in our study. **This was close to study done by Hamed et al, 2019(16)** who had reported MS spinal cord lesions in 34.4% of their patients. Regarding spinal lesions, **Bonacchi et al 2020(15)** had described a strong correlation between cervical MS lesions and EDSS. **This was in line with our study and contrariwise to Chen et al, 2020(14)**, how found that spinal cord affection is an independent predictor of disability shows weak correlation with EDSS. In our study, among the 22 patients with spinal cord affection, we found that 5 patients of them with moderate disability (EDSS 2 - 4) and 17 patient had significant disability (EDSS  $\geq$  4).

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The definite interconnection between infratentorial MS lesions and EDSS was discussed by **Almutairi et al, 2020(11)** who reported the presence of at least 2 infratentorial lesions with an EDSS score of 3. **In our study and in agreement with Elkholy et al, 2020(9)**, the same results were reported as we found that 20 (83.3%) patient with positive infratentorial lesions had moderate disability with EDSS 2 to 4 and about 17 (85%) patient had significant disability with EDSS  $\geq$  4.

Duration of the disease is another factor of prognostic value for the development of ICLs. **We found** that ICL was much more common in later stages of multiple sclerosis (disease duration  $>$ 10 years). **That was in line with the study done by Elkholy et al, 2020 (9) yet contrariwise to Matsushita et al, 2018(18) who did disagree these results and reported that** in MS, CLs develop regardless of age and disease duration.

For MS subtypes, we found that the risk of entering secondary progression increased with disease duration. Ten patients were included in our study with disease duration  $>$ 10 years, we found that 6 patients (60%) were classified as SPMS subtype. About 76.9% of our patients with SPMS had EDSS  $\geq$  4. On the other hand, 100% of patients with PPMS included in our study had EDSS  $\geq$  4. **Eshaghi et al, 2021(19) as well as Cree et al, 2021 (20) agreed our results and the latter reported that** progression to SPMS and PPMS are associated longer disease duration and greater early increase in EDSS score.

A major limitation of our study was the observed DIR-related artifacts in the cranial posterior fossa, choroid plexus, and periventricular regions which caused by cerebrospinal fluid or sinus and bigger vessels impulses. To overcome this, multiple slices and other MRI sequences such as T2 and FLAIR were used to help identify MS lesions from these artifacts. DIR performance in the spinal cord region is considered another restriction in our study due to motion phenomena such as swallowing, aliasing, or obesity-induced in-homogeneity.



## 5. **Conclusion**

In conclusion, MRI plays a major role in multiple sclerosis early diagnosis, especially GM lesions displaying its impact on patient disability. DIR provides a more accurate description of MS lesions and a slightly improved lesion detection rate. Performing DIR sequencing is a useful method that can influence early diagnosis and treatment decisions.

## **List of Abbreviations**

Magnetic Resonance Imaging (MRI). Multiple Sclerosis (MS). Central Nervous System (CNS). Spinal Cord (SC). White Matter (WM). Gray Matter (GM). Double Inversion Recovery (DIR). Fluid-Attenuated Inversion Recovery (FLAIR). Expanded Disability Status Scale (EDSS).

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To my family. To radiology department technicians who care and aid in patient's examination.

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## **Author Contributions**

SAF & OIS contributed to the idea of the manuscript, drafting it, final review of the data, statistical tables and radiographic imaging, and the completion of the research manuscript. RFA participated in data collection and assisted with manuscript writing and patient's radiological examination (supervised). All authors have read and approved the final version of the manuscript.

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## **Data and materials availability**

Data used and analyzed in this study are provided by each author upon reasonable request.

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## **Declarations**

## **Ethics approval and consent to participate**

This study approval was granted by the Ethics Committee of Faculty of Medicine of Azhar University for Girls, in Egypt (Date 23\2\2022. No.202201234). All patients included in this study provided written informed consent to participate in this study.

## **Consent for publication**

All patients included in this study provided written informed consent to publish the data contained in this study.

## **Competing interests**

Authors have no relevant financial or non-monetary interests to disclose.



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