Diagnostic Accuracy and Correlation between Double Inversion Recovery (DIR), FLAIR and T2W Imaging Sequences with EDSS in Detection of Lesions at different Anatomical Regions in MS Patients

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Abstract

The aim of our study is to evaluate the diagnostic accuracy of double inversion recovery (DIR) in detection of multiple sclerosis (MS) lesions as well as the correlation between the expanded disability status scale (EDSS) and lesion load measurement detected by DIR, fluid attenuated inversion recovery (FLAIR) and T2 weighted imaging (T2WI) in order to reveal the essential role of DIR sequence in assessing clinical inability as a practicable experiment. A total of 97 patients were assessed on a 3T Siemens Skyra MRI scanner using DIR, FLAIR, and T2W_TSE sequences. EDSS was used to assess the physical disability in patients with MS. The diagnostic accuracy of DIR, FLAIR and T2WI sequences was also determined in different anatomical regions. Sensitivity and specificity were assessed by relative operating characteristics/ receiver operating characteristics (ROC) curve at different cut off points. Spearman correlation was applied to identify the significant relationships between the number of lesions displayed by DIR, FLAIR and T2WI at different regions and EDSS score. Our results pointed out the highest sensitivity (92.9%) and specificity (73.5%) for the number of lesions in infratentorial region at the cut-off point of 4.5 and the highest correlation between the number of lesions and EDSS was observed in infratentorial region (r= 0.584, p<0.001) for DIR sequence. According to the findings of ROC analysis, the number of lesions detected by DIR technique in the infratentorial region is the best predictor of EDSS as a gold standard. DIR can be used as a complementary technique comparing to conventional T2 and FLAIR sequences and describe physical and cognitive dysfunction as well. Due to the higher potential of the DIR sequence to reveal a greater number of MS lesions and to overcome the technical defect of conventional MRI sequences in the diagnosis of cortical lesions, it is recommended that DIR sequences be routinely added to MRI imaging protocols for patients with MS.

Key Words: Multiple Sclerosis (MS), Magnetic Resonance Imaging (MRI), Double Inversion Recovery (DIR), Expanded Disability Status Scale (EDSS), Relative Operating Characteristics/ Receiver Operating Characteristics (ROC).

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease causes demyelination of nerve cells in brain and spinal cord (Abidi et al., 2017; Almutairi et al., 2020). In diagnostic criteria, magnetic resonance imaging (MRI) is a valuable modality which plays a key role in early diagnosis of MS. MS has been reported as one of the most common reason of acquired neurological inability among the youth worldwide, accounting for about 1.14% of the neurologic diseases presented (Elnekeidy et al., 2014; Kumar et al., 2013).

Brain white matter (WM) involvement is well known from previous studies, but cortical involvement has been stated in some recent histopathological and radiological findings in MS patients (Abidi et al., 2017; Almutairi et al., 2020; Vural et al., 2013). Previous studies with gadolinium (Gd) injection have specified that blood-brain barrier (BBB) dysfunction is the early stage of MS pathogenesis in neuroimaging and perivascular immunodeficiency findings (Alvarez et al., 2011). However, there are several reports related to the pathogenesis of grey matter (GM) damage that is associated with primary or secondary nerve tissue damages (Mckee & Daneshvar, 2015). Demyelination in deep grey matter has been reported prominently in caudate nucleus and hypothalamus associated with inflammation (Haider et al., 2014). A great number of previous studies have been conducted to search for an association between conventional T2 weighted imaging (T2WI) sequence and the expanded disability status scale (EDSS) (Almutairi et al., 2020; Barkhof, 1999). The extent of neurological injuries as well as the inability in MS patients can be clinically assessed with the help of EDSS which is the most widely used assessment method today (Almutairi et al., 2020; Sahraian & Eshghi, 2010). EDSS is one of the ordinal variables which is sensible in matching clinical finding with anatomical structural damages in brain (Almutairi et al., 2020; Sbardella et al., 2013).

However, MRI is assessed as a gold standard in diagnosis, treatment monitoring and response evaluation in multiple sclerosis. Cortical lesions cannot be evaluated by conventional MRI because of their relatively smaller size, lower poor contrast comparing to their surrounding normal appearing grey matter (NAGM), also can be obscured by cerebrospinal fluid (CSF) partial volume effect (Kaunzner & Gauthier, 2017; Salminen et al, 2016). MRI has been introduced as the most precise method for assessment of multiple sclerosis lesions due to its ability to evaluate anatomical structures in three cross sections including axial, coronal and sagittal (Almutairi et al., 2020; Elnekeidy et al., 2014). Currently various new MR techniques such as magnetic resonance spectroscopy (MRS), diffusion tensor imaging (DTI) and pseudo-continuous arterial spin labeling (pCASL) are used to identify more lesions and link them to patient's disability (Abidi et al., 2017; Almutairi et al., 2020; Ertan et al., 2018).

Recently, many efforts have been made to enhance the sensitivity of MRI to reveal more MS lesions in different anatomical areas (Abidi et al., 2017; Almutairi et al., 2020). The lower sensitivity of the fluid attenuated inversion recovery (FLAIR) technique in display of infratentorial lesions compared to its highest sensitivity near the CSF such as juxtacortical and periventricular WM has been stated in previous studies. In contrast, T2 weighted imaging sequences are more sensitive to demonstrate infratentorial lesions, despite their disability to disclose juxtacortical and cortical lesions (Abidi et al., 2017; Elnekeidy et al., 2014).

Double inversion recovery (DIR) technique has enhanced MRI sensitivity in diagnosis of cortical lesions. Two combined inverter pulses are used to simultaneously suppress WM and CSF signals and intensifies detection of cortical lesions. The potential benefits of double inversion recovery over conventional MRI protocols is the display of MS lesions in both the infratentorial and supratentorial regions as well as the improved appearance of primary lesions. The sequence meaningfully enhances the visibility of lesions in both GM and WM (Abidi et al., 2017; Almutairi et al., 2020; Ertan et al., 2018). DIR and FLAIR sequences differ in the use of the second additional inversion pulse. Contrast in DIR is obtained by combining the contrast of FLAIR and STIR sequences (Abidi et al., 2017; Ertan et al., 2018).

Although DIR is not a new technique, it has received a great deal of attention over the past 10 years. After the introduction of three-dimensional sequence, DIR was specifically used to diagnose cortical lesions in MS as well as several common central nervous system (CNS) diseases such as cortical microinfarcts, hippocampal sclerosis, subarachnoid hemorrhages, brain tumors, meningitis and other diseases that not mentioned...
The aim of our study is to determine the diagnostic accuracy of DIR, FLAIR and T2WI sequences in diagnosis of MS lesions in different anatomical regions and to evaluate the relationship between EDSS and the number of lesions identified by three sequences to introduce DIR as a practical test for clinical disabilities.

**McDonald Criteria**

Today, the diagnosis of MS is based on McDonald's criteria and has been found to require evidence of lesions distribution in two or more regions in the CNS "dissemination in space (DIS)" and occurred at two different occasions "dissemination in time (DIT)" (Schoonheim et al., 2012). In diagnostic criteria, all revised prescriptions have been aimed to establish early detecting of the lesions with greater sensitivity and specificity to allow treatment as soon as possible. Preliminary research has shown that McDonald’s new criteria allow early diagnosis of MS with higher sensitivity after the first clinical event (Filippi et al., 2019; Schwenkenbecher et al., 2019). Currently, the new McDonald guidelines protocol states that the location of the lesion is more pronounced than the size of the lesion seen by MRI techniques (Gajofatto et al., 2018; Simon et al., 2006).

**Expanded Disability Status Scale (EDSS)**

EDSS is an important indicator used in evaluation of physical disabilities and monitoring changes in disability levels over the time. That is an ordinal scale ranging from 0 to 10, where 0 indicates normal neuronal function without impaired neural findings, while a score of 10 means death from MS. The EDSS of 0 to 5 means less disability, however scores between 5 and 9 are conventionally defined by impairment (Meyer-Moock et al., 2014). EDSS represents an important role in assessing the degree of disability with the help of functional system score (FSS). This tool is one of the most common scales for recording the neurological status of MS patients to assess disease progress and treatment effectiveness (Twork et al., 2010).

**Methods**

In the present study, the data were retrospectively prepared from February 2019 to June 2019. All images were obtained using a 3T scanner with a standard 16 channel head coil and the same method and MRI sequences parameters, similar to our previous study (Almutairi et al., 2020). Three sequences including DIR, FLAIR and T2WI performed in axial plane with identical anatomic position. The protocols and content validity was approved by the members of supervisory committee, including an expert in the field of radiological imaging and an expert in the clinical fields of MS patients. Their comments and suggestions were appropriately acknowledged in order to improve the effectiveness of the research work. 97 patients including female (N=63) and male (N=34) signed a written consent prior to MRI examination. The age of patients ranged between 22 to 41 years and the healthy group was between 20 to 49 years. The duration of disease in patients ranged between 1 to 14 years and most of them were between 2 to 3 years. The patients were evaluated regarding to their clinical investigation into three subtypes including primary progressive MS (PPMS), relapsing remitting MS (RRMS) and clinically isolated syndrome (CIS). The clinical symptoms of the disease including visual disorders, numbness, headache, muscle weakness and dysfunction were assessed based on clinical research.

All the patients underwent a thorough neurological examination prior to the MRI scan by a neurologist to evaluate their performance capacity using EDSS according to modified Mc Donald criteria. Routine brain MRI sequences were performed in addition to DIR, FLAIR and T2W_TSE techniques. The number of lesions in each anatomical regions was calculated separately along with the total number of MS plaques by three sequences. Correlation between the number of identified lesions and EDSS scores was determined using DIR, FLAIR and T2W imaging techniques. The diagnostic accuracy of the three sequences in different anatomical regions was also analyzed. Distribution of EDSS score among MS patients is shown in Table 1.

**Imaging Analysis**

All images in the three sequences were evaluated by two certified radiologists expertised in neuroradiological. Readers were blinded to the clinical presentation and the results of the paraclinical tests. MS lesions with the size of ≥2-3 mm were observed as high signal intensity spots in DIR, FLAIR and T2W images. In contrast to these...
lesions, a small number of striped points known as flow artifacts in the areas outside of the cortex, originate from large arteries or cerebral sinuses which are suggested as artifacts, not MS plaques (Abidi et al., 2017; Almutairi et al., 2020). The number of identified lesions in each technique were classified into infratentorial, juxtacortical, subcortical, periventricular and cortical lesions regarding to their anatomical locations previously described by Almutairi et al. (2020).

Statistical Analysis
Statistical analysis was performed by utilizing IBM SPSS statistics software, version 25.0. The data analysis was represented by using descriptive statistic. In case of normal data distribution, inferential statistic like Pearson/Spearman correlation coefficient, one-way repeated measure ANOVA and paired-sample t-tests were used to differentiate the three sequences. Non-parametric methods such as Friedman and Wilcoxon tests and Spearman correlation were used to identify the relationship between variables that do not correspond to the assumption of normal distribution.

Sensitivity and specificity at different cut off point were tested by relative operating characteristics/receiver operating characteristics (ROC) curve. In order to evaluate the relationship between EDSS score and load measurement, Spearman correlations were applied to investigate the existence of linear relation as well as identifying meaningful relationships between the load measurement and EDSS score at different regions with three sequences including DIR, FLAIR and T2WI.

Results
The frequency analysis showed that the majority of our patients were at RRMS (n=87), 5 cases were at PPMS and 5 cases at CIS. In frequency analysis of clinical symptoms, it was shown that the numbness (46.4%) had the highest percentage among the patients, then followed by visual disturbances (40.2%), muscle weakness (40.2%) and the lowest frequency was for headache (12.4%). Although, 28.9% of cases had other symptoms such as dysfunction. Using EDSS revealed that the highest frequency was related to patients with a score of 1 which presented no disability and minimal symptoms in functional system. Lower EDSS scores are considered non-disability and a score of higher than 3 is classified as patient with mild disability, it was found that 13.4% of MS patients had at least mild disability while 86.6% had no sign of disability (Table. 1).

Table 1. Distribution of EDSS score among MS patients

<table>
<thead>
<tr>
<th>(EDSS) Score</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6</td>
<td>6.2</td>
</tr>
<tr>
<td>1</td>
<td>46</td>
<td>47.4</td>
</tr>
<tr>
<td>2</td>
<td>31</td>
<td>32</td>
</tr>
<tr>
<td>2.5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>7.2</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>4.1</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>2.1</td>
</tr>
</tbody>
</table>

The mean of total lesions in all anatomical area was calculated based on DIR (M=37.67), for FLAIR (M=29.57) and for the T2WI (M=27.47). The total number of lesions detected by DIR was meaningfully higher than FLAIR which follow by T2WI. Significantly greater number of MS lesions revealed by DIR technique in the areas of juxtacortical, subcortical and periventricular regions (Fig.1) regarding to FLAIR that follow by T2W_TSE.
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Figure 1. Presence of multiple lesions in subcortical and periventricular regions in a male patient aged 33y with EDSS score of 3 and blurred vision. Lesions are markedly obvious with greater delineation in DIR (A) comparing to FLAIR (B) and T2W imaging sequences.

A significant higher mean number of intracortical lesions (Fig. 2) were displayed by DIR (M=2.35) compared to FLAIR (M=1.29) and T2W (M=0.62).

Figure 2. Axial cuts of brain with different sequences DIR (A), FLAIR (B), and T2W (C). A 32 year old patient with RRMS who referred with difficulty in walking, numbness and three years disease duration as well as EDSS=2, showing multiple cortical lesions (yellow arrows) and white matter juxtacortical lesions with better delineation on DIR (A) compared to other pulse sequences.

In infratentorial, number of lesions detected by DIR (M=3.84) was significantly higher than T2WI (M=2.87) and FLAIR (M=2.31) sequences. Cerebellum and brain stem lesions (Fig. 3) in infratentorial were higher in number and better delineated in DIR, even comparing to the T2W_TSE which still discussed as a gold sequence at this region.

Figure 3. Comparison of DIR (A), FLAIR (B), T2W (C) sequences in infententorial area in a 25y RRMS female patient with EDSS score of 3 diagnosed with blurred vision and numbness for two years. DIR image at same level demonstrated a well delineated lesion at right aspect of pons (red arrow) as well as two small lesions at left side and one in the white matter of right cerebellar hemisphere that not seen obviously in FLAIR (B) and T2W images.
In our findings, the highest correlation coefficients between the number of lesions and EDSS were observed in infratentorial region (r = 0.584, p<0.001) by DIR sequence which was positive, significant and strong (Table. 2).

In periventricular region the relation between the number of lesions and EDSS displayed moderate, positive and significant by DIR (r = 0.414, p<0.001), FLAIR (r = 0.463, p<0.001) and T2WI (r = 0.373, p<0.001). Our results demonstrated a positive, significant and almost weak relationship between the number of lesions and EDSS in cortical (r = 0.273, p=0.007), juxtacortical (r = 0.219, p=0.031) and subcortical (r = 0.210, p=0.039) by DIR sequence. FLAIR sequence also displayed positive and significant at these regions, but with moderate relationship in subcortical (r = 0.310, p=0.002) and weak relation in both juxtacortical (r = 0.212, p=0.037) and cortical region (r = 0.228, p=0.024) (Table. 2).

In T2W, the relationship between the number of lesions and EDSS, in subcortical region (r = 0.286, p=0.004) was positive and significant but almost weak relationship. There was no significant relationship between number of lesions and EDSS in juxtacortical (r = 0.101, p=0.326) and cortical (r = 0.167, p=0.101) by T2WI sequence (Table. 2).

**Table 2. Relationship between the number of lesions and EDSS**

<table>
<thead>
<tr>
<th>Region</th>
<th>DIR</th>
<th>FLAIR</th>
<th>T2W</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Correlation Coefficient P value</td>
<td>Correlation Coefficient P value</td>
<td>Correlation Coefficient P value</td>
</tr>
<tr>
<td>Infratentorial</td>
<td>0.584**</td>
<td>&lt;0.001</td>
<td>0.527**</td>
</tr>
<tr>
<td>Juxtacortical</td>
<td>0.219*</td>
<td>0.031</td>
<td>0.212*</td>
</tr>
<tr>
<td>Subcortical</td>
<td>.210*</td>
<td>0.039</td>
<td>.310**</td>
</tr>
<tr>
<td>Periventricular</td>
<td>.414**</td>
<td>&lt;0.001</td>
<td>.463**</td>
</tr>
<tr>
<td>Cortical</td>
<td>.273**</td>
<td>&lt;0.001</td>
<td>0.228*</td>
</tr>
</tbody>
</table>

**Correlation is significant at the 0.01 level (2-tailed). *Correlation is significant at the 0.05 level (2-tailed).**

Diagnostic Accuracy of DIR Sequence in Detection of MS Lesion in Different Anatomical Area

The highest area under curve (AUC) in DIR sequence observed for the number of lesions in infratentorial region (AUC=0.883, p<0.001). The number of lesions in periventricular (AUC=0.733, p=0.005) and total number of lesions (AUC=0.713, p=0.011) were also statistically significant, while the AUC were not significant for other regions. These results indicated that for the number of lesions in infratentorial, the cut-off point of “4.5”, will give the highest sensitivity (92.9%) and specificity of 73.5% (Fig. 4). According to the finding of ROC analysis and the level of agreement between DIR images and EDSS, it was found that the number of lesions in infratentorial are the best predictor for EDSS as a gold standard.

![Figure 4. Illustration of ROC curve for DIR sequence](image)

![Figure 5. Illustration of ROC curve for FLAIR sequence](image)
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**Discussion**

Previous studies reported conventional MRI sequences failed to display cortical lesions despite the progression in new MR techniques such as MRS and DTI. The diagnosis of MS lesions is still based on routine MRI protocols, which play an important role in early detection of MS or CIS which suggests MS disease (Simon et al., 2006).

In our study, brain imaging sequences in MS patients were obtained using both conventional (T2, FLAIR) and DIR techniques. The relationship between the number of lesions and EDSS scores in each sequence was assessed separately. The main goal of our study was to compare the accuracy of the new MRI technique (DIR) with the conventional MRI sequences in detection of MS lesions and analyze the correlation between the lesion load and disability in different anatomical regions.

A wide range of new MR imaging techniques have increased the sensitivity of MRI to identify MS plaques in different areas in brain. We compared the sensitivity and specificity of DIR sequence regarding to FLAIR and T2WI sequences in detection of MS lesions as well as the relation between the number of detected lesions and disability. Three pulse sequences displayed different sensitivities and specificities to demonstrate inflammatory brain lesions depends on their anatomic location.

Highest sensitivity (92.9%) and specificity (73.5%) were observed by DIR sequence in infratentorial region at cut off point of "4.5" with the accuracy of 0.883 (p<0.001). There was a statistically meaningful relationship based on the findings by DIR sequence in infratentorial involvement and clinical outcomes in MS patients (AUC=0.883, p<0.001). Actually, the higher sensitivity and specificity of DIR regarding to FLAIR and T2WI techniques suggested infratentorial lesions as the best indicator to distinguish disabilities in patients with MS. In our findings, the accuracy of DIR sequence was not significant in cortical lesions.

Our findings are consistent with the study by Wattjes et al., (2007) which reported a higher sensitivity in the diagnosis of infratentorial lesions by DIR technique. They stated that despite the prominent rounded artifacts in DIR sequence such as vascular and flow artifacts in infratentorial region, the higher sensitivity of DIR in detecting lesions in this region was not affected by a possible misinterpretation of the lesions.

In our results, the highest correlation coefficients between the lesions and EDSS was in infratentorial (Fig. 7) region by DIR (r=0.584, p<0.001) sequence which was positive, significant and strong. The correlation in FLAIR (r=0.527, p<0.001) and T2WI sequences (r=0.503, p<0.001) was strong, positive and significant as well. A significant and positive relation between EDSS and number of lesions was observed in other anatomical areas in three sequences, however the relationship was almost moderate or weak.

Some previous studies noted a positive correlation between the number of lesions and EDSS in cortical area (Calabrese & De Stefano, 2014; Calabrese et al., 2007). Vural et al. (2013) indicated a meaningful dependence between EDSS and the number of lesions detected by DIR in juxtacortical (r = 0.398; p = 0.02) and periventricular WM (r = 0.465, p = 0.006). There was no significant relation between the total number of lesions and EDSS scores in both DIR and FLAIR sequences.

Our findings are inconsistent with the findings of Harrison et al. (2015) who reported the number of cortical lesions associated with cognitive impairment and EDSS scores. They found that the correlation between EDSS scores and cerebral cortex involvement was twice as high as the correlation between the EDSS and WM lesion volume. They also stated that the EDSS score increased with increasing of the illness duration and number of attacks, in addition to the fact that they stated no association between the location of the lesions and EDSS score.

According to our results, the significant association
between infratentorial lesions and EDSS, is worth discussing. Detection of infratentorial lesions is very important because it indicates long-term disability in MS patients, leading to early diagnosis and treatment of the disease (Minneboo et al., 2004; Shan et al., 2017). The time interval between the onset of the symptoms and diagnosis of MS has narrowed in recent decades due to the developments in diagnostic imaging techniques and modalities (Almutairi et al., 2020; Cerqueira et al., 2018). The posterior cerebral fossa includes the basic structures especially the corticospinal tracts in brainstem, cerebellum and the connectivities which are responsible for mobility and coordination. The specific structure of the infratentorial region and the presence of high nerve fiber density can illustrate the relationship between clinical results and MRI outcomes more strongly than other areas of the brain (Hickman et al., 2001; Prosperini et al., 2011). It may be theorized that demyelinating lesions may cut off all the white matter pathways that cross the brainstem including white matter connection paths between spinal cord, cerebellum, vestibular nuclei, thalami and cortical regions. Recently, the effects of WM abnormality on balance ability have been observed even in a sample of adults without having a degree of impairments or coincidental neurological disease (Narayanan & Murray, 2016; Prosperini et al., 2011).

The main limitation of DIR sequence reported by previous studies, is several narrow elongated hyper intensities with a ribbon like appearance known as artifacts. The artifacts are distinguished from the lesions by their bilateral prevalence in several consecutive sections or with the help of other MRI sequences such as T1-weighted or FLAIR sequences (Abidi et al., 2017; Almutairi et al., 2020; Calabrese et al., 2007). These artifacts are scored using control images of healthy individuals in DIR sequence with the same imaging parameters used for MS patients imaging (Geurts et al., 2011).

In the present study, a radiologist acquainted with these cerebrospinal fluid artifacts or larger vascular artifacts, paid special attention to the slices adjacent to the suspected lesions and excluded the artifacts in the areas such as the temporal anterior lobes, occipital lobes and frontal lobes. Using 3D DIR technique instead of 2D DIR as well as higher magnetic field strength made cerebrospinal fluid and vessels artifacts much less visible.

Conclusions
Using various types of MRI techniques provides the basis for rapid treatment and rehabilitation due to better depiction of complicated constructional impairment. DIR improves cortical lesions detection in comparison with conventional MRI techniques in patients with MS. DIR is a very helpful sequence for assessing further lesions in the CNS and describing physical and cognitive dysfunction in addition to disease progression and disability in MS patients. The higher sensitivity and diagnostic accuracy of DIR sequence in detection of infratentorial lesions and the strong correlation between infratentorial lesions and EDSS are the reasons which led us to suggest the use of DIR sequence in routine protocol for MS patients.

Figure 7. A 25-year-old female with EDSS=3 using 3D DIR (A), FLAIR (B) and T2W (C) imaging sequences. A small lesion depicted in the pons by DIR which not visualized in corresponding FLAIR and T2W techniques.
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Sequences
orial lesions, balance deficit
S.
D. What can imaging tell us
S
S. Reducing CSF Partial
urosurgery
- cognitive impairment and dementia?.
H
S. A. Infratentorial Lesions
48x58


