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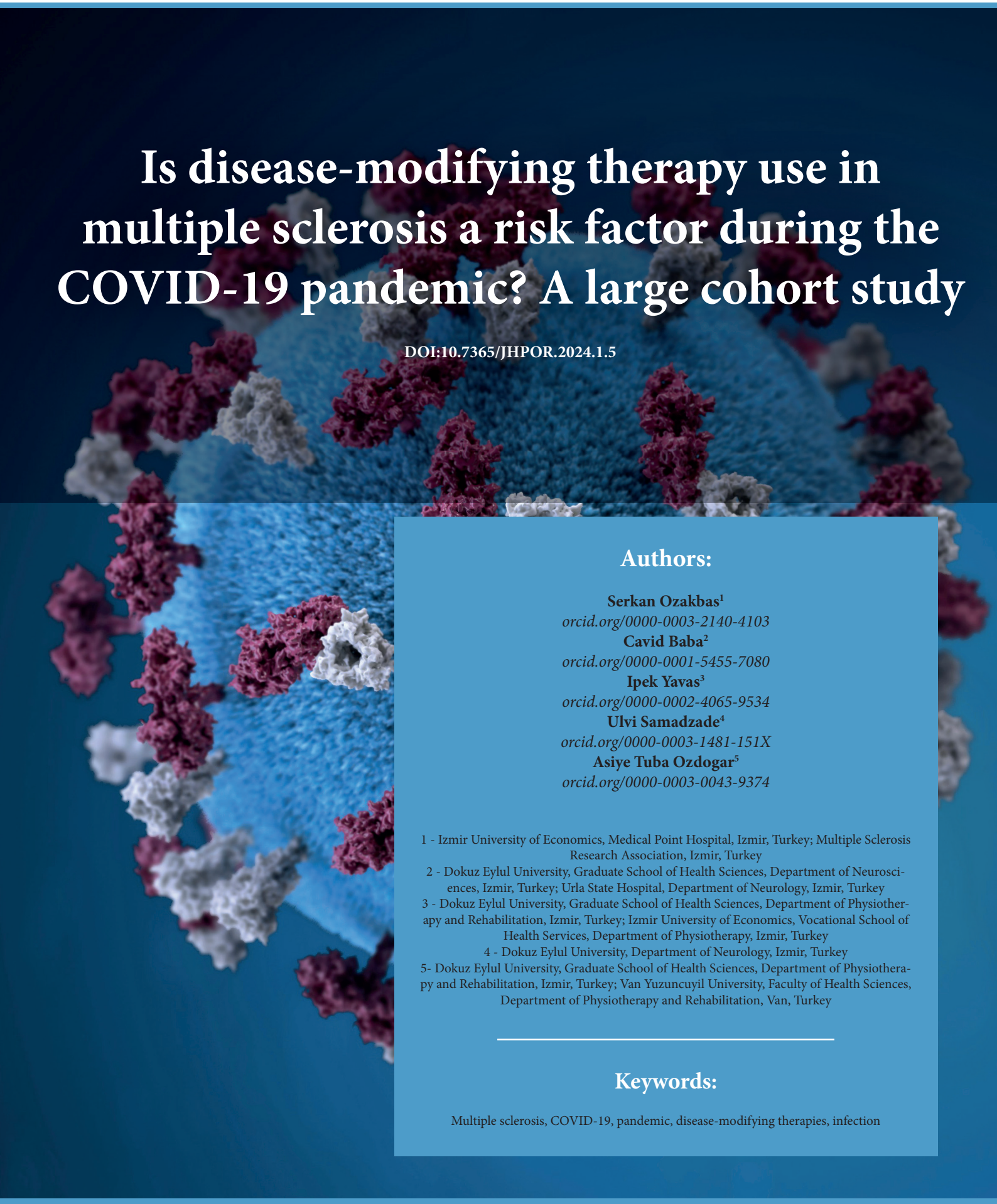

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Abstract

Objective: This study aims to investigate the relationship between disease-modifying therapies (DMTs) used in people with MS (pwMS) and the risk of COVID-19 infection.

Methods: This longitudinal cohort study included the MS cohort of 3402 people followed for COVID-19 infection. The whole MS cohort was interviewed at least once for information about COVID-19. A semi-structured interview was developed and performed by a team consisting of a medical doctor, nurse, and physiotherapist. Clinical information was obtained from the patient's medical records. This study was approved by the Noninvasive Research Ethics Board (Date: 08.09.2021, Decision No: 2021/25-06).

Results: Of the 487 pwMS infected with COVID-19, 35 reported reinfections. The major differences regarding DMT between pwMS with and without COVID-19 infection were observed for fingolimod, ocrelizumab, and azathioprine. Forty-three (8.9%) people experienced the COVID-19 infection severely or critically; 12 (37.5%) had MS treatment with ocrelizumab. Fifty percent of pwMS who were treated in intensive care (7/14 patients) and died (3/6 patients) were being treated with ocrelizumab. As a result of regression analysis, being younger and using dimethyl fumarate, fingolimod, ocrelizumab, and cladribine DMTs were the main factors associated with having COVID-19 infection group.

Conclusions: Current results show that disability due to MS and increased disease duration are not risk factors for COVID-19 infection, while age is negatively associated with contracting COVID-19 infection. These results show no relationship between the MS clinic and COVID-19 infection. We have found that using certain DMTs in pwMS increases the risk of contracting COVID-19 infection.

Highlights

- MS-related disability and increased disease duration are not risk factors for COVID-19.
- There is a negative relationship between age and contracting COVID-19.
- The use of dimethyl fumarate, cladribine, fingolimod, and ocrelizumab in pwMS increases the risk of exposurig COVID-19.

1. Introduction

The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a global health emergency on January 30, 2020, and a pandemic on March 11, 2020, by the World Health Organization. As of May 2022, the number of COVID-19 confirmed cases worldwide has been reported as 510 million, and the number of confirmed cases in Turkey has been reported as 14 million.[1, 2]

Immunocompromised patients infected with COVID-19, especially those with comorbidities, may have a higher risk for severe outcomes than the general population [3]. This increased risk for acquired and opportunistic infections in people with autoimmune diseases is associated with disease-specific immune dysregulation and/or immunosuppression from immune therapies. Immune modification is especially relevant in COVID-19 infection in persons with autoimmune diseases.[4]

Multiple sclerosis (MS) is a chronic central nervous system inflammatory disease of autoimmune etiology, mediated by activated T cells with evolving evidence of a significant contribution from B cells and cells of the innate immune system.[5] Preliminary data from registries of people with MS (pwMS) indicate that the risk of COVID-19 and associated morbidity (including attitudes towards the pandemic) in the MS population is similar to that of the general population.[6–8] Approved disease-modifying therapies (DMTs) for MS act by different mechanisms, such as inhibition of immune cell migration, alteration of immune cell function, and inhibition of cell replication.[9]

In addition to the effects of drugs used in the treatment of MS, changes in the immune system and brain pathophysiology in MS also affect the susceptibility to COVID-19 infection and the clinical course. Although the differences between the mechanisms of action of DMTs affect the risk of infection to different extents, in general, MS guidelines recommend the continuation of DMTs to prevent the activity of the disease.[10–12]

In this study, we aimed to assess the relationship between DMTs used in pwMS and the risk of COVID-19 transmission. The data obtained aims to contribute to the treatment management of pwMS in cases of new COVID-19 variants or similar epidemic situations that may develop in the future.

2. Methods

2.1. Design

This study has a retrospective cohort. The necessary permissions for this study were obtained from the Ministry of Health of the Republic of Turkey and Dokuz Eylul University Noninvasive Clinical Research Ethics Committee (Date: 08.09.2021, Decision No: 2021/25-06). Participants were informed at the beginning of the telephone interview, and their verbal consent was obtained. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement. [13]

2.2. Participants

The interview process (data collection) with pwMS, which started with the pandemic (March 2020), ended in April 2022. PwMS, which was followed up at the Dokuz Eylul University and met the inclusion criteria, were included in the study. Inclusion criteria were: (1) being over the age of 18 and (2) being definitively diagnosed with MS or clinically isolated syndrome, according to the McDonald diagnostic criteria.[14] In addition, the eligibility criteria for the group with COVID-19 infection were defined as having suspected or confirmed COVID-19 infection between March 11, 2020, and February 28, 2022. Confirmed COVID-19 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is defined as a positive real-time polymerase chain reaction (RT-PCR) test, while suspected COVID-19 is confirmed as having close contact with confirmed COVID-19 and/or having radiological evidence, signs or symptoms consistent with COVID-19. There were no exclusion criteria.

2.3. Procedure

Since the first case was seen in Turkey, the cases of COVID-19 infection of the patients in our unit were closely followed. The entire MS Cohort was interviewed at least once face-to-face, via text message, or by phone for information about COVID-19. In addition, patients were asked to inform the unit if they had a COVID-19 infection. A healthcare professional conducted a semi-structured telephone interview with all patients with COVID-19 infection, and detailed information about the COVID-19 infection processes was obtained. Demographic data of pwMS experiencing COVID-19 infection was obtained from patient-provided information; clinical information was obtained from patient-provided information and medical records. In addition, demographic and clinical information of pwMS who did not experience COVID-19 infection were obtained from medical records. The course of COVID-19 was classified as asymptomatic, mild, severe, and critical. Mild was used to identify outpatients with few symptoms, severe was used to identify hospitalized, and critical was used to identify patients in intensive care.

2.4. Outcomes

Demographic and clinical measurement. Age, gender, MS type, disease duration, Expanded Disability Status Scale (EDSS)[15], and MS treatment were obtained from the patient and related medical records.

Semi-structured interview. The semi-structured interview content was planned in three sessions by a healthcare team of medical doctors, nurses, psychologists, and physiotherapists. In the first session, experts discussed the interview content based on their preliminary studies and created 50 questions. Voting took place to determine the most relevant questions in the next session. In the last session, the questions were discussed for the last time, and the team approved the 34 most relevant questions. The questions included details of the COVID-19 process, such as COVID-19 course, pneumonia, hospitalization or intensive care, outpatient use of drugs, and symptoms observed during COVID-19. The interviews were conducted by a healthcare professional working in the MS clinic.

2.5. Sample size and Statistical analysis

We aimed to reach the entire universe, which is why, due to the study design (retrospective cohort), pwMS were followed up routinely in the Multiple Sclerosis Unit of Dokuz Eylul University Hospital Neurology Department. The pwMS met all inclusion criteria.

Data were analyzed using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY; 2019). Descriptive analyses were presented as percentages and mean (SD) for continuous and categorical variables. Kruskal-Wallis Test was used to compare the clinical and demographic characteristics of the pwMS with and without COVID-19 infection. Univariate and multivariate logistic regression were used to explain the relationship between having COVID-19 infection and age, disability level (assessed with EDSS), disease duration, type of MS, and using DMTs.

3. Results

Of 3402 pwMS registered in our MS center, 487 got COVID-19 infection. The pwMS with COVID-19 infection have lower EDSS scores, disease duration, and age than those without COVID-19. Also, the COVID-19 MS cohort group has a higher rate of CIS and relapsing type of MS, while the MS cohort has a higher rate of a progressive form of MS (Table 1).

Table 1. Demographic and clinical characteristics of the participants				
		COVID-19 MS Cohort (n=487)	MS Cohort (n=3402)	P Value
Age, years	Mean (SD)	40.3 (11.4)	44.8 (12.6)	<0.001
	Range	18-81	18-90	
Sex, n (%)	Female	342 (70.2%)	(68.8%)	0.439
	Male	145 (29.8%)	(31.2%)	
Clinical phenotype, n (%)	Clinical Isolated Syndrome	11 (2.3%)	(7.2)	<0.001
	Relapsing remitting MS	425 (87.3%)	(77.3%)	
	Secondary progressive MS	39 (8.0%)	(11.9%)	
	Primary progressive MS	12 (2.5%)	(3.6%)	
MS disease duration, years	Mean (SD)	10.7 (8.2)	14.0 (9.0)	<0.001
	Range	0-46	0-55	
EDSS of last visit	Mean (SD)	1.7 (2.0)	2.27 (2.33)	<0.001
	Range	0-8.5	0-9.5	
Significant p values are presented in bold. EDSS: Expanded Disability Status Scale; SD: standard deviation.				

Table 2. Distribution of DMTs' in pwMS with and without COVID-19 Infection		
	MS Cohort (%)	COVID-19 MS Cohort (%)
None	9.9	4.3
Interferon and Glatiramer acetate	35.5	21.8
Fingolimod	25.7	34.1
Natalizumab	3.8	4.9
Ocrelizumab	10.5	16.4
Teriflunomide	6.2	7.2
Dimethyl fumarate	4.5	7.4
Cladribine	1.0	2.3
Rituximab	0.8	0.4
Azathioprine	1.9	1
Phase 3 drug study	0.2	0.2

Table 3. COVID-19 Course by MS Treatment						
	COVID-19 Infection (n= 487)	MS Treatment		COVID-19 Reinfection (n= 35)	MS Treatment	
Death, n (%)	6 (1.2%)	Ocrelizumab	3 (50.0%)	0	0	
		Teriflunomide	1 (16.7%)			
		Glatiramer acetate	1 (16.7%)			
		None	1 (16.7%)			
Severe/Critically ill, n (%)	43 (8.9%)	Ocrelizumab	12 (37.5%)	3 (8.4%)	Ocrelizumab	3 (100%)
		Fingolimod	7 (21.9%)			
		None	3 (9.4%)			
		Interferon	3 (9.4%)			
		Teriflunomide	3 (9.4%)			
		Glatiramer acetate	2 (6.3%)			
		Dimethyl fumarate	1 (3.1%)			
		Natalizumab	1 (3.1%)			
Pneumonia, n (%)	18 (3.7%)	Glatiramer acetate	4 (22.2%)	2 (5.6%)	Fingolimod	1 (50%)
		Teriflunomide	3 (16.7%)			
		Ocrelizumab	3 (16.7%)			
		None	3 (16.7%)		Ocrelizumab	1 (50%)
		Interferon	2 (11.1%)			
		Dimethyl fumarate	1 (5.6%)			
		Fingolimod	1 (5.6%)			
		Natalizumab	1 (5.6%)			
Hospitalization, n (%)	32 (6.6%)	Ocrelizumab	12 (37.5%)	3 (8.3%)	Ocrelizumab	3 (100%)
		Fingolimod	7 (21.9%)			
		Teriflunomide	3 (9.4%)			
		None	3 (9.4%)			
		Interferon	3 (9.4%)			
		Glatiramer acetate	2 (6.3%)			
		Natalizumab	1 (3.1%)			
		Dimethyl fumarate	1 (3.1%)			
Intensive Care, n (%)	14 (2.9%)	Ocrelizumab	7 (50%)	2 (5.6%)	Ocrelizumab	2 (100%)
		None	2 (14.3%)			
		Fingolimod	2 (14.3%)			
		Glatiramer acetate	1 (7.1%)			
		Teriflunomide	1 (7.1%)			
		Dimethyl fumarate	1 (7.1%)			
Oxygen Support, n (%)	24 (4.9%)	Ocrelizumab	9 (37.5)	3 (8.6%)	Ocrelizumab	1 (50%)
		Fingolimod	5 (20.8%)			
		None	2 (8.3%)			
		Interferon	2 (8.3%)			
		Glatiramer acetate	2 (8.3%)			
		Teriflunomide	2 (8.3%)			
		Dimethyl fumarate	1 (4.2%)			
		Natalizumab	1 (4.2%)			
Mechanical Ventilation, n (%)	9 (1.8%)	Ocrelizumab	5 (55.6%)	1 (2.9%)	Ocrelizumab	1 (50%)
		None	2 (22.2%)			
		Glatiramer acetate	1 (11.1%)			
		Teriflunomide	1 (11.1%)			
*Participants could be placed in more than one classification						

Table 4. Comparison of EDSS score between groups according to DMTs			
	EDSS score – MS Cohort	EDSS score – COVID-19 MS Cohort	p
None	2.60 (2.82)	1.73 (2.48)	0.451
Injection	1.76 (2.01)	0.79 (1.12)	<0.001
Teriflunomide	1.90 (2.06)	1.11 (1.25)	0.088
Dimethyl fumarate	1.64 (1.65)	0.97 (1.27)	0.017
Fingolimod	1.83 (1.86)	1.34 (1.43)	0.008
Natalizumab	1.91 (1.69)	1.37 (0.94)	0.281
Ocrevus	5.03 (2.03)	4.70 (2.09)	0.335
Cladribine	0.76 (1.01)	0.77 (0.90)	0.867
Azathioprine	5.94 (1.97)	-	-

Table 5. Logistic regression analysis of factors associated with having COVID-19 infection						
	having COVID-19 infection					
	Univariate			Multivariate		
Risk Factors	OR	95.0% CI	P value	OR	95.0% CI	P value
Age	1.029	1.021 1.038	<0.001	-1.021	1.010-1.032	<0.001
EDSS	1.120	1.067-1.174	<0.001	-1.039	0.983-1.097	0.176
Disease duration	1.036	1.023-1.049	<0.001	-1.014	0.998-1.030	0.094
Type of MS (references: CIS)						
RRMS	5.634	2.628-12.082	<0.001	2.962	0.810-10.826	0.101
SPMS	3.397	1.487-7.761	0.004	3.504	0.915-13.421	0.067
PPMS	3.409	1.297-8.963	0.013	3.010	0.733-12.361	0.126
MS treatment (references: none)						
Injection (Interferon+Glatiramer acetate)	2.737	1.450-5.165	0.002	1.124	0.388-3.261	0.829
Teriflunomide	5.755	2.845-11.641	<0.001	2.634	0.871-7.966	0.086
Dimethyl fumarate	9.629	4.728-19.609	<0.001	3.404	1.113-10.411	0.032
Fingolimod	6.765	3.613-12.666	<0.001	2.927	1.016-8.436	0.047
Natalizumab	7.566	3.601-15.898	<0.001	3.012	0.969-9.358	0.057
Ocrevus	8.499	4.417-16.352	<0.001	7.040	2.464-20.115	<0.001
Cladribine	13.789	5.297-35.896	<0.001	4.636	1.273-16.879	0.020
Azathioprine	0.000	0.000-	0.997	0.000	0.000-	0.997

Significant p values are presented in bold.
RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; PPMS: primary progressive multiple sclerosis; EDSS: Expanded Disability Status Scale

The majority of our MS cohort used interferon, glatiramer acetate, and fingolimod. Compared to the clinical MS population, a higher rate of pwMS infected with COVID-19 used interferon, glatiramer acetate, and ocrelizumab. The distribution of DMTs is presented in Table 2.

Out of 487 pwMS with COVID-19 infection, six died. Half of the dead pwMS were using ocrelizumab treatment during infection. Moreover, the pwMS who use ocrelizumab treatment had higher rates of severe/critical illness, hospitalization, intensive care, oxygen support, and mechanical ventilation. These rates were also higher in the COVID-19 reinfection group. In the first infection, 205 (42.1%) people used COVID-19-specific medication (favipiravir); also, in the second infection, four people used it. The detailed information is shown in Table 3. A comparison of EDSS scores between pwMS with and without COVID-19 infection according to DMTs is shown in Table 4.

Based on the multivariate logistic regression analysis, being younger and using dimethyl fumarate, fingolimod, ocrelizumab, and cladribine DMTs were the main factors associated with having COVID-19 infection group. Table 5 presents the logistic regression analysis evaluating factors associated with having COVID-19 infection.

4. Discussion

In this study, we found that the younger age and DMT (dimethyl fumarate, cladribine, fingolimod, and ocrelizumab) are associated with increased odds of contracting COVID-19 infection, while MS type, disease duration and EDSS score are not. We speculated that younger people are inclined to socialize and be active in work life, making them susceptible to exposure to COVID-19. Although we cannot compare young and old pwMS for COVID-19, as our participants mostly reported a mild course of COVID-19, our data support such a trend.

As a result of regression analysis, patients treated with dimethyl fumarate, cladribine, fingolimod, and ocrelizumab have a higher risk of exposure to COVID-19 infection compared to those without treatment. Considering the EDSS distributions according to drugs, we found that the EDSS scores of people who used dimethyl fumarate and fingolimod who had COVID-19 were statistically significantly lower than those who did not. Louapre et al. investigated which factors are associated with COVID-19 severity.[16]. They included 347 pwMS with COVID-19 and showed that any DMT is not a risk factor for developing a severe form of COVID-19. However, the authors highlighted that studies with a larger cohort are needed to determine whether any DMT subgroup is a risk factor for COVID-19. Our cohort has a large sample for all DMTs except cladribine (n=30). The reason why there is no difference in people using cladribine is due to the small number of people who use it.

We are aware that we have a major limitation in being unable to present work/socialization situations for our entire cohort. However, the difference between EDSS levels will help to predict this information. We theorize that people using dimethyl fumarate, cladribine, and fingolimod are more socialized with lower EDSS scores, so it may seem like they are at risk for more COVID-19 infections. On the other hand, there are two reasons for the higher incidence of COVID-19 in the ocrelizumab patient group, which has more progressive forms and, therefore, higher EDSS scores. First, these people had to come to our center under all circumstances, that is, leave the house, in order to receive ocrelizumab treatment. Second, ocrelizumab treatment modulates the immune response to cause a more severe – and possibly easier – COVID-19 transmission.

Lymphopenia may develop due to dimethyl fumarate and cladribine, which may increase the risk of infection.[17, 18] As a result of our study, we found that these two DMTs increase the risk of being infected with COVID-19. Reder et al. did not report an additional risk for Dimethyl fumarate in their study.[19] Although there is no information about the risk of infection with COVID-19 for fingolimod, it has been reported that they undergo a process similar to the general population.[20, 21]

Ocrelizumab is associated with B cell depletion and an increased risk of severe infections in MS.[22, 23] Although previous evidence does not present the incidence of contracting COVID-19 for people taking ocrelizumab, it does include information about the course of COVID-19. There are a few studies reported that mortality rates in people treated with this medicine were similar to pwMS who were using one of the other treatments or not taking medication. Our findings are not similar to those[24, 25] Our results show that people treated with ocrelizumab report COVID-19 infection seven times more frequently, and the disease course is more severe than other patients. Sormani et al., like us, confirmed that patients treated with anti-CD20 had a higher risk of severe COVID-19.[26]

Dyczkowska ve Kalinowska-Łyszczarz emphasizes that, due to inconsistent evidence of relapses and worsening disability, the effects of COVID-19 in pwMS are still unknown, and for clinicians caring for people with MS, an individualized approach to risks and benefits is needed in decision-making during the COVID-19 pandemic.[27] It is a fact that DMTs are indispensable in MS. The potential risk posed by COVID-19 appears less threatening than the possible irreversible disability of MS. We think that this risk can be taken and that it would be appropriate to continue using DMTs unless a negative situation is observed. Our study has some strengths and limitations. First, this

is a large cohort study; contacting our whole cohort is our strength. In addition, although it is a single-center study, the standardization of treatment approaches and, thus, the reliability of our data increases the power of the study. One of the most important limitations of our study is that the working/socialization status of the pwMS during the pandemic was not recorded and, therefore, could not be reported in detail. Another important limitation is the absence of a healthy control group and the lack of immunological responses.

5. Conclusion

Current results show that disability due to MS and increased disease duration are not risk factors for COVID-19 infection, while age is negatively associated with contracting COVID-19 infection. In addition, no significant relationship was found between the types of MS clinics. These results show no relationship between the MS clinic and COVID-19 infection. We have found that using certain DMTs in pwMS increases the risk of contracting COVID-19 infection. However, given that DMTs are indispensable in MS and the potential risk posed by COVID-19 is far less significant than the possible irreversible disability of MS, this risk is negligible. Considering this information, we consider it appropriate to continue with DMTs. This experience gained during the pandemic sheds light on how to act in possible epidemics or pandemics where the continuation of treatments is controversial.

Abbreviations

COVID-19: coronavirus disease 2019, EDSS: Expanded Disability Status Scale, MS: multiple sclerosis, pwMS: people with multiple sclerosis.

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Authors' contributions

SO was responsible conceptualization, methodology, ınvestigation, resources, data curation, writing-review & editing, visualization, and project administration.
IY and ATO was responsible conceptualization, methodology, formal analysis, ınvestigation, resources, data curation, writing-original draft, and visualization.
CB and US and was responsible conceptualization, methodology, ınvestigation, data curation, writing-review&editing, and visualization.

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Availability of data and materials

The datasets generated and analysed in the current study are available from the corresponding author on reasonable request.

Conflicting of Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics approval and consent to participate

Ethical permissions for the study were obtained from the Republic of Dokuz Eylul Ministry of Health and Dokuz Eylul University Noninvasive Clinical Research Ethics Committee (Date: 08.09.2021, Decision No: 2021/25-06). All ethical rules and regulations were followed while conducting the study and the participants were included in the study based on informed consent. This study was conducted in accordance with the guidelines outlined in the declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors completed the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported no conflicts of interest concerning authorship, research, or publication of this article.

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