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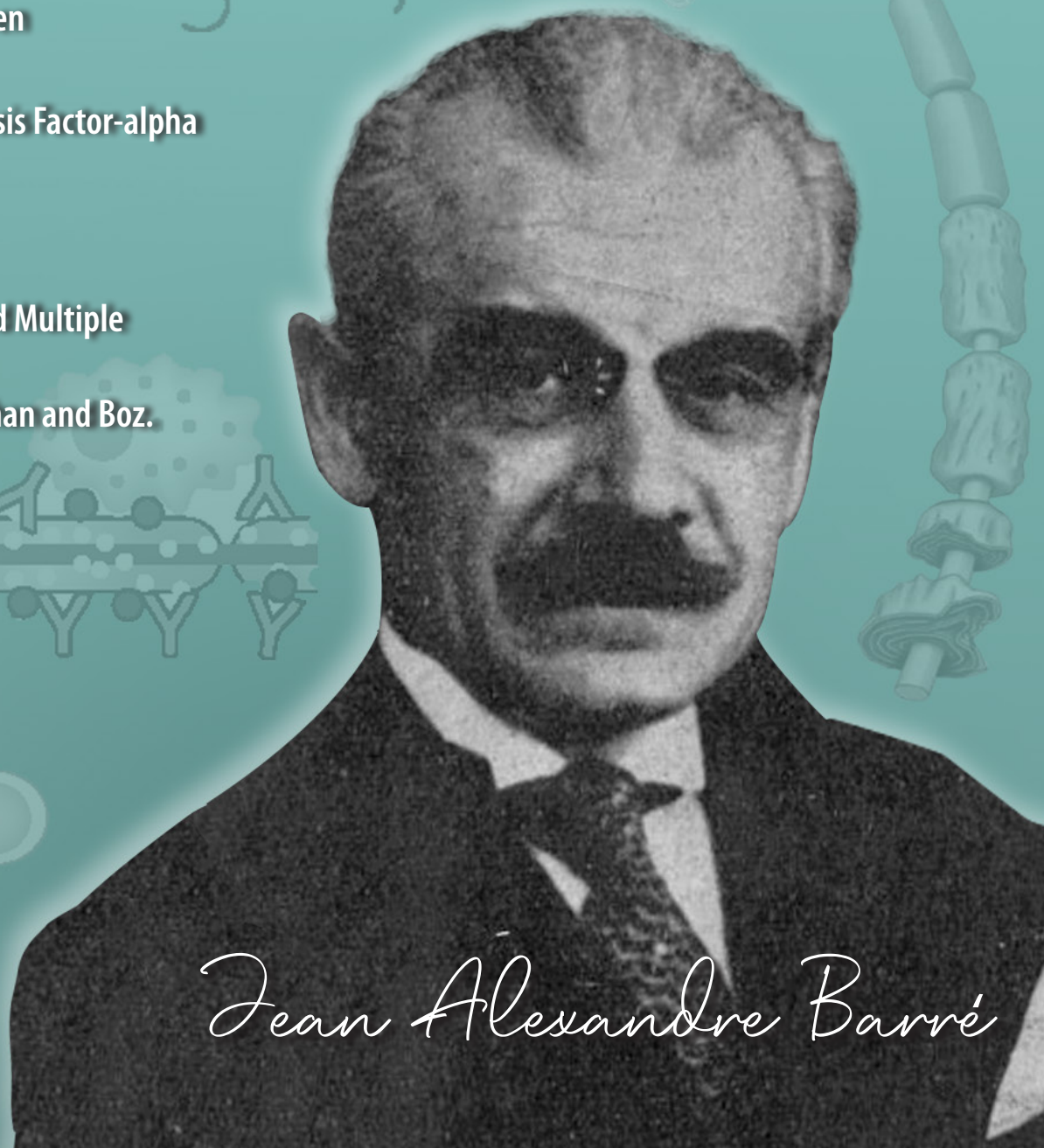

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MS ARAŞTIRMALARI DERNEĞİ

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RESEARCH ARTICLE



# Observational Record Study of Patients with Multiple Sclerosis Presenting to the Neurology Outpatient Clinic of Kocaeli University Faculty of Medicine Hospital

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## Abstract

**Objective:** Multiple sclerosis (MS) is a chronic inflammatory, demyelinating, and neurodegenerative disease with complex etiological factors. Variability in the MS distribution has spurred numerous studies linking it to the environmental and genetic factors. This study aimed to evaluate the demographic, environmental, clinical, and radiological attributes of patients with MS in relation to established and emerging risk factors.

**Materials and Methods:** A cross-sectional assessment of 250 patients (out of 607 initially examined) was conducted from the Kocaeli University Faculty of Medicine Neurology Outpatient Clinic, noting their clinical and laboratory data. These data were subsequently acquired from hospital records. Statistical analyses included the use of the Kolmogorov-Smirnov test, Student's t-test, analysis of variance, Mann-Whitney U test, Kruskal-Wallis test, and Spearman's correlation analysis.

**Results:** The mean age of patients with MS was 40.31±11.6 years, with women constituting 70.7% of all patients. The main initial attack symptoms corresponded with the following lesion sites: supratentorial (38.7%), brainstem (32.4%), optic nerve (22.3%), and spinal region (6.7%). Lifestyle factors revealed that 55.6% of patients consumed salty foods and 48.4% smoked. Furthermore, a significant 68.8% of patients were found to have vitamin D (vitD) deficiency, with an average level of 16.3±8.41 ng/mL. A significant correlation was observed between vitD deficiency and increased disability (as measured by the expanded disability status scale) and lesion counts.

**Conclusion:** This study reinforces the association between vitD deficiency and the progression and severity of MS. The findings highlight the need for addressing modifiable risk factors such as vitD intake, smoking, and dietary habits for the management and prevention of MS.

**Keywords:** Multiple sclerosis, vitamin D deficiency, epidemiology, risk factors

## Introduction

Multiple sclerosis (MS) is a chronic inflammatory demyelination of the central nervous system and is the leading cause of morbidity in young adults. In addition to demyelination, the ensuing axonal degeneration is currently known as the primary cause of irreversible neurological disability in MS. In this regard, MS is described as an inflammatory, demyelinating, and neurodegenerative disease (1) and has a variable geographical distribution. Although MS is more common among Caucasians and those of European descent, it is less frequent among Asians and African-Americans. Its prevalence increases proportionally with distance from the equator, excluding the polar regions. This trend might be associated with vitamin D (vitD) deficiency. Some epidemiological studies have been conducted on communities migrating from countries with low MS prevalence to those with higher prevalence. If the age during migration is <15 years, the prevalence matches that of the adopted country. For those migrating after the age of 15 years, the prevalence aligns with their country of origin. This phenomenon is believed to be a result of complex interactions between environmental factors such as sunlight exposure, temperature and humidity changes, dietary habits, bacterial or viral infectious agents, and genetic factors (2). Despite that the etiology of MS remains unclear, the disease is believed to occur as a result of an autoimmune response in the central

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nervous system, triggered by environmental factors such as viral infections in genetically predisposed individuals. Besides these, studies targeting the etiology of MS have implicated factors, such as obesity, well-water consumption, keeping pets, trauma, accidents or surgeries, chemical agents, organic solvents, vaccinations, pregnancy, vitD deficiency, smoking, and climatic conditions (3). Among these, vitD deficiency, smoking, and adolescent obesity have been frequently discussed in recent years due to their preventable nature. This study aimed to record demographic, environmental, clinical, and radiological findings of patients with MS into a computerized database, facilitating comparisons with results from national and international centers. The data generated in this study are expected to provide significant contributions to both national and international epidemiological and clinical research.

By systematically examining the demographic, environmental, clinical, and radiological characteristics of patients with MS in the context of established and emerging risk factors, this study aimed to provide valuable insights that can inform preventive strategies, therapeutic interventions, and further investigations into the multifaceted nature of MS.

## Materials and Methods

### Study Groups

In this cross-sectional study, 250 patients aged ≥18 years, who were followed up at Kocaeli University Faculty of Medicine Neurology Outpatient Clinic for MS and within the MS spectrum, were included. This study has no exclusion criteria, and a total of 607 patients, 429 women and 178 men, were examined. Among the examined patients, 181 women and 69 men, totaling 250 patients, were included in the study. After recording the clinical and laboratory data of patients using a standard form, they were sourced from hospital records. The participants' age, gender, disease duration, expanded disability status scale (EDSS score), and radiological findings were recorded. The study was approved by the Ethics Committee of the Kocaeli University Faculty of Medicine (protocol no: 2014/264, date: 14.10.2014). The study participants were informed about the study, and an informed consent form was signed.

### Statistical Analysis

Statistical evaluations were performed using the IBM SPSS 20.0 software (SPSS Inc., Chicago, IL, USA). The data normality was assessed using the Kolmogorov-Smirnov test. Numeric variables displaying normal distribution were expressed as means ± standard deviations, non-normally distributed numeric variables were expressed as medians ($25^{th}$-$75^{th}$ percentiles), and categorical variables were presented as frequencies (percentages). Between-group differences for numeric variables with normal distribution were determined by the Student's t-test and one-way analysis of variance, whereas numeric variables without normal distribution were evaluated using the Mann-Whitney U test and Kruskal-Wallis test. For multiple comparisons, the Tukey and Dunn tests were employed. Relationships between numeric variables were assessed using the Spearman's correlation analysis, and relationships between categorical variables were evaluated with the chi-square test. A p-value of <0.05 was considered statistically significant.

## Results

The average age of the general patient group examined was 40.31±11.6 years. The average ages of 429 female patients (70.7%) and 178 male patients (29.3%) were 40.68±11.6 and 39.40±11.6 years. Of the 250 patients studied, 181 were women (72.4%) and 69 were men (27.6%). The average ages of female and male patients were 38.20±10.74 and 37.93±10.67 years, respectively. The average age during the diagnosis for the included patients was 33±9.05 years: 33±9.77 and 32.55±10.15 years for female and male patients, respectively. No significant difference was observed between the two groups (p=0.650). The average disease duration for all patients was 6.40±5.61 years: 6.43±5.77 and 6.55±5.19 years for female and male patients, respectively. No significant difference was observed between the two groups (p=0.805).

The locations of the patients' lesions were grouped into two main categories. In 60 patients (23.7%), lesions were located at the juxtacortical and/or periventricular regions, whereas in 190 patients (76.3%), lesions were present in all of the juxtacortical, periventricular, and infratentorial regions. Then, 200 patients (79.9%) had T1 lesions, and 45 patients (17.7%) had lesions that captured contrast. In this group, cervical imaging could not be performed for 11 patients, making their data incomplete. The distribution of patient diagnoses according to MS clinical subtypes is shown in Figure 1.

Among the study participants, 139 (55.6%) reported consuming salty foods, whereas 121 (48.4%) smoked. The average vitD level among the participants was 16.3±8.41 ng/mL. Patients with vitD values of <20 ng/mL, considered deficient, which totaled 172 (68.8%). The average body mass index (BMI) of patients was 25.77±4.37 kg/m$^2$. Those with a BMI of 30 kg/m$^2$, thus classified

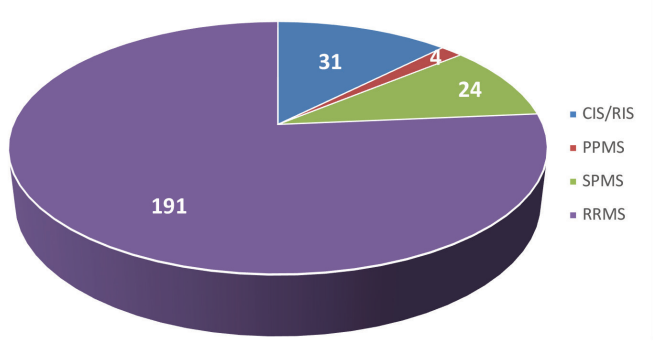


**Figure 1.** Percentage distribution and number of patients by multiple sclerosis clinical phenotypes

as obese, consisted of 32 (12.8%) years. The average EDSS score of patients was calculated to be 1.88. Further, 45 patients had an EDSS score of ≥4. The average relapse count was 3±2.52.

No significant correlation was identified between salt consumption and both regions were associated with the initial attack symptoms and the lesion location (p-values of 0.235 and 0.190, respectively). Similarly, no significant correlation was found for T1 lesion presence, contrast-enhancing lesion presence, T2 lesion count, cervical lesion count, gender, and MS clinical subtype (with p-values of 0.302, 0.138, 0.173, 0.862, 0.420, and 0.175, respectively). Significant correlations were observed between smoking and both gender and salt consumption (p<0.001 and p=0.006, respectively). About 37.6% and 76.8% of female and male patients smoked (p<0.001). The vitD average for the entire patient group was 16.38±8.41 ng/mL. Compared to the 172 individuals with vitD levels of lower than the cutoff value of 20 ng/mL, 78 individuals exceeded this level. In the correlation analysis between vitD and parametric values, a negative correlation with EDSS (p<0.001) and a positive correlation with BMI (p=0.038) were observed. No correlation was identified with the number of relapses (p=0.066). Correlations were found between the T2 lesion count, cervical lesion count, and vitD values (p=0.006 and p=0.027, respectively). Comparing groups with EDSS scores of ≤4 and ≥4, significant differences in vitD values were found between the two groups (p=0.001). As the T2 lesion count increased, so did the number of patients with vitD levels of <20. Similarly, as the cervical lesion count increased, more patients had vitD levels of <20. The average BMI of the patient group was 25.77±8.30 kg/m$^2$. In contrast to the 218 individuals with BMIs of lower than the cutoff value of 30 kg/m$^2$, 32 individuals exceeded this level. In the correlation analysis with nonparametric variables, no correlation was identified between BMI and other variables.

Significant differences were observed in the cervical lesion count and MS clinical subtype between groups with vitD levels of <20 and >20 (p<0.001 for both). About 88.9% of those with an EDSS score of >4 had vitD levels of <20 ng/mL, compared to 64.4% of those with EDSS scores of <4.

## Discussion

In our study, the demographic, radiological, and laboratory data of 250 patients were followed up in our clinic with environmental factors. The supratentorial region was the most common area involved causing the first attack symptom in patients with MS. Although no significant correlation was found between the lesion site and EDSS, a significant relationship was observed between the number of relapses and EDSS. Moreover, as the number of lesions and their location increased, EDSS also increased.

The most prominent among environmental factors was the negative correlation between patients' vitD levels and EDSS. No statistically significant relationships were found between environmental factors, such as smoking, salt, and BMI, and EDSS. Although our study identified a relationship between the vitD and disease, a relationship with other environmental factors was not found. In our study, the female-to-male ratio was slightly above expectations. A study conducted throughout Europe found a higher ratio in Italy and Greece than in other countries, suggesting that the female-to-male ratio might be higher in the Mediterranean geography. Moreover, autoimmune diseases are known to be more common in women, and autoimmunity is influenced by genetic and environmental factors. The geography of a country may contribute to this process. Due to the abundance of industrial establishments in the Marmara region where our city is located, environmental factors might play a decisive role in triggering autoimmunity (4).

MS is a chronic disease affecting young adults. It is most commonly seen between ages of 20-40 years. Bencsik et al. (5), have shown that the average age of onset is 28 years. Piperidou et al. (6), found the average age of onset in women to be 27.2 and 30.4 in men. McDonnell and Hawkins (7) have shown the average age of onset for MS to be 31.6 years. In this study, the average age of onset was determined as 33.05 in both sexes: 32.55 in men and 33.23 in women. No significant difference was found between the average ages of onset in patients of both genders (p=0.650). The average ages were also within the expected range.

In our study, the supratentorial region was the most common area causing the initial attack symptom. Patients with involvement in this region mostly presented symptoms, such as weakness, numbness in a part of the body, walking disorder, and lateralizing signs. In a study conducted by Kantarci et al. (8), in 1998, the initial symptoms of patients with MS were sensory in 30.7% of patients, motor in 28.6%, brainstem and cerebellar in 21%, visual disorders in 14.4%, and sphincter disorders in 5.1%. In another study conducted by Yüceyar et al. (9), with 122 patients, sensory symptoms were the most common initial attack symptom in 46%, with 99 patients having monoregional and 22 having polyregional symptoms. In a study by Houzen et al. (10), 48.1% of patients presented with sensory findings, 40.7% with motor findings, and 18.5% with visual impairment. In a study conducted by Tola et al. (11), in Spain, 55% started with sensory symptoms, 49% with pyramidal signs, 31% with brainstem symptoms, 24% with cerebellar symptoms, and 14% with optic neuritis. Our study's findings were consistent with those of the literature. Smoking status was the only parameter in our study that was correlated with salt. Smokers consumed more salt. Out of 25 people who smoked and had an EDSS score of ≥4, 20 preferred salty foods. Although it did not seem statistically significant (p=0.070), a significant arithmetic difference was observed. The primary reason for the statistical insignificance was thought to be the inadequacy of the sample. In a study with

an adequate sample size, we anticipate that the combination of smoking and salt might have a cumulative effect on the EDSS. Both animal and human models demonstrated that high salt intake induces Th17 lymphocytes (12). Th17 lymphocytes have been reported to expose that the high salt intake are associated with proinflammatory cytokines and show high pathogenicity (13). Farez et al. (14) examined 70 RR patients with MS for 2 years; they found that the risk of attack in those with moderate-high salt intake was increased 2.75 times and the risk of new lesion development by 3.4 times compared to those who did not consume as much salt.

Smoking was correlated with the salt intake and, additionally, with gender. As expected, men smoked more than women. In a study conducted by Hernán et al. (15) with 201 patients with MS and 1903 healthy controls, smoking was reported as a risk factor for the development of new MS and for patients with existing RR MS forms to transition to the SP MS form. In a meta-analysis by Hawkes (16) data from six studies were reviewed, showing that the risk of MS increased in those who smoked before the disease. In a study conducted in Norway by Riise et al. (17), MS developed over time in 87 out of 22,312 individuals, and smoking was identified as a risk factor for MS development in this group. Handel et al. (18), emphasized that smoking causes deterioration in patients with MS; however, the cause of progression could not be definitively shown and needed further studies for confirmation. In our study, no statistically significant relationship was observed between smokers and patients with the disease. We had defined smoking status as either currently smoking or those who had smoked in the past and quit. Nonsmoking status was defined as having never smoked. The lack of statistical significance could be due to this categorization, or it could be considered that there were not enough patients with adequate distribution for this parameter. In our study, vitD was evaluated in two different ways. First, parametrically without grouping patients, and later non-parametrically by setting the deficiency limit of 20 ng/mL as the cut-off and evaluating patients in two groups: >20 and <20 ng/mL the cutoff vitD values. A negative correlation with EDSS was observed in both categorical and noncategorical evaluations. In the non-categorical evaluation, in addition to the EDSS, a positive correlation with BMI was observed, while in the categorical evaluation, a correlation with T2 and number of cervical lesion was observed. In a long-term study conducted on 7 million military personnel in the United States, a negative relationship was found between active vitD levels and the risk of MS (19). In a retrospective study conducted in Italy, among patients with the first clinical signs suggestive of MS, those with low vitD levels were found to have a higher risk of developing clinical MS (20). Another study conducted in the United States reported that nurses who received a daily 400 IU vitD supplement had a 40% lower risk of developing MS compared to those who did not (21). A study conducted in Sweden with 192 patients and 92 healthy controls revealed that high vitD levels were reported to reduce the risk of developing MS (22). In a prospective study conducted by Simpson et al. (23), with 145 patients with RR MS between 2002 and 2005, high vitD levels were reported to reduce relapse frequency. Parallel to other studies, our study also found that the vitD level showed a negative correlation with EDSS. Although seasonal differences and whether or not a vitamin supplement was taken were overlooked, such a correlation strengthens the vitD-EDSS relationship. The fact that those with a higher number of T2 and cervical lesions had lower vitD levels once again reveals that having a low vitD level contributes to the disease progression.

### Study Limitations

The study's sample size may have limited the ability to detect statistically significant relationships between certain environmental factors and EDSS scores in patients with MS. This study does not address the potential prognostic markers and their impact on long-term outcomes of patients with MS.

## Conclusion

In conclusion, this study presents significant findings that help us better understand the course of MD and the factors affecting it. It reveals that the supratentorial region plays a critical role at the disease onset, that there is a clear relationship between the number of relapses and EDSS scores, and particularly that vitD levels are a potential factors in the course of MS. However, the potential effects of other environmental factors on MS have not yet been clarified. This indicates the need for more detailed research in the future to better understand the role of these factors. Additionally, this study has laid a valuable foundation for future research on the pathophysiology and treatment of MS. Based on this study, future research projects should consider further investigation of the impact of various environmental factors including, but not limited to, diet, physical activity, and specific geographic locations on the progression and management of MS.

### Ethics

**Ethics Committee Approval:** The study was approved by the Ethics Committee of the Kocaeli University Faculty of Medicine (protocol no: 2014/264, date: 14.10.2014).

**Informed Consent:** The study participants were informed about the study, and an informed consent form was signed.

### Authorship Contributions

Surgical and Medical Practices: S.D.B., Concept: S.D.B., H.E., Design: S.D.B., H.E., Data Collection or Processing: S.D.B., Analysis or Interpretation: S.D.B., Literature Search: S.D.B., H.E., Writing: S.D.B

**Conflict of Interest:** No conflict of interest was declared by the authors.

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RESEARCH ARTICLE



# The Impact of Restless Legs Syndrome on Quality of Life in Patients with Multiple Sclerosis

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## Abstract

**Objective:** This study aimed to examine the effect of restless legs syndrome (RLS) on quality of life in patients with multiple sclerosis (MS) using the MS Quality of Life Scale-54 (MSQOL-54).

**Materials and Methods:** A total of 80 patients (49 women and 31 men) were included in this study. The questionnaire was based on the International RLS Study Group diagnostic criteria for RLS. The Pittsburgh Sleep Quality Scale, Fatigue Severity Scale, and MSQOL-54 were used.

**Results:** RLS was significantly higher in patients with MS than in the healthy control group (p=0.001). The MSQOL-54 scale mean values were significantly higher in patients with MS than in the healthy control group (p=0.000). Poor sleep quality, and a statistically significant difference was observed between the two groups (p=0.007). Patients with poor sleep quality had significantly lower mean MSQOL-54 values. A significant association was noted between poor sleep quality and RLS (p=0.023). Moreover, chronic fatigue was significantly higher in the patient group (p=0.021). In addition, chronic fatigue was significantly higher in patients with RLS (p=0.049) In the patient group, no relationship was observed between mean values of the MSQOL-54 scale and the mean and RLS.

**Conclusion:** RLS was associated with poor sleep quality and chronic fatigue in patients with MS and may exert an indirect effect on quality of life; therefore, diagnosis and treatment are crucial.

**Keywords:** Fatigue, multiple sclerosis, quality of life, restless legs syndrome, sleep quality

## Introduction

Multiple sclerosis (MS), a chronic immune-related disease of the central nervous system (CNS), is characterized by inflammation, demyelination, and neurodegeneration and leads to considerable disability, especially in young adults (1). MS presents with various clinical symptoms, including nystagmus, dysarthria, intent tremors, optic neuritis, myelitis, and brain-cerebellum syndromes based on the location of demyelinated plaques in the CNS (2). Restless legs syndrome (RLS) is a common, chronic, multifactorial movement disorder characterized by an uncontrollable urge to move the legs and is often accompanied by uncomfortable or painful sensations, especially at night or during periods of rest (3).

RLS is particularly common in patients with MS, with studies showing a prevalence rate of 12.5-65.1%, which is significantly higher than that in the general population (4,5). RLS in patients with MS is linked to several factors, including older age, longer disease duration, higher levels of disability, and the presence of spinal cord lesions, especially in the cervical region (6). In addition, patients with MS who have RLS often experience poorer sleep quality, increased daytime fatigue, and a higher risk of anxiety, depression, and neuropathic pain, which collectively affect the quality of life (7). Voxel-based lesion analysis identified associations between RLS and MS lesions in the subcortex of the left gyrus precentralis, which suggests that dysfunction in the efferent motor system due to cerebral lesions contributes to RLS in MS (8). Moreover, the role of iron metabolism and dopaminergic dysfunction is critical as low levels of alpha-synuclein, which is involved in dopamine receptor trafficking, have been observed in patients with MS who have RLS, potentially contributing to the pathogenesis of the syndrome. Furthermore, inflammatory demyelination, rather than axonal degeneration, appears to be the underlying

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mechanism, as evidenced by RLS symptoms coinciding with acute MS attacks (9).

This study aimed to determine the impact of RLS on quality of life in patients with MS using the MS Quality of Life Scale-54 (MSQOL-54).

## Materials and Methods

Patients aged 18-60 years who reported to the neurology outpatient clinic of Harran University Faculty of Medicine and were clinically and definitively diagnosed with MS according to the McDonald 2017 criteria and were in remission period were included in this study. A signed informed consent form was obtained from all patients. Ethics committee approval was obtained from Harran University Ethics Committee (decision no: 11, date: 09.09.2019).

Participants who had an MS attack within the last 3 months, who had received steroid treatment within the last 3 months, who had known systemic diseases such as connective tissue disease, and who were taking medications that may affect sleep cycles (such as benzodiazepines, modafinil, and melatonin) were excluded from the study. The control group comprised age- and sex-matched participants with no history of illness or drug use and normal physical and neurologic examinations. The study included 80 patients (49 women and 31 men). Neurologic examinations were performed for all patients, and disability status was determined for each patient using the Kurtzke Expanded Disability Status Scale. Participants' body mass index was calculated by dividing their body weight in kilograms by the square of their height in meters. The participants were interviewed using a preset standardized questionnaire to measure the prevalence of RLS. The questionnaire was based on the International RLS Study Group diagnostic criteria for RLS (10). The Pittsburgh Sleep Quality Scale was used to assess the sleep quality. According to this scale, a total score of ≤5 was considered as poor sleep quality and that of 6-21 as good sleep quality (11). The Fatigue Severity Scale that contained nine questions was used in patients with MS and the healthy control group. Each question was scored between 0 and 7, and the total score was averaged. A score of <4 was considered as no fatigue and that of >4 as severe fatigue syndrome (12). MSQOL-54, a multidimensional MS-specific health-related quality of life inventory that includes the generic Short Form-36 core items supplemented with 18 MS-targeted items, was applied to assess the quality of life. The scale comprises two sections, namely, physical and mental health, with higher scores indicating a better quality of life (13).

### Statistical Analysis

The Statistical Package for Social Sciences for Windows version 20.0 (SPSS, Chicago, IL, USA) was used for evaluation. For the comparison of measurement data between the two groups (patients with MS and the control group), Student's t-test was used for normally distributed data, the Mann-Whitney U test for non-normally distributed data, and the chi-squared test for qualitative data. Data obtained via measurement were expressed as mean ± standard deviation and those obtained via counting as number (%). The significance level was set as $p<0.05$.

## Results

A total of 80 patients with MS and 55 healthy individuals were included in this study. The clinical and demographic characteristics of the patient and control groups are presented in Table 1. Of the patients with MS, 63 (78.80%) had relapsing-remitting MS and 17 (21.30%) had progressive MS.

RLS was significantly higher in patients with MS than in the healthy control group (p=0.001). The MSQOL-54 scale mean values were significantly higher in patients with MS than in the healthy control group (p=0.000). Totally, 56 (65.00%) patients in the patient group and 26 (17.6%) in the control group had poor sleep quality, and a statistically significant difference was observed between the two groups (p=0.007). Patients with poor sleep quality had significantly lower mean MSQOL-54 values (mental p=0.006, physical p=0.014, total p=0.007). RLS was present in 29 of the patients with poor sleep quality, which was significantly higher than that in the group with good sleep quality (p=0.023). Chronic fatigue was significantly higher in the patient group than in the control group (p=0.021). In addition, chronic fatigue was significantly higher in patients with RLS in the patient group (p=0.049) In the patient group, no relationship was found between the mean values of the MSQOL-54 scale and the mean and RLS (Table 2).

## Discussion

RLS is more common in patients with MS than in the general population (4). Comparison of SF-36 scores of patients with RLS and the general population indicated that the disorder had a substantial impact on the patient's quality of life (14). In this study, the effect of the presence of RLS on the quality of life of patients diagnosed with MS was analyzed using MSQOL-54.

Consistent with the literature, in this study, it was observed that the rate of RLS was higher in patients with MS than in the control group. The presence of RLS in patients with MS was associated with several factors, including longer disease duration, higher levels of disability, and advanced age (15). However, there was no association between RLS and the clinical characteristics of the patients. Common terms that people with RLS used to describe their symptoms were "need to move", "crawling", "tingling", "restless", "cramping", "feeling like something is crawling inside", "pulling", "electric", "tension", "discomfort", "pain", and "itching" (16). The use of polysomnography might have increased the number of patients with RLS because some patients may describe their current clinic as MS-related pain.

**Table 1. Clinical and demographic characteristics of the patient and healthy control groups and comparison of MSQOL-54 scale mean values between groups**

| | Patient n=80 | Control n=55 | p-value |
|---|---|---|---|
| **Gender (%)** | | | |
| Female | 49 (61.20%) | 36 (65.5%) | 0.377 |
| Male | 31 (38.80%) | 19 (34.5%) | |
| **Age (Mean ± SD)*** | 36.71±10.66 | 36.49±9.37 | 0.899 |
| **BMI (Mean ± SD)** | 25.09±4.17 | 25.35±3.18 | 0.691 |
| **RLS** | 35 (43.80%) | 9 (16.4%) | **0.001** |
| **MSQOL-physical** | 58.51±19.52 | 69.86±17.25 | **0.001** |
| **MSQOL-mental** | 58.81±21.68 | 67.25±21.17 | **0.026** |
| **MSQOL-total** | 117.32±36.76 | 137.16±36.90 | **0.004** |
| **Fatigue (%)** | 43 (53.8%) | 19 (34.5%) | **0.021** |
| **Poor sleep quality** | 56 (65.00%) | 26 (17.5%) | 0.007 |

*Mean ± SD: Mean score ± Standard deviation, BMI: Body mass index, RLS: Restless legs syndrome, MSQOL: Multiple Sclerosis Quality of Life Scale

**Table 2. Quality of life of patients and control group**

| | HBS positive (mean ± SD) n=35 | HBS negative (mean ± SD) n=45 | p-value |
|---|---|---|---|
| **MSQOL-physical** | 53.9±14.9 | 59.0±23.01 | 0.282 |
| **MSQOL-mental** | 54.5±19.4 | 58.0±23.02 | 0.501 |
| **MSQOL-total** | 108.4±32.5 | 117.04±44.8 | 0.367 |

*Mean ± SD: Mean score ± Standard deviation, MSQOL: Multiple Sclerosis Quality of Life Scale

The quality of life was lower in patients with MS than in the control group, but it was not associated with RLS in this study. The severity of RLS symptoms was positively linked to poorer sleep quality, increased anxiety, and decreased cognition. Furthermore, poor sleep quality, a common problem in patients with MS, was independently associated with poor quality of life, and RLS exacerbated this problem by causing excessive daytime sleepiness and sleep disturbances (7,17). RLS in patients with MS was linked to increased sleep latency, decreased total sleep time, and a higher percentage of light sleep stages, which led to poorer sleep quality. This condition was also associated with increased fatigue and a higher risk of anxiety and depression, which further worsened the sleep quality and well-being (17,18). There was a relationship between poor sleep quality and the presence of RLS in patients with MS, but there was no association between poor sleep quality and decreased quality of life. Hence, it appears that RLS may indirectly reduce the quality of life by worsening the sleep quality and causing chronic fatigue.

### Study Limitations

The limitations of this study are the small number of patients, the lack of polysomnography, and the lack of evaluation according to the educational level and cognitive functioning of the patients.

## Conclusion

Overall, the coexistence of RLS and MS creates a compound burden that significantly impairs the quality of life of affected individuals, which emphasizes the need for comprehensive management strategies that consider both conditions simultaneously. The presence of RLS in patients with MS requires increased awareness and early diagnosis to improve their quality of life. Effective management of RLS can potentially alleviate the associated psychiatric comorbidities and sleep disturbances. Considering the impact of the disease on cognitive functions in patients with MS, studies should be conducted to ensure that such questionnaires are short, understandable, and comprehensive.

### Ethics

**Ethics Committee Approval:** Ethics committee approval was obtained from Harran University Ethics Committee (decision no: 11, date: 09.09.2019).

**Informed Consent:** A signed informed consent form was obtained from all patients.

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RESEARCH ARTICLE



# Tumor Necrosis Factor-alpha Inhibitors: Can They Induce an Idiopathic Inflammatory Demyelinating Disease in the Central Nervous System?

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## Abstract

**Objective:** Tumor necrosis factor-α (TNF-α) inhibitors are used extensively in the treatment of inflammatory diseases in rheumatology, ophthalmology, and neurology. Despite their therapeutic benefits, inflammatory demyelinating lesions or relapses have been observed following TNF-α inhibitor use.

**Materials and Methods:** Of the 295 patients who were screened, 258 were included in the study. The demographic characteristics, diagnoses, accompanying diseases, TNF-α agent(s) used, drug usage, and exposure times were recorded. The neurological symptoms and clinical visits were also documented.

**Results:** The study included 142 females and 116 males, with a mean age of 43.82±11.81 years. Twenty-eight patients used three or more TNF-α inhibitors for an average of 72.42 months. Fifty-eight patients used two TNF-α inhibitors for 55.7 months, and 172 patients used a single TNF-α inhibitor for 45.27 months. During the follow-up, a brain magnetic resonance imaging (MRI) was obtained in 63 patients. Most of these MRIs showed asymptomatic lesions that met one Barkhof criteria and scored one on Fazekas scale for deep and periventricular white matter lesions. One patient with idiopathic uveitis exhibited symptoms of a demyelinating lesion.

**Conclusion:** TNF-α inhibitors appear to be mostly safe with regards to the induction of inflammatory demyelinating diseases/lesions. However, patients with idiopathic uveitis may be predisposed to developing or presenting with inflammatory/demyelinating lesions of the central nervous system.

**Keywords:** TNF-α, multiple sclerosis, rheumatology, uveitis, demyelinating disease

## Introduction

Tumor necrosis factor-alpha (TNF-α) is a proinflammatory cytokine produced by both innate and acquired immune cells, including macrophages and lymphocytes (1). It can also be secreted by microglia, neurons, and astrocytes in the central nervous system (CNS) (1). In pathological conditions, TNF-α can cause tissue injury. In acute phases of multiple sclerosis (MS), elevated TNF-α expression has been observed within demyelinating plaques (2). However, TNF-α inhibitors may reportedly worsen MS relapses despite positive outcomes in experimental autoimmune encephalomyelitis models (3,4). Recent case reports have suggested a link between TNF-α inhibitors and symptoms indicative of MS or demyelinating disease (5). Thus, in this study, we aimed to evaluate patients treated with TNF-α inhibitors for neurological and demyelinating disease symptoms during their follow-up.

## Materials and Methods

In this retrospective study, patients being treated with TNF-α inhibitor for a rheumatological disease, who had visited the rheumatology department for follow-up, were included in the study. The demographic characteristics of all the patients were collected. Among the included participants, patients who were admitted under the neurology department before the study

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period and who underwent imaging any time point during the follow-up period were screened. Patients who developed uveitis were analyzed separately. Details regarding exposure duration and number of TNF-α agents were collected.

The lesions detected on magnetic resonance imaging (MRI) were evaluated using the radiologically isolated syndrome (RIS) criteria because they were asymptomatic. The proposed diagnostic criteria of RIS are as follows:

A. The presence of incidentally identified white matter anomalies that meet the following MRI criteria:

1) Ovoid, well-circumscribed, and homogeneous foci with or without involvement of the corpus callosum; 2) T2 hyperintensities measuring ≥3 mm and fulfilling the Barkhof criteria (at least three out of four) for dissemination in space (DIS); 3) anomalies not exhibiting a clear vascular pattern; and 4) structural neuroimaging abnormalities that cannot be explained by another disease process.

B. No history of clinical symptom remittance that is consistent with neurological dysfunction.

C. The MRI anomalies do not account for clinically apparent impairments in social, occupational, or general functioning.

D. The MRI anomalies are not the direct physiological effects of substances (recreational drugs or toxic substances) or a medical condition.

E. Exclusion of individuals with MRI phenotypes suggestive of leukoaraiosis or extensive white matter changes that lack clear involvement of the corpus callosum.

F. The CNS MRI anomalies are not better accounted for by another disease process (6,7).

The MRI lesions were also evaluated using the Barkhof criteria as follows: a) ≥9 lesion on T2-weighted images, exhibiting hyperintensity or ≥1 gadolinium enhancing; b) ≥1 infratentorial lesion; c) ≥1 juxtacortical lesion; and d) ≥4 periventricular lesions.

The sites and severity of the lesion were categorized using the Fazekas scale for white matter lesions as follows: (a) periventricular white matter (PVWM), graded as 0= absent, 1= "caps" or pencil-thin lining, 2= smooth "halo", and 3= irregular periventricular signal extending into the deep white matter; and b) deep white matter (DWM), graded as 0= absent, 1= punctate foci, 2= beginning confluence, and 3= large confluent areas (8). The mean number of lesions, dissemination in time (DIT), and DIS (periventricular, cortical/juxtacortical, infratentorial, and spinal) were noted. During the follow-up the presence of any of the following characteristics were noted: ovoid lesion, lesions perpendicular to the ventricle, and black hole lesions or lesion with gadolinium enhancement.

This study was approved by the Ethics Committee of University of Health Sciences Turkey, Kartal Dr. Lutfi Kirdar City Hospital (approval number: 514/194/8, date: 27.01.2021). Written informed consent was obtained from all the participants.

### Statistical Analysis

All statistical analyses were performed using SPSS (version 21.0). The frequencies and percentages, means and standard deviations, or medians with minimum and maximum values were calculated for the data. Additional analyses were not required.

## Results

### Demographic Characteristics

Out of the 295 screened patients, 258 were included. The study included 142 females (55.08%) and 116 males (44.96%). The mean age of the study participants was 43.82±11.81 years (females, 46.16±11.93 years; males, 40.96±11.05 years). The diagnoses included in the study were ankylosing spondylitis (n=150), rheumatoid arthritis (n=82), Behçet's disease (n=8), psoriatic arthritis (n=17), and enteropathic arthritis (n=1) (Table 1).

Of the 258 included patients, 130 had a systemic disease. Eighty-four patients had vascular risk factors such as hypertension (n=67; hypertension alone, n=27), diabetes mellitus (n=37), coronary artery disease (n=15), hyperlipidemia (n=13), dysrhythmia, (n=5), and pulmonary embolism (n=3). The other patients had non-vascular diseases such as asthma (n=14), thyroid dysfunction (n=10), kidney stones (n=5), Hepatitis B virus infection (n=5), uveitis (n=13), and epilepsy (n=4).

### TNF-α Exposure Duration

Of the 295 patients, 173 were prescribed a single TNF-α inhibitor for an average of 45.75±32.91 months. The drugs used were etanercept (n=43), adalimumab (n=59), infliximab (n=14), certolizumab (n=29), and golimumab (n=28). Fifty-seven patients were prescribed two TNF-α inhibitors for an average of 56.35±47.07 months. Twenty-eight patients were prescribed three or more TNF-α inhibitors for an average of 72.42±30.35 months (Table 2).

**Table 1. Demographic characteristics of the study patients**

| Demographic characteristics | |
|---|---|
| Age (mean ± SD; year) | 43.82±11.81 |
| Female (n, %)<br>Male (n, %) | 142 (55.08%)<br>116 (44.96%) |
| Ankylosing spondylitis (n, %) | 150 (58.13%) |
| Rheumatoid arthritis (n, %) | 82 (31.78%) |
| Behçet's disease (n, %) | 7 (2.71%) |
| Psoriatic arthritis (n, %) | 17 (6.589%) |
| Enteropathic arthritis (n, %) | 1 (0.387%) |
| Idiopathic uveitis | 1 (0.387%) |

SD: Standard deviation

### Neurological Symptoms and Neurology Outpatient Visits

During their rheumatological follow-up, 81 patients visited the neurology outpatient clinic for the following symptoms: headache (n=42), vertigo (n=12; four with a headache, one with a transient ischemic attack, and two with seizures), extrapyramidal symptoms (restless legs syndrome; n=4), facial numbness and ataxia (n=1), and hemiparesis (n=1). The other 21 patients had neck pain, back pain, and disc herniation/bulging without any specific neurological findings.

### Imaging Findings

An MRI was obtained in 63 patients. Of these, 12 were brain and cervical spine scans, 19 were cervical spine scans alone, six were diffusion-weighted images, and one was a hypophysis scan. A cranial computerized tomography (CT) was obtained in 29 patients.

Of the 19 patients with brain MRIs, 15 exhibited abnormalities on their MRI. An extraparenchymal subdural hematoma, arterial infarction, and bilateral frontal encephalomalasia was observed in one patient each.

**Table 2. Mean duration of exposure to TNF-α inhibitor**

| TNF-α inhibitor mean exposure | Time (month) |
|---|---|
| **Single agent (n=173)** | |
| Etanercept (n=43) | 44.09±35 |
| Adalimumab (n=59) | 52.98±35.56 |
| Infliximab (n=14) | 59.2±40.17 |
| Sertolizumab (n=29) | 28.96±19.27 |
| Golimumab (n=28) | 42.17±24.41 |
| **Two different agents (n=57)** | 56.35±47.07 |
| **>3 agents (n=28)** | 72.42±30.35 |
| **All patients (n=258)** | 45.75±32.91 |

TNF-α: Tumor necrosis factor-alpha

The 15 patients with an MRI lesion were grouped according to the Barkhof criteria, Fazekas DWM and PVWML locations, and lesion type (Table 3). The mean lesion count was eight. According to the MRI, the lesions were localized as follows: periventricular (n=10), cortical/juxtacortical (n=8), new T2 lesion (N/A), ovoid pattern (n=0), perpendicular to the ventricle (n=0), corpus callosum (n=2), black hole (n=2), >3 mm lesion (n=10), gadolinium enhancement (n=1), and infratentorial/spinal cord (n=0). According to the Barkhof criteria of lesions scored 0 (n=6), 1 (n=4), 2 (n=3), and >3 (n=2).

Most of the patients had periventricular and juxtacortical lesions that scored 0 and 1 on the Barkhof scale. Furthermore, most of them scored 1 and 2 on Fazekas scale, indicating an ischemic origin rather than a demyelinating disease. One patient was meeting MS DIT criteria according to the McDonald's 2017 criteria.

### Analysis of Patients with Uveitis

Thirteen patients were treated with TNF-α inhibitors developed uveitis with or without a rheumatological disease. Of the 13 patients, 8 (61.53%) were female and 5 (38.46%) were male. The mean age of the patients in this group was 44.69±11.22 years.

The rheumatological diagnoses of the patients in this group were ankylosing spondylitis (n=6), Behçet's disease (n=3), rheumatoid arthritis (n=3), and idiopathic (n=1). The neurological signs/symptoms observed in this group were headache (n=3), extrapyramidal movement disorder (n=1), cerebral venous thrombosis (n=1), radiculopathy (n=1), ataxia with sensorial dysfunction (n=1), and right hemiparesis with decreased consciousness (n=1).

The mean treatment time in patients who were prescribed a single TNF-α inhibitor (adalimumab, n=6; infliximab, n=3; and etanercept, n=1) was 41.7±31.56 months. The mean treatment time in the two patients who were prescribed two TNF-α inhibitors (adalimumab + infliximab or adalimumab + etanercept) was 44.66±3.05 months.

**Table 3. Distribution of patients according to Barkhof criteria, lesion localization on MRI, mean lesion count, and Fazekas scale for asymptomatic white matter lesions**

| MRI lesion localization | Periventricular | Cortical/juxtacortical | New T2 lesion | Ovoid pattern | Perpendicular to ventricle |
|---|---|---|---|---|---|
| **Patient group** | 10 | 8 | N/A | 0 | 0 |
| | **Corpus callosum** | **Black hole** | **>3 mm lesion** | **Gd-Enhancement** | **Infratentorial/spinal** |
| | 2 | 2 | 10 | 0 | 0 |
| **Barkhof criteria** | **0** | **1** | **2** | **>3** | |
| | 6 | 4 | 3 | 2 | |
| **Fazekas scaling** | **0** | **1** | **2** | **3** | |
| DWM | 2 | 7 | 2 | 0 | |
| PVWM | 1 | 7 | 3 | | |

SD: Standard deviation, MRI: Magnetic resonance imaging, GD: Gadolinium, DWM: Deep white matter, PVWM: Periventricular white matter

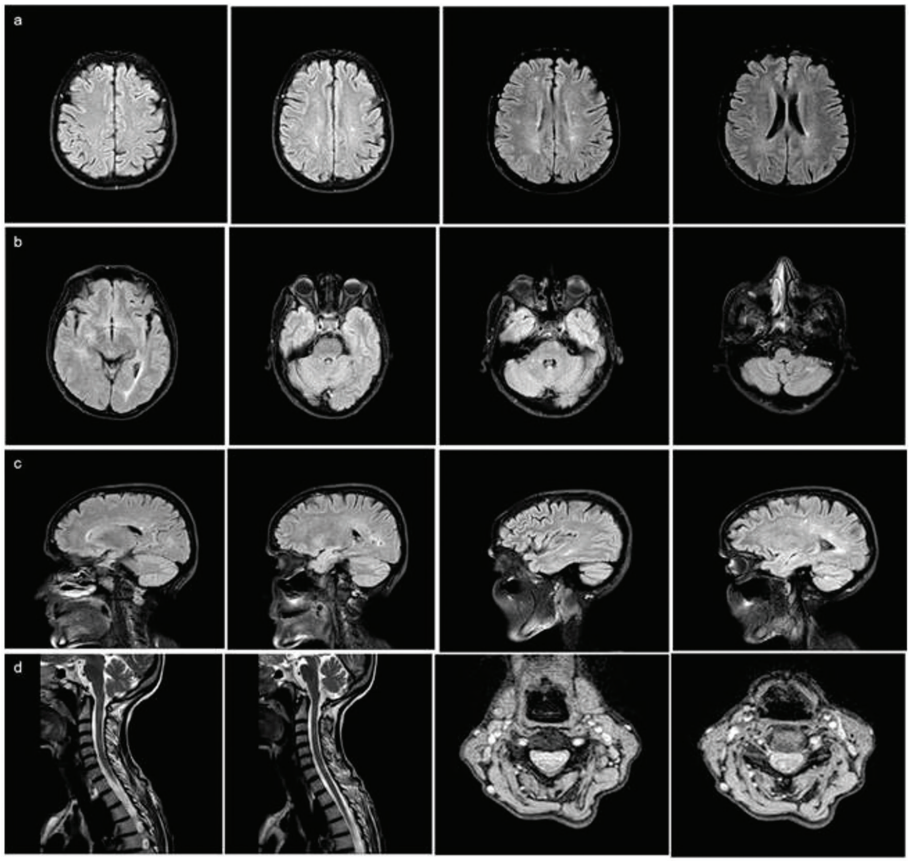


**Figure 1.** (a, b) Axial and (c) sagittal FLAIR sequences and (d) sagittal-axial T2-weighted magnetic resonance images of the cervical spinal of a patient. Periventricular, cerebellar, pontine and cervical spinal demyelinating lesions are observed

Seven patients had undergone an MRI examination. Of the seven MRIs, three were cervical spine scans, three were brain scans, and one was a brain and cervical spine scan. The MRI lesions in one patient were consistent with that of Neuro-Behçet's disease (involvement of the diencephalon and left temporal lobe). This patient was initially treated with a cyclophosphamide infusion once a month. However, at the one-year follow-up, the lesion had progressed and exhibited contrast enhancement. Thus, treatment with infliximab was initiated, which yielded clinical recovery. After three years of infliximab infusions, he developed ataxia. An MRI was obtained, which showed a hyperintense non-enhancing lesion in the left cerebellar hemisphere. This finding was suggestive of an inflammatory/demyelinating lesion. However, the patient was lost to follow-up.

### Representative Case Presentation

A 48-year-old female with idiopathic uveitis presented to the neurology outpatient clinic with facial numbness and an ataxic gait. She had been using adalimumab for three years and was ophthalmologically stable. Neurological examination revealed left facial hypoesthesia and right-sided ataxia. Her MRI revealed periventricular, juxtacortical, right cerebellar, left pontine and cervical spine chronic demyelinating lesions (Figure 1). The thoracic and abdominal CT were reported as normal, and tests for vasculitis were negative. Cerebrospinal fluid (CSF) was obtained via a lumbar puncture. The protein and glucose levels in the CSF were normal, and tests for viruses, microbes, and mycobacterium in the CSF were negative. However, lymphocytes and oligoclonal bands were detected in the CSF. Furthermore, the immunoglobulin G index was 0.4. The MRI findings fulfilled the 2017 McDonald criteria for DIS and DIT. Thus, the patient was diagnosed to have TNF-α inhibitor-associated inflammatory demyelinating disease. The patient was started on subcutaneous methotrexate injections at a dose of 15 mg/week. At the last follow-up, she was clinically and radiologically stable.

## Discussion

This study has demonstrated the presence of inflammatory demyelinating diseases of the CNS in patients being treated with TNF-α inhibitors. However, it is still unclear whether the condition is a coincidental finding or caused by the drug (1,9). In our study, almost all the patients had no inflammatory/demyelinating symptom or sign. There are two types of TNF receptors, TNFR1 and TNFR2) (1). TNFR1 mediates apoptosis and demyelination, while TNFR2 activates cell survival, inflammation resolution, and myelination (10).

In a study consisting of 4,391 patients with a 10-year follow-up, the prevalence of neuroinflammation was 0.4% during the treatment with TNF-α inhibitors, making it a rare complication (11). However, after the onset of an inflammatory relapse/lesion, the autoimmune disease process may persist even after the cessation of TNF-α inhibitors. In a four-patient case study, two patients had developed recurrent demyelinating lesions after the treatment had ended. Furthermore, these patients had a family history of autoimmune diseases (1). Despite these findings and the view that latent MS can be aggravated due to TNF-α inhibitor use, no association between drug usage and MS aggravation has been found.

In one study with a long follow-up period, the MRI of most patients showed new lesions or relapses after TNF-α inhibitor cessation, confirming a relapsing CNS demyelinating disease course (12).

A nationwide survey in France identified 33 patients with demyelinating disease of the central and peripheral nervous systems. Of the 22 patients with CNS demyelinating lesions, five were diagnosed as MS according to McDonald's criteria (9). In our study, the asymptomatic MRI lesions were evaluated using the Barkhof criteria, Fazekas scale, and RIS criteria. Most of the lesions were not consistent with an inflammatory demyelinating lesion. In our study, only two patients were symptomatic, and they both had uveitis. One of these patients had findings that met the MS criteria, and the other patient had Neuro-Behçet's disease.

Patients with uveitis who are or are not diagnosed with a rheumatological disease could progress to an inflammatory demyelinating disease course while under treatment with TNF-α inhibitors. Although intermediate uveitis is more frequently present in patients with MS, anterior, posterior and panuveitis can also be seen (12-14). A similar observation was reported by Cunningham and Zierhut (15). They mentioned that there was no apparent evidence that TNF-α inhibitors can directly cause an inflammatory demyelinating disease. However, two of our patients with uveitis developed a demyelinating disease after treatment with TNF-α inhibitors. Furthermore, patients with idiopathic uveitis may exhibit evidence of central demyelination. Therefore, initiation of TNF-α inhibitors in such patients should be undertaken with caution (15).

In our study, only a few patients exhibited symptoms of uveitis. Furthermore, patients with idiopathic uveitis may be at risk for developing inflammatory/demyelinating lesions due to TNF-α inhibitor use because of a possible accompanying or underlying demyelinating disease course.

### Study Limitations

The retrospective nature and limited number of participants with demyelinating diseases in the study may not accurately represent the susceptible patient group.

## Conclusion

TNF-α inhibitors appear to be safe, and mostly do not aggravate inflammatory or demyelinating lesions. However, using TNF-α inhibitors in patients with idiopathic uveitis may induce an autoimmune CNS reaction/disease.

### Ethics

**Ethics Committee Approval:** This study was approved by the Ethics Committee of University of Health Sciences Turkey, Kartal Dr. Lutfi Kirdar City Hospital (approval number: 514/194/8, date: 27.01.2021).

**Informed Consent:** Written informed consent was obtained from participants.

### Authorship Contributions

Surgical and Medical Practices: A.K.K., R.B., M.E.T., Concept: A.K.K., M.E.T., Design: A.K.K., M.E.T., Data Collection or Processing: A.K.K., R.B., M.E.T., Analysis or Interpretation: A.K.K., R.B., M.E.T., Literature Search: A.K.K., R.B., M.E.T., Writing: A.K.K., R.B., M.E.T.

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RESEARCH ARTICLE



# Clinical Course and Outcomes of COVID-19 in Patients with Multiple Sclerosis

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## Abstract

**Objective:** Multiple sclerosis (MS) patients may be particularly susceptible to severe coronavirus disease-2019 (COVID-19), caused by the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). To determine variables associated with COVID-19 severity in MS patients, as well as investigate their prognosis and outcomes.

**Materials and Methods:** Information regarding COVID-19 occurrence in MS patients was obtained in this single-center observational study. Demographic variables, medical history, and clinical features of MS were documented during patient visits or via phone interviews. Factors associated with severe COVID-19 were identified through multivariate analyses.

**Results:** This study included 433 MS patients (296 female, 137 male, age 40.2±11.8) with confirmed COVID-19 infection and 773 MS patients (532 female, 241 male, age 43.6±12.0) without COVID-19. Before contracting COVID-19, 212 patients (49.0%) received the full vaccination against SARS-CoV-2. The re-COVID Expanded Disability Status Scale (EDSS) scores were comparable in patients with (2.5±2.1) and without (2.6±2.1) COVID-19 infection. Of these, 296 (68.4) patients exhibited mild, 98 (22.7) had moderate, and 39 (9.0) exhibited severe COVID-19. Mortality occurred in 13 patients with severe COVID-19 infection. Multivariate regression analysis revealed older age, high EDSS scores, and the use of anti-CD20 therapy as risk factors for severe COVID-19.

**Conclusion:** Most MS patients experienced successful recovery following the COVID-19 infection. A high EDSS score, being older, and anti-CD20 medications increase the potential for developing severe COVID-19 and mortality.

**Keywords:** Anti CD-20, COVID-19, multiple sclerosis

## Introduction

Coronavirus disease-2019 (COVID-19) is a systemic infectious disease that primarily affects the respiratory tract (1). Multiple sclerosis (MS) is a chronic neurodegenerative and inflammatory disease of the central nervous system that is the primary cause of progressive disability in young adults. The potential for more severe COVID-19 outcomes during the pandemic has been a topic of concern, particularly among MS patients who are receiving immunosuppressive medication or those with substantial disability (2-5).

Furthermore, B-cell-depleting medications such as ocrelizumab may mitigate severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) antibody production and attenuate vaccine response. Therefore, immunosuppressive medications may theoretically excerbate MS in these patients (6-10). Recent research suggests that anti-CD20 and fingolimod may elicit a diminished immunoglobulin-G response to the anti-spike protein following COVID-19 immunization (5,11-15).

This study aimed to investigate the clinical features and consequences of SARS-CoV-2 infection in MS patients and determine the risk factors associated with a more severe infection at one of the largest MS centers in Northeastern Turkey.

## Materials and Methods

The study included MS patients from a broader area of the Eastern Black Sea region who presented at the

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neuroimmunology clinic at the Karadeniz Technical University Medical Faculty. Since 2000, the MSRegistry (Imed) database has documented all observational data about MS patients. Real-time data entry, or a close approximation of it, was the standard practice during clinical visits.

Patients diagnosed with MS who had at least one outpatient visit at our clinic within the previous three years are monitored using our local electronic data registry, MSRegistry.

We evaluated patients for COVID-19 infections during in-person visits or over the phone when they contacted our clinic. We also collected data about COVID-19 infections from the pertinent electronic health records.

To ascertain their post-COVID status, we conducted follow-up interviews via telephone or telemedicine with all 433 MS patients. In cases where patients were unable to participate in the interview, we obtained data from a caregiver.

During our most recent visit, we obtained additional information regarding the MS status from our electronic records.

The Expanded Disability Status Scale (EDSS) was used to assess disability. The comorbidities that were investigated included cardiovascular illness, hypertension, diabetes, renal disease, chronic liver disease, other neurological disorders, lung disease, or other medical diseases.

The COVID-19 vaccination records and COVID polymerase chain reaction (PCR) test results were reviewed using the national personal health record system. A person was considered fully vaccinated if, within the past six months, they had received one or more doses of the mRNA vaccine or at least two doses of the inactive vaccine. Participants who received their most recent immunization within the previous 14 days were not included in the study. Patients who had not received all of the recommended doses of the COVID-19 vaccine were considered as partially vaccinated.

A definitive diagnosis of COVID-19 infection was made on confirmation of a positive PCR test result for SARS-CoV-2 on a nasopharyngeal swab. In contrast, MS patients whose PCR test was either negative or not conducted but who exhibited the clinical symptoms and signs of the infection and were in close contact with an individual with a validated diagnosis of COVID-19 were considered to have an unconfirmed COVID-19 infection. This study was approved by the Ethics Committees of the Karadeniz Technical University (protocol no: 2021/271, date: 07.10.2021) and the Turkish Ministry of Health. Each participant provided written informed consent.

### Study End-points

The primary endpoint was the COVID-19 severity in MS patients. The clinical severity of COVID-19 was classified using the following categories of disease severity: Mild: Patients who were ambulatory and either asymptomatic or symptomatic, displaying any of the diverse COVID-19 signs and symptoms, but did not exhibit abnormal chest imaging or dyspnea. Moderate: Patients with an oxygen saturation of 94% or above requiring oxygen support and hospitalization but not critical care. Severe: Patients requiring admission to the intensive care unit; those whose oxygen saturation was less than 94%; or COVID-19 resulting in death.

### Statistical Analysis

The R software (version 4.1.2) was employed for statistical analysis (16). For continuous variables, descriptive data are shown as the mean and standard deviation; for categorical variables, they are shown as numbers and percentages (%). The quantitative variables were compared using the t-test, Mann-Whitney U, or Kruskal-Wallis test, depending on their distribution. Chi-square analysis was employed to examine categorical variables and presented as contingency tables. We conducted multivariate ordinal regression analyses with the severity of COVID-19 and their 95% confidence intervals (CI) to determine variables that could potentially influence COVID-19 severity. Age, sex, age at onset, MS duration, EDSS, annualized relapse rate, smoking history, co-morbidity, use of disease-modifying therapy (DMT), and pre-covid vaccination status (fully vaccinated as reference) were included as independent variables. The severity of COVID-19 was considered as the dependent variable (mild, moderate, or severe COVID-19). The level of significance was established at $p<0.05$.

## Results

### Study Population

This study included 1204 MS patients, after excluding 779 cases from the 1983 records in our MS Registry. Four hundred thirty-three patients with MS and concurrent COVID-19 were identified between 1 March 2020 and 28 February 2022. In Figure 1, the progression of the number of COVID-19 cases over time is depicted. In patients who experienced multiple episodes of COVID-19 infection, only the first episode was in the analyses.

Table 1 illustrates the clinical characteristics of MS patients with and without COVID-19. MS patients with COVID-19 were slightly older compared to the non-COVID-19 group (43.612.0± vs. 40.211.9±, $p<0.001$). The number of patients who were administered anti-CD20 was higher in the COVID-19 group (23.8% vs. 17.3%). The EDSS scores were comparable between the COVID-19 and non-COVID-19 groups [median (interquartile range): 2.0 (1.0-4.0) vs. 1.5 (1.0-3.5), $p=0.262$].

The results of the multivariate analysis, which estimated the link between demographics or clinical variables and COVID-19 severity, are presented in Table 2.

Significant risk factors for severe COVID-19 infection were identified by multivariate analyses, including older age, higher EDSS, and treatment with anti-CD20 therapy. The age of onset,

sex, and smoking status were not associated with severe COVID-19 outcomes in this cohort (Table 2). A higher risk of severe COVID-19 was associated with anti-CD20 therapies [odds ratio: 7.45, 95% CI: (2.66-26.6)] versus other DMTs.

Figure 2 illustrates the number of cases and severity of COVID-19 in relation to the treatment categories. Patients who received anti-CD20 were more likely to experience severe COVID-19 cases than those who did not receive anti-CD20.

Clinical features deceased patients are shown in Table 3. Variables such as older age, higher EDSS, longer MS duration, and usage of anti-CD20 drugs were associated with mortality. Nine patients had received ocrelizumab infusions, two received a natalizumab infusion, and two had received injection therapy in the six months prior to their death. The EDSS scores of the deceased patients ranged between 5.0 and 7.5 (mean, 6.11.5±).

In a total of 433 COVID-19 patients, 395 (239 fully vaccinated, 103 partially vaccinated, and 53 unvaccinated) had available vaccination status.

Figure 3 displays the number of deceased and recovered patients according to their respective treatment groups.

## Discussion

Many aspects of human life have been significantly affected by the COVID-19 pandemic, particularly for those who are afflicted with chronic diseases such as MS. The primary cause of these concerns was the disability resulting from the disease's natural course, as well as the immunosuppressive agents used in treatment. Numerous national and international studies have been conducted in the few years following the advent of the COVID-19 pandemic to investigate the course of COVID-19 disease in MS patients. Similarly, this study sought to evaluate the course of COVID-19 in MS patients who were monitored between March 2020 and February 2022.

In our cohort, most MS patients experienced modest to moderate progression of COVID-19, which is consistent with numerous prior studies (8,9,17-22). Although the mortality rate

**Table 1. Clinical features in MS patients with and without COVID-19**

| Characteristics | | Non-COVID (n=773) | COVID-19 (n=433) | p-value |
|---|---|---|---|---|
| Sex | Female | 532 (69.0) | 296 (68.4) | 0.869 |
| Age (years) | Mean (SD) | 43.6 (12.0) | 40.2 (11.9) | <0.001 |
| Age category (years) | <40 | 300 (38.9) | 235 (54.3) | <0.001 |
| | 40-65 | 436 (56.5) | 190 (43.9) | |
| | >65 | 35 (4.5) | 8 (1.8) | |
| Age onset (years) | Mean (SD) | 31.9 (10.6) | 28.9 (9.9) | <0.001 |
| MS duration (years) | Mean (SD) | 11.7 (9.6) | 11.8 (10.1) | 0.807 |
| EDSS (median) | Median (IQR) | 2.0 (1.0 to 4.0) | 1.5 (1.0 to 3.5) | 0.262 |
| Smoking status | Non-smoker | 418 (54.2) | 272 (62.8) | <0.001 |
| | Smoker | 229 (29.7) | 148 (34.2) | |
| Co-morbidity | False | 302 (71.9) | 233 (70.6) | 0.757 |
| | True | 118 (28.1) | 97 (29.4) | |
| Vaccination status | Unvaccinated | 53 (6.9) | 84 (19.4) | 0.003 |
| | Partially vaccinated | 103 (13.4) | 137 (31.6) | |
| | Fully vaccinated | 239 (31.0) | 212 (49.0) | |
| Ongoing MS treatment | None | 143 (18.5) | 28 (6.5) | <0.001 |
| | IFNB1&GA | 174 (22.6) | 85 (19.6) | |
| | Teriflunomide | 61 (7.9) | 39 (9.0) | |
| | Dimethyl fumarate | 74 (9.6) | 48 (11.1) | |
| | Fingolimod | 126 (16.3) | 95 (21.9) | |
| | Cladribin | 22 (2.9) | 14 (3.2) | |
| | Natalizumab | 32 (4.2) | 19 (4.4) | |
| | Anti-CD20 | 133 (17.3) | 103 (23.8) | |
| | Other | 6 (0.8) | 2 (0.5) | |

MS: Multiple sclerosis, COVID-19: Coronavirus disease-2019, SD: Standard deviation, EDSS: Expanded Disability Status Scale, IQR: Interquartile range

was 3% in our study, the literature reports results ranging from 0.9% to 7.9% (8-10,17-19,23-25).

A study conducted in a different center in Turkey revealed that the mortality rate due to COVID-19 in MS patients was 0.9%. The average age was lower than other studies, and it was emphasized that advanced age is a determinant of COVID-19 severity (17). Multivariate analyses of our data identified older age, higher EDSS score, and anti-CD20 therapy as significant risk factors for severe COVID-19 infection in MS patients. Mortality was also associated with older age, higher EDSS, longer MS duration, and the use of anti-CD20 drugs in this cohort. Higher EDSS score and older age were the most prevalent risk factors in nearly all MS registries (3,11,14,15,26-29).

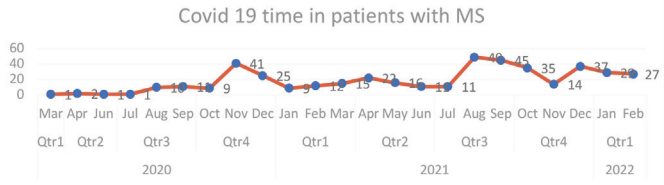


**Figure 1.** Duration of COVID-19 in MS patients

COVID-19: Coronavirus disease-2019, MS: Multiple sclerosis

Our findings are consistent with several previous studies of an association between anti-CD20 therapies and an elevated risk of severe COVID-19. However, it remains uncertain whether this association is independent or depends on the clinical course of MS (8,9,18,20,22,24,30). Januel et al. (31) discovered that in relapsing-remitting MS patients, anti-CD20 therapies were linked to an increased risk of severe COVID-19, while there was no association between anti-CD20 therapy and the risk of severe COVID-19 in PMS patients. Additionally, in a limited number of studies, no relationship was found between anti-CD20 treatment and severity of COVID-19 (26,27).

In conclusion, comparable to the general population, most MS patients recovered successfully from COVID-19. Nevertheless, severe COVID-19 and mortality were linked to age, high EDSS scores, and treatment with anti-CD20 medications.

**Table 2. Risk factors for severe COVID-19. Multivariate analysis model based on COVID-19 severity**

| Characteristic | OR | 95% CI | p-value |
|---|---|---|---|
| **Sex** | | | |
| Female | - | - | 0.4 |
| Male | 1.39 | 0.68, 2.80 | |
| Age (years) | 1.08 | 1.05, 1.11 | <0.001 |
| Age onset (years) | 1.01 | 0.97, 1.05 | 0.7 |
| EDSS (median) | 1.33 | 1.11, 1.59 | 0.002 |
| Relapses 1 year-pre | 0.73 | 0.38, 1.33 | 0.3 |
| **Smoking status** | | | |
| Non-smoker | - | - | |
| Smoker | 1.58 | 0.89, 2.84 | 0.12 |
| **Vaccination status** | | | |
| Fully vaccinated | - | - | |
| Partially vaccinated | 3.81 | 2.11, 7.01 | <0.001 |
| Unvaccinated | 1.46 | 0.73, 2.89 | 0.3 |
| Co-morbidity | 1.92 | 1.08, 3.39 | 0.025 |
| **Ongoing MS treatment** | | | |
| None | - | - | |
| IFNB1&GA | 1.77 | 0.60, 6.56 | 0.3 |
| Teriflunomide | 1.14 | 0.29, 4.85 | 0.9 |
| Dimethyl fumarate | 1.86 | 0.56, 7.30 | 0.3 |
| Fingolimod | 2.45 | 0.85, 8.88 | 0.13 |
| Cladribin | 3.47 | 0.76, 17.0 | 0.11 |
| Natalizumab | 4.55 | 1.18, 20.2 | 0.033 |
| Anti-CD20 | 7.45 | 2.66, 26.6 | <0.001 |
| Other | 6.25 | 0.22, 182 | 0.2 |

OR: Odds ratio, CI: Confidence interval, EDSS: Expanded Disability Status Scale, MS: Multiple sclerosis, COVID-19: Coronavirus disease-2019

### Study Limitations

The absence of sufficient data regarding the impact of obesity and other comorbidities, which have since been demonstrated to be factors associated with increased mortality, on the course of COVID-19 is one of the limitations of our study. Another limitation was the lack of comprehensive vaccination data, which prevented us from evaluating the effect of vaccination on the disease course.

## Conclusion

Most MS patients in our sample experienced successful recovery after developing COVID-19. Severe COVID-19 and mortality were found to be more prevalent in older patients with a high EDSS score and who were receiving treatment with anti-CD20. Despite the positive correlation between anti-CD20 treatment and poor prognosis and death, the conflicting results reported in the literature and the limited number of patients receiving anti-CD20 treatment suggest that additional studies should be

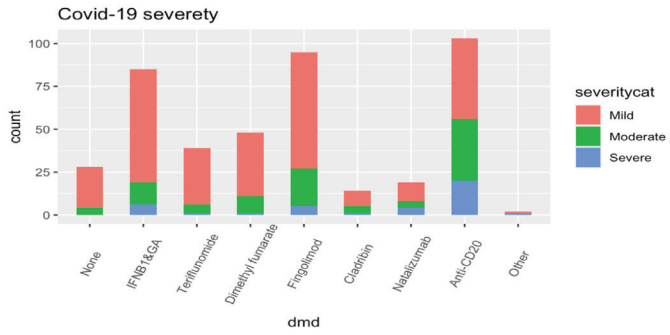


**Figure 2.** Number of COVID-19 cases and its severity in the various treatment groups

COVID-19: Coronavirus disease-2019

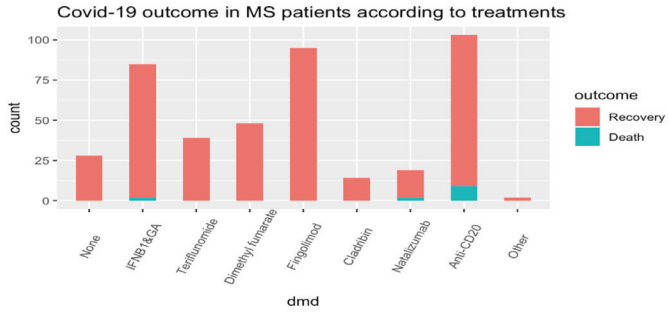


**Figure 3.** Clinical characteristics of the deceased and recovered patients in the treatment groups

COVID-19: Coronavirus disease-2019, MS: Multiple sclerosis

**Table 3. Clinical features of deceased and recovered patients**

| Characteristics Total n (%) | | Recovered COVID-19 patients (n=420, 97%) | Deceased COVID-19 patients (n=13, 3%) | p-value |
|---|---|---|---|---|
| Sex | Female | 292 (69.0) | 7 (53.8) | 0.391 |
| | Male | 131 (31.0) | 6 (46.2) | |
| Age (years) | Mean (SD) | 39.7 (11.5) | 56.2 (12.5) | <0.001 |
| Age onset (years) | Mean (SD) | 28.6 (9.8) | 36.8 (11.4) | 0.003 |
| MS duration (years) | Mean (SD) | 11.6 (10.0) | 21.9 (10.3) | <0.001 |
| EDSS | Mean (SD) | 2.4 (2.0) | 6.1 (1.5) | <0.001 |
| Smoking status | Non-smoker | 264 (62.4) | 10 (76.9) | 0.521 |
| | Smoker | 146 (34.5) | 3 (23.1) | |
| Co-morbidity | | 95 (29.0) | 3 (60.0) | 0.309 |
| Vaccination status | Fully vaccinated | 211 (49.9) | 1 (7.7) | 0.011 |
| | Partially vaccinated | 130 (31.0) | 7 (53.8) | |
| | Unvaccinated | 79 (19.1) | 5 (38.5) | |
| Ongoing MS treatment | None | 29 (6.9) | 0 (0.0) | 0.004 |
| | IFNB1&GA | 84 (19.9) | 2 (15.4) | |
| | Teriflunomide | 39 (9.2) | 0 (0.0) | |
| | Dimethyl fumarate | 48 (11.3) | 0 (0.0) | |
| | Fingolimod | 96 (22.7) | 0 (0.0) | |
| | Cladribin | 14 (3.3) | 0 (0.0) | |
| | Natalizumab | 17 (4.0) | 2 (15.4) | |
| | Anti-CD20 | 94 (22.2) | 9 (69.2) | |
| | Other | 2 (0.5) | 0 (0.0) | |

COVID-19: Coronavirus disease-2019, SD: Standard deviation, EDSS: Expanded Disability Status Scale, MS: Multiple sclerosis. Data are presented as n (%) or median (Q1-Q3)

employed to investigate the relationship between anti-CD20 treatment and disease.

### Ethics

**Ethics Committee Approval:** This study was approved by the Ethics Committees of the Karadeniz Technical University (protocol no: 2021/271, date: 07.10.2021).

**Informed Consent:** Each participant provided written informed consent.

### Authorship Contributions

Design: C.B., Data Collection or Processing: S.Z.K., C.B., Analysis or Interpretation: C.B., Literature Search: S.Z.K., C.B., Writing: S.Z.K., C.B.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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