Prediction of response to disease-modifying therapy in multiple sclerosis

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ORiGInAL STUDY

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Abstract

Background: Multiple sclerosis is an idiopathic inflammatory disease of the central nervous system and the second most common cause of disability in young adults. Choosing an effective treatment is crucial to preventing disability.

Aim: To identify predictors of disease-modifying therapy (DMT) after 1 year of treatment.

Patients and methods: In this retrospective study, 150 patients with confirmed diagnosis of relapsing-remitting multiple sclerosis were recruited from the MS Unit at the Neurology Departments from both Ain-Shams University and Cairo University Student Hospital. All of the study population received either interferons or fingolimod. Modified Rio score was used to classify patients to responders and nonresponders. In this study, 128 patients were found responders and 22 were found nonresponders.

Results: There was a significant difference between responders and nonresponders regarding age of the participants. The age was significantly older in responders compared with nonresponders (mean of 32.37 ± 7.248 vs. 28.55 ± 5.361 years, respectively; P = 0.019). Sex was not a significant predictor of response to therapy. Regarding the Expanded Disability Status Scale at the time of enrollment, it was significantly higher in nonresponders (median (interquartile range) of 2 (1–3)) compared with responders (median (interquartile range) of 1 (0–2.5)) (P = 0.029). Both total number of relapses throughout the course of disease and number of relapses in the last year were significantly higher in nonresponders compared with responders (P < 0.001). All of the studies MRI parameters including number of T2 lesions, black holes, current enhancing lesions, along with spinal lesions had no significant correlation with response to therapy. After performing regression analysis, modified Rio score was a significant predictor for response to DMT (P = 0.001). A longer duration of therapy with DMT was predictive for response to DMT (P = 0.032). Moreover, the compliance to medications (P = 0.005) and the lower total number of relapses throughout the course of disease (P = 0.004) were significant predictors for response to DMT among the study population.

Conclusion: In this study, modified Rio score, a longer duration of therapy with DMT, the compliance to medications, and the lower total number of relapses throughout the course of disease were found to be a significant predictors for response to DMT among the study population.

Keywords: Disease-modifying therapy, Multiple sclerosis, Predication, Response

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system leading to demyelination and diffuse neurodegeneration in both brain and spinal cord [1]. MS is the most common progressive neurologic disease of young adults worldwide [2]. MS diagnosis based on McDonald’s diagnostic criteria, which link clinical manifestation with characteristic lesions demonstrated by MRI, cerebrospinal fluid analysis, and visual-evoked potentials [3]. Subtypes of MS are considered important not only for prognosis but also for treatment; they include relapsing-remitting multiple sclerosis (RRMS), primary progressive MS, secondary progressive MS, and progressive relapsing MS [4]. The primary aim of treatment is to reduce disease activity to optimize neurologic reserve, cognition function, and physical function [5].

Received 23 December 2020; revised 29 December 2020; accepted 6 January 2021.
Available online 16 November 2023

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https://doi.org/10.5929/2537-0928.1044
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Numerous disease-modifying therapies (DMTs) exist that reduce relapses, reduce MRI activity, and delay disability, especially when initiated early in the disease when the inflammatory component of the disease is strongest [6].

The interferon beta (IFNβ) has been shown to reduce relapse rates and new MRI activity; they also delay disability progression as measured by the Expanded Disability Status Scale (EDSS) [7].

Oral fingolimod, a sphingosine 1-phosphate receptor agonist, is the first oral agent and the first in a novel class of DMTs to be approved for use in the US for the treatment of relapsing forms of MS, a valuable emerging option for the treatment of adult patients with relapsing forms of MS [8].

It is important to monitor treatment efficacy, as breakthrough disease can lead to irreversible neurologic disability, and transitioning into a progressive form of MS may close the therapeutic window of opportunity for the DMTs [9].

A baseline brain MRI should be performed with the initiation of a new DMT, and a follow-up brain MRI to assess treatment response should be performed 6 months after starting a new DMT and then every 6 months to 2 years [10].

Both clinical and MRI measures have proven useful in detecting disease activity and progression in patients with RRMS who are treated with DMT, and these two measures have been used in combination to assess treatment response [11].

2. Aim

The aim of this study was to identify clinical and radiological predictors of response to DMTs in patients with RRMS after 1 year of therapy.

3. Patients and methods

This retrospective study recruited 150 patients with confirmed diagnosis of RRMS from the MS Unit at the Neurology Departments from both Ain-Shams University and Cairo University Student Hospital. All of the study population received either IFNs or fingolimod.

The study included patients with diagnosis of RRMS based on MAGNIMS 2017 criteria [12]. Patients above 18 years old and less than the age of 50 years, from both sex who agreed to participate in the study after obtaining a written informed consent were included, whereas patients with primary progressive MS and secondary progressive MS were excluded from the study.

Patients were subjected to clinical assessment including detailed medical history, age, sex, past history, family history, date of onset and the nature of the first MS-related presenting symptoms, date of diagnosis of MS, total number of relapses during the course of disease before starting a DMT, detailed history of any of DMTs, and number of relapses since starting the current DMT. Assessment of functional disability was done using EDSS. The EDSS is routinely done by the MS Units’ consultants and specialists. The EDSS scores were obtained from the patients’ records throughout their illness, namely, the EDSS scores before and after 1 year from starting the current DMT.

MRI scans of the patients were reviewed before and after 1 year from starting the current DMT for the number of T2 lesions, T1 hypointense lesions, and the presence of any T1 gadolinium-enhancing lesions.

All patients were informed about the aim of our study and methodology, and they had agreed to participate in our research study in a written consent.

Patients were classified into two groups, that is, responders and nonresponders, according to modified Rio score. In this score, patients are classified as being at low risk (score = 0), intermediate risk (score = 1), or high risk (score = 2–3) of a poor response to treatment after 1 year of therapy. Responders are patients with a score 0 or 1 and nonresponders are patients with a score of 2 or 3 [13].

3.1. Statistical analysis

(1) Data were statistically described in terms of range, mean ± SD, median, frequencies (number of cases), and relative frequencies (percentages) when appropriate.

(2) Results were tabulated and statistically analyzed by personal Acer windows computer and statistical package IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp. Pearson and Spearman’s correlation coefficient (r) were used when appropriate to correlate between clinical variables and radiological findings. Strength of correlation was interpreted as follows: 1 = perfect correlation, more than 0.70 = strong correlation, more than 0.50 = moderate correlation, more than 0.30 = weak correlation, and 0 = no linear correlation. The difference between parameters was considered: statistically nonsignificant at P value more than or equal to 0.05.

4. Results

This study included 150 patients with the diagnosis of RRMS. Overall, 105 patients (70% of study
population) were females and 45 (30%) patients were males (Table 1).

Regarding the nature of the first MS-related symptoms, it was noticed that sensory symptoms were the most common (54% of study population experienced sensory symptoms in their initial attack), followed by multifocal symptoms (19% of study population had multifocal symptoms as their initial attack).

Visual deficits were initial symptoms in 10% of population, whereas coordination-related symptoms were initial symptoms in 9% of population. Pyramidal-related symptoms were noticed as initial symptoms in 7% of population, whereas brain stem-related symptoms were initial symptoms in 1% of population.

The underlying table shows a comparison between the MRI characteristics done 1 year before enrollment in the study and that was done at the time of their enrollment in the study. It showed that the majority of patients had more than 10 lesions on T2-weighted image done before 1 year (74.7%), followed by 6–10 (21.3%) lesions, confluent (3.3%), and 0–5 (0.7%) lesions. However, the MRI findings at the time of enrollment in the study revealed the presence of similar parameters with the following percentages: 76, 19.3, 4, and 0.7%, respectively. Black holes were detected in 16 (10.7%) patients at the MRI done 1 year before enrollment compared with 18 (12%) patients at the time of enrollment (Table 2).

Regarding DMTs commenced for the study cases, 105 patients received IFN β (70%), whereas the remaining 45 (30%) cases were on fingolimod therapy. Regarding the type of IFN β, IFN β-1a (Rebif) was commenced for 44 (29.3%) cases, followed by IFN β-1a (Avonex) (42 cases – 28%), and IFN β-1b (Betaferon) (19 cases – 12.7%) (Table 3).

Among the study population, 132 (88%) patients were compliant on treatment (receiving >80% of the monthly dose of DMT), whereas only 12% were noncompliant.

Fingolimod (Gilenya) is considered the most common medication patients were compliant upon, whereas IFN β-1a subcutaneous (Rebif) was the one with least compliance in the study group. Comparing between these medications regarding compliance, there was no significant difference (P = 0.289) (Fig. 1).

Regarding response to treatment, estimated modified Rio score for the study population after 1 year on medications is showed in Fig. 2.

After 1 year of therapy, patients were classified as being at low risk of a poor response to treatment if the score is 0, intermediate risk of a poor response to treatment if the score is 1, or high risk of a poor response to treatment if the score is 2 or 3. The patients with a score of 2 or 3 were defined as nonresponders, and patients with a score of 0 or 1 were defined as responders [13].

In this study, 128 (85.3%) patients were classified as responders, whereas the remaining 22 (14.7%) cases were nonresponders (Table 4).

### Table 1. Clinical characteristics of study population.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Range</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current age (years)</td>
<td>19–50</td>
<td>31.81 ± 7.118</td>
</tr>
<tr>
<td>Age at 1st symptom (years)</td>
<td>14–47</td>
<td>27.33 ± 7.018</td>
</tr>
<tr>
<td>Duration till diagnosis from first symptom (years)</td>
<td>0–7</td>
<td>0.33 ± 1.052</td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>1–9</td>
<td>4.53 ± 3.385</td>
</tr>
<tr>
<td>Total relapses</td>
<td>1–8</td>
<td>2.88 ± 1.601</td>
</tr>
<tr>
<td>Relapses in the last year</td>
<td>0–3</td>
<td>0.68 ± 0.754</td>
</tr>
<tr>
<td>EDSS before 1 year of enrollment</td>
<td>0–2.5</td>
<td>1 (0–2.5)</td>
</tr>
<tr>
<td>EDSS at time of enrollment</td>
<td>0–3</td>
<td>1 (0–3)</td>
</tr>
</tbody>
</table>

EDSS, Expanded Disability Status Scale; IQR, interquartile range.

### Table 2. Comparison between the MRI characteristics done 1 year before enrollment and at the time of enrollment in the study.

<table>
<thead>
<tr>
<th>MRI characteristics</th>
<th>1 year before enrollment</th>
<th>At time of enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of patients</td>
<td>Percentage</td>
</tr>
<tr>
<td>Total number of T2 lesions</td>
<td>0–5</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>6–10</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>&gt;10</td>
<td>112</td>
</tr>
<tr>
<td>Confluent</td>
<td>5</td>
<td>3.3</td>
</tr>
<tr>
<td>Presence of T1 hypointense lesions (black holes)</td>
<td>16</td>
<td>10.7</td>
</tr>
<tr>
<td>Presence of spinal cord lesions</td>
<td>16</td>
<td>10.7</td>
</tr>
<tr>
<td>Enhancing lesions in MRI</td>
<td>10</td>
<td>6.2</td>
</tr>
</tbody>
</table>

### Table 3. Disease-modifying therapy among study population.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Total</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon beta-1a intramuscular (Avonex)</td>
<td>42</td>
<td>28.0</td>
</tr>
<tr>
<td>Interferon beta-1a subcutaneous (Rebif)</td>
<td>44</td>
<td>29.3</td>
</tr>
<tr>
<td>Interferon beta-1b subcutaneous (Betaferon)</td>
<td>19</td>
<td>12.7</td>
</tr>
<tr>
<td>Fingolimod</td>
<td>45</td>
<td>30.0</td>
</tr>
</tbody>
</table>
There was a significant difference between responders and nonresponders regarding age of the participants. The comparison between both groups showed that the age was significantly older in responders compared with nonresponders (mean of 32.37 ± 7.248 vs. 28.55 ± 5.361 years respectively; \( P = 0.019 \)). Sex was not a significant predictor of response to therapy (\( P = 0.764 \)).

Time elapsing between first MS-related symptoms and diagnosis was not significantly different between responders (mean of 30 ± 1.031 years) and nonresponders (mean of 0.45 ± 1.184 years) (\( P = 0.539 \)). The duration of illness did not appear to be significantly different between the two groups (\( P = 0.236 \)). It had mean values of 4.39 ± 3.314 and 5.32 ± 3.759 years in responders and nonresponders, respectively.

The EDSS before 1 year from enrollment in the study was not significantly different between the two groups (\( P = 0.053 \)), as responders and nonresponders had median [interquartile range (IQR)] of 1 (0–2.5) and 1 (0–2), respectively. Regarding the EDSS at the time of enrollment, it was significantly higher in nonresponders [median (IQR) of 2 (1–3)] compared with responders [median (IQR) of 1 (0–2.5)] (\( P = 0.029 \)).

Both total number of relapses throughout the course of disease and number of relapses in the last year were significantly higher in nonresponders compared with responders (\( P < 0.001 \)).

There was no significant difference between responders and nonresponders regarding the type of DMT (\( P = 0.420 \)). No significant difference was detected between responders and nonresponders regarding the duration of drug administration (\( P = 0.532 \)). It had mean values of 2.73 and 2.45 years in responders and nonresponders, respectively.

The compliance to treatment did not differ between responders and nonresponders (\( P = 0.652 \)) (Table 5).

All of the studied MRI parameters, including number of T2 lesions, black holes, current enhancing lesions, along with spinal lesions, had no significant correlation with response to therapy, as shown in Table 6.

**Table 4. Responders and nonresponders according to modified Rio score.**

<table>
<thead>
<tr>
<th>Frequency</th>
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<tr>
<td>Responders 128</td>
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<td>Nonresponders 22</td>
<td>14.7</td>
</tr>
<tr>
<td>Total 150</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Fig. 1. Compliance of patients on current DMT. DMT, disease-modifying therapy.

Fig. 2. Modified Rio score among the study population.

The EDSS before 1 year from enrollment in the study was not significantly different between the two groups (\( P = 0.053 \)), as responders and nonresponders had median [interquartile range (IQR)] of 1 (0–2.5) and 1 (0–2), respectively. Regarding the EDSS at the time of enrollment, it was significantly higher in nonresponders [median (IQR) of 2 (1–3)] compared with responders [median (IQR) of 1 (0–2.5)] (\( P = 0.029 \)).

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<td>Total 150</td>
<td>100.0</td>
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</table>
After performing regression analysis, modified Rio score was a significant predictor for response to DMT ($P = 0.001$). A longer duration of therapy with DMT was predictive for response to DMT ($P = 0.032$). Moreover, the compliance to medications ($P = 0.005$), and the lower total number of relapses throughout the course of disease ($P = 0.004$) were significant predictors for response to DMT among the study population (Fig. 3).

5. Discussion

In patients with MS, the proper choice of DMT leads to the reduction in disease activity. The rapid identification of treatment nonresponders is critical for the timely change in the therapeutic strategy.

Current evidence showed that there is only a limited period early in the course of MS which is critical for maintaining neurological function and preventing subsequent disability ‘windows of opportunity.’ Both early intervention after diagnosis and early treatment optimization in the event of insufficient response to initial treatment are critical to achieving a favorable outcome and reducing the progressive burden imposed by MS on the patients, their families, and society as a whole.

The disease course is evaluated largely based on three outcomes, progression of disability, incidence of relapses, and presence of brain lesions on MRI, individually or in combination.

In this study, we have examined prediction of response to DMTs (IFN β and fingolimod) in 150 patients with RRMS. This study was performed at the Neurology Departments of Ain-Shams University and Cairo University Student Hospitals.

In this study, we used the modified Rio score to categorize patient outcome, as it defines patients with a score $= 2$–$3$ as nonresponders and patients with a score $= 0$–$1$ as responders [13]. It was found that 128 patients (85.3% of study population) were classified as responders, whereas the remaining 22 (14.7%) patients were nonresponders.

In one study conducted by Horakova et al. [14], which included a total of 172 cases with MS on IFN, 90 (52%) cases fulfilled the criteria of nonresponders, which they were defined by using selected variables (EDSS, relapse rate, and number of new T2 lesions in the initial year of treatment).

Of course, the response to treatment is much less than the reported by our study and that could be owing to the different definition of response accredited by both studies. In addition, the previous study scheduled follow-up for 6 years after treatment, a prediction phase in the initial year of treatment with IFN, and a response phase (years, 2–6 of treatment), during which the patients were evaluated as ‘responders’ or ‘nonresponders’ to treatment. If a longer follow-up period is planned, the more relapses should be encountered, and that

### Table 5. Comparison between responders and nonresponders as regards clinical characteristics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Responders ($n = 128$)</th>
<th>Nonresponders ($n = 22$)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>39</td>
<td>6</td>
<td>0.764</td>
</tr>
<tr>
<td>Female</td>
<td>89</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Age (years) (mean $\pm$ SD)</td>
<td>32.37 $\pm$ 7.248</td>
<td>28.55 $\pm$ 5.361</td>
<td>0.019</td>
</tr>
<tr>
<td>Age at onset of first MS-related symptoms (years) (mean $\pm$ SD)</td>
<td>28.04 $\pm$ 6.976</td>
<td>23.23 $\pm$ 5.871</td>
<td>0.003</td>
</tr>
<tr>
<td>Time elapsing between first MS-related symptoms and diagnosis (years) (mean $\pm$ SD)</td>
<td>0.30 $\pm$ 1.031</td>
<td>0.45 $\pm$ 1.184</td>
<td>0.539</td>
</tr>
<tr>
<td>Duration of illness (years) (mean $\pm$ SD)</td>
<td>4.39 $\pm$ 3.14</td>
<td>5.32 $\pm$ 3.759</td>
<td>0.236</td>
</tr>
<tr>
<td>Nature of 1st symptom (mean $\pm$ SD)</td>
<td>3.45 $\pm$ 3.434</td>
<td>4.00 $\pm$ 3.842</td>
<td>0.499</td>
</tr>
<tr>
<td>EDSS before 1 year of enrollment [median (IQR)]</td>
<td>1 (0–2.5)</td>
<td>1 (0–2)</td>
<td>0.537</td>
</tr>
<tr>
<td>EDSS at time of enrollment [median (IQR)]</td>
<td>1 (0–2.5)</td>
<td>2 (1–3)</td>
<td>0.029</td>
</tr>
<tr>
<td>Total relapses (mean $\pm$ SD)</td>
<td>2.60 $\pm$ 1.433</td>
<td>4.50 $\pm$ 1.596</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Relapses in the last year (mean $\pm$ SD)</td>
<td>0.45 $\pm$ 0.515</td>
<td>2.00 $\pm$ 0.535</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Current DMT (used in the previous year) (mean $\pm$ SD)</td>
<td>2.41 $\pm$ 1.181</td>
<td>2.64 $\pm$ 1.255</td>
<td>0.428</td>
</tr>
<tr>
<td>Duration of use (years) (mean $\pm$ SD)</td>
<td>2.73 $\pm$ 1.990</td>
<td>2.45 $\pm$ 1.565</td>
<td>0.532</td>
</tr>
<tr>
<td>Compliance on current treatment (mean $\pm$ SD)</td>
<td>1.13 $\pm$ 0.332</td>
<td>1.09 $\pm$ 0.294</td>
<td>0.652</td>
</tr>
</tbody>
</table>

DMT, disease-modifying therapy; EDSS, Expended Disability Status Scale; IQR, interquartile range; MS, multiple sclerosis.

### Table 6. Comparison between responders and nonresponders as regards MRI characteristics.

<table>
<thead>
<tr>
<th>MRI characteristics</th>
<th>Responders ($n = 128$)</th>
<th>Nonresponders ($n = 22$)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of T2 lesions 1 year before enrollment (mean $\pm$ SD)</td>
<td>2.79 $\pm$ 0.512</td>
<td>2.91 $\pm$ 0.294</td>
<td>0.287</td>
</tr>
<tr>
<td>Total number of T2 lesions at enrollment (mean $\pm$ SD)</td>
<td>2.82 $\pm$ 0.509</td>
<td>2.91 $\pm$ 0.294</td>
<td>0.428</td>
</tr>
<tr>
<td>Number of black holes 1 year before enrollment (mean $\pm$ SD)</td>
<td>0.15 $\pm$ 0.487</td>
<td>0.23 $\pm$ 0.528</td>
<td>0.490</td>
</tr>
<tr>
<td>Number of black holes at enrollment (mean $\pm$ SD)</td>
<td>0.13 $\pm$ 0.453</td>
<td>0.21 $\pm$ 0.425</td>
<td>0.481</td>
</tr>
<tr>
<td>Current spinal lesions (mean $\pm$ SD)</td>
<td>1.91 $\pm$ 0.281</td>
<td>1.86 $\pm$ 0.351</td>
<td>0.456</td>
</tr>
</tbody>
</table>
may also explain the difference between the two studies regarding treatment response.

In the current study, there was a significant difference between responders and nonresponders regarding age of the participants \((P = 0.019)\). Responders were significantly older compared with nonresponders.

In line with our findings, Villoslada et al. [15], conducted a study in Pamplona, Spain, on 202 patients over 2 years; it found that patients responsive to therapy were older compared with nonresponders. That supports our results.

On the contrary, other studies reported that older age at treatment commencement was risk factor for poor response [15,16]. However, in one study, there was no significant difference between responders and nonresponders regarding patient age [14].

After regression analysis, the age of patient was not predictor of response to treatment, which may explain the variety of results in different studies.

In this study, the age of patient at the onset of first MS-related symptoms onset was significantly older in responders compared with nonresponders \((P = 0.003)\). These two observations that responders were older and had their first MS-related symptoms at older age may hypothesize the onset of MS at relatively older age groups might be considered a predictor of response to DMT, or might reflect that older patients and having MS at relatively old age seem to be adherent to treatment and follow-up, and hence have a good response to treatment. The latter explanation was postulated, as one study about the natural history of disease reported that the later onset has been associated with a greater possibility of reaching EDSS score of 6 in a shorter period [17].

One study conducted by Olival et al. [18], stated that patient age at disease onset did not significantly differ between responders and nonresponders \((P = 0.54)\).

In this study, sex was not a significant predictor of response to therapy \((P = 0.764)\). The effect of sex on clinical features of MS is not as clear as the effect on MS prevalence; however, there is evidence that women generally have an earlier onset of disease and show in general less progression of disability than men [19].

In the current study, time elapsing between first MS-related symptoms and diagnosis was not significantly different between responders and nonresponders \((P = 0.539)\). In one study conducted by Mezei et al. [20], the time between symptom onset and diagnosis was not significantly different between responders and nonresponders.

In the current study, the duration of illness did not appear to be significantly different between the two groups \((P = 0.236)\).

Similarly, other authors reported that the duration of illness was not significantly different between responders and nonresponders [14,20].

There was no significant difference in EDSS score between responders and nonresponders at 1 year before their enrollment \((P = 0.537)\) and at the time of enrollment. The EDSS was significantly higher among nonresponders compared with responders \((P = 0.029)\), which strengthens the validity of results.

![Fig. 3. Linear regression analysis for significant predictors of response to therapy in patients with RRMS. RRMS, relapsing-remitting multiple sclerosis.](image-url)
of this study and reinforces the other clinical parameters than disability in the prediction of response in this study specifically.

In their study, Olival et al. [18] and Mezei et al. [20] reported that there was no significant difference between responders and nonresponders regarding EDSS at treatment commencement. Our results were in contrast to O’Rourke et al. [21] who identified EDSS upon the initiation of treatment as a predictor of disability accumulation over 5 years of follow-up.

In the current study, the total number of relapses and the number of relapses in the last year were significantly higher in nonresponders compared with responders ($P < 0.001$). After regression analysis, the lower number of total number of relapses was a significant predictor of treatment response ($P = 0.004$). This supports the total number of relapses throughout the course of disease is an important predictor for response to treatment and shall be considered by the neurologists while following up patients with MS and influence their decision about initial choice of DMT and need for escalation as well.

In line with our findings, Horakova and colleagues reported that responders had significantly lower number of relapses. Moreover, one study that included more than 2000 Danish patients beginning immunomodulatory treatment with IFN $\beta$ or glatiramer acetate identified the pretreatment relapse rate as a predictor of relapses and disease progression on subsequent treatment [22].

In the current study, all of the studies MRI parameters including number of T2 lesions, black holes, current enhancing lesions, along with spinal lesions had no significant correlations with response to therapy. Many previous studies have reported that the correlation between T2-lesion measures and disability within various disease phenotypes has been rather disappointing [23–26]. That supports our findings. Furthermore, there is a plateauing relationship between T2 burden lesion load and disability for EDSS values above 4.5, indicating that alternative metrics to T2-lesion load should be taken into account [27].

Conversely, the incidence of new T2 lesions has been reported to be associated with clinical relapses [28]. In fact, each new lesion increased 10-fold the risk of progression, about 10-fold for a single new T2 lesion, about 20-fold for two new T2 lesions, and about 30-fold for more than three new T2 lesions [29].

Horakova et al. [14] also reported that the number of T2 new lesions was significantly higher in nonresponders compared with responders. It had mean values of 2.8 and 1.5 in responders and nonresponders, respectively. The total lesion number in T2 images was a significant predictor of disease nonresponse ($P = 0.02$).

Río et al. [30] previously showed that MRI activity in combination with either relapsing activity or disability progression within the initial year of treatment predicts nonresponse to IFN over the following 2 years.

Furthermore, other older studies suggested that the extent of new lesions on MRI examination after 12 or 24 months of treatment can identify those patients with a poor response to IFN $\beta$ and a higher increase of disability [31–33].

In the current study, there was no significant difference between responders and nonresponders regarding the type of treatment commenced ($P = 0.420$). In accordance with our findings, similar studies have previously confirmed the nonsignificant difference regarding response among the drugs used [34–36].

At first, there was no significant difference between responders and nonresponders regarding the duration of drug administration ($P = 0.532$). Likewise, Horakova et al. [14] reported that there was no significant difference between responders and nonresponders regarding the duration of DMT. However, the duration of DMT intake was a significant predictor for response to DMT after regression analysis ($P = 0.032$). This finding shall encourage the fact that DMTs shall be continued as long as controlled disease activity and the neurologists shall not address patients with MS to discontinue treatment until the appearance of evidence-based results from multicentered randomized controlled trials.

In the current study, compliance on DMT was an independent predictor of response to therapy ($P = 0.004$). This seems logical and was previously reported that suboptimal adherence to treatment has a negative effect on patient morbidity and mortality outcomes as well as on the overall cost of patient care [37]. Moreover, this finding shall encourage their patients to adhere to their DMTs and investigate it at each follow-up visit.

To summarize, patients presented with higher total number of relapses, short therapy duration, or noncompliant on DMT should be expected to have a poor response to DMT. Therefore, a neurologist should have a low threshold to change the treatment plan or drug dosage if any clinical or radiological progression noted.

This study has some limitations such as the retrospective design, and no biomarkers have been evaluated. These drawbacks should be considered in the upcoming studies.
5.1. Conclusion

Many factors contribute to patients’ outcome regarding being a responder or a nonresponder to DMT. In this study after performing regression analysis, modified Rio score was found to be significant predictor for response to DMT. A longer duration of therapy with DMT was predictive for response to DMT. Moreover, the compliance to medications and the lower total number of relapses throughout the course of disease were significant predictors for response to DMT among the study population.

Ethics information

The institutional committee’s ethical criteria were followed during all proceedings. The Ethics Committee approved the study.

Conflicts of interest

No conflict of interest.

References


