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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).

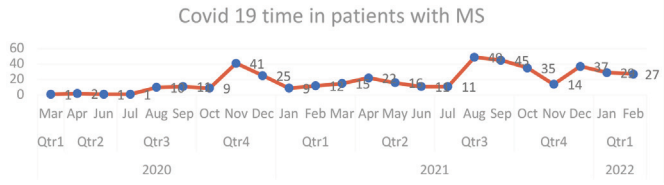

Figure 1. Duration of COVID-19 in MS patients

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

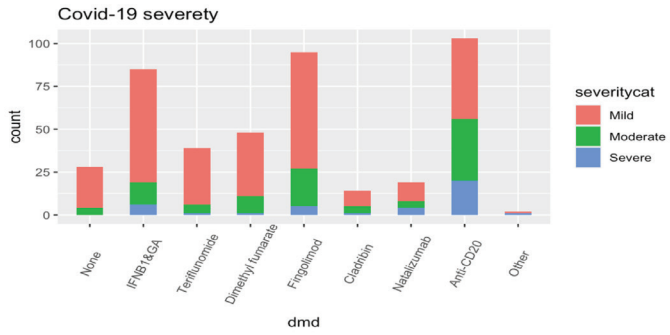

Figure 2. Number of COVID-19 cases and its severity in the various treatment groups

COVID-19: Coronavirus disease-2019

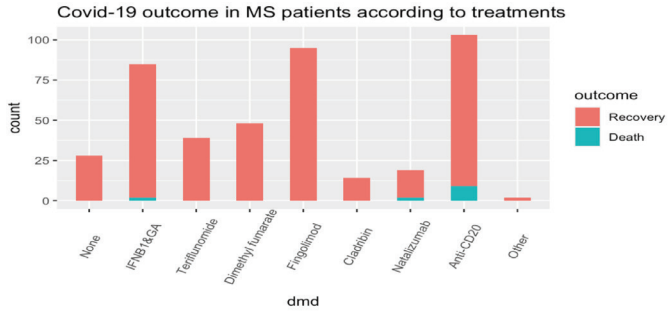

Figure 3. Clinical characteristics of the deceased and recovered patients in the treatment groups

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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