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The outcome of a national MS-Covid-19 study: What the Turkish MS cohort reveals?

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ABSTRACT

Background: The pandemic of the new type of corona virus infection 2019 [Covid-19] also affect people with Multiple Sclerosis (pwMS). Currently, the accumulating information on the effects of the infection regarding the

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Disease modifying treatment
Disease severity

demographic and clinical characteristics of the disease, as well as outcomes within different DMTs, enable us to have better practices on the management of the Covid-19 infection in pwMS.

Objective: To investigate the incidence of coronavirus disease 2019 (Covid-19) and to reveal the relationship between the demographic-clinical and therapeutic features and the outcome of Covid-19 infection in a multi-center national cohort of pwMS.

Methods: The Turkish Neurological Society-MS Study Group in association with the Italian MuSC-19 Study Group initiated this study. A web-based electronic Case Report Form (eCRF) of Study-MuSC-19 were used to collect the data. The demographic data and MS histories of the patients were obtained from the file tracking forms of the relevant clinics.

Results: 309 MS patients with confirmed Covid-19 infection were included in this study. Two hundred nineteen (219) were females (70.9%). The mean age was 36.9, ranging from 18 to 66, 194 of them (62.8%) were under 40. The clinical phenotype was relapsing-remitting in 277 (89.6%) and progressive in 32 (10.4%). Disease duration ranged from 0.2 years to 31.4 years. The median EDSS was 1.5, ranging from 0 to 8.5. The EDSS score was ≤ 1 in 134 (43%) of the patients. 91.6% of the patients were on a DMT, Fingolimod was the most frequently used drug (22.0%), followed by Interferon (20.1%). The comorbidity rate is 11.7%. We were not able to detect any significant association of DMTs with Covid-19 severity.

Conclusion: The Turkish MS-Covid-19 cohort had confirmed that pwMS are not at risk of having a more severe COVID-19 outcome irrespective of the DMT that they are treated. In addition, due to being a younger population with less comorbidities most had a mild disease further highlight that the only associated risk factors for having a moderate to severe COVID-19 course are similar with the general population such as having comorbid conditions and being older.

1. Introduction

The new type of corona virus infection (coronavirus disease 2019 [Covid-19]) attributable to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first seen in Wuhan, China, in December 2019. By September 30, 2020, as a rapidly spreading infection, the virus infected close to 35 million people and caused nearly one million deaths (WHO Coronavirus Disease, <https://covid19.who.int>). In Turkey the first official case was reported on March 11, and the first death on 17th March 2020. As of September 30th, when our data entry was stopped the total number of cases were 318663, and the total number of deaths were 8195 in Turkey (<https://covid19.saglik.gov.tr>, <https://covid19.saglik.gov.tr>, 2020).

People with Multiple Sclerosis (pwMS) have also been affected in this pandemic. MS is an immune-mediated, neuro-inflammatory and neuro-degenerative disease involving the central nervous system. A considerable number of pwMS are treated with disease modifying therapies (DMT) of which many have immunosuppressive properties. The estimated number of people with MS (pwMS) is 2.8 million worldwide (Browne et al., 2014). This number is around 70,000 in Turkey, of whom approximately 40,000 are treated with a DMT. The impact of Covid-19 infection on pwMS was not clear at the onset of the pandemic. Since then both the increasing clinical experience globally and a limited number of published observational studies enabled us to learn more on the effects of Covid-19 infection in pwMS and their various treatments. Currently, the accumulated information on the effects of the infection regarding the demographic and clinical characteristics of the disease, as well as on the different DMT that pwMS are on, had allowed us to have better estimates on the outcomes and management of the Covid-19 infection in pwMS. However, the unsettled issues are still considerable.

In this study, we have investigated the relationship between the demographic-clinical and therapeutic features of pwMS and the outcome of Covid-19 infection in the Turkish MS cohort. We also compared our outcomes with the largest MS-Covid-19 series published so far, to better understand the Covid-19 impact on MS.

2. Methods

2.1. Data collection

The Turkish Neurological Society-MS Study Group in association with the Italian MuSC-19 Study Group initiated this study. The Turkish Neurological Society MS Study Group is an organization covering all

active MS Centers in Turkey. This study was open to any center that volunteered to contribute their data of their MS patients who had Covid-19 infection. Thirty-four centers participated in the study.

We used the web-based electronic Case Report Form (eCRF) of Study-MuSC-19 to collect the data as described in detail previously (Sormani et al., 2021). The demographic data and MS histories of the patients were obtained from the file tracking forms of the relevant clinics. The approvals were obtained from the Republic of Turkey Ministry of Health and Kocaeli University Ethics Committee (E-29549770-903.02.01-4007).

2.2. Study population

The study included pwMS with suspected or confirmed Covid-19 between March 11, 2020 and September 30, 2020. Only patients with a complete follow up to death or recovery were included in this analysis.

The confirmed cases were pwMS, who had at least one positive RT-PCR test for Covid-19. The unconfirmed cases were either pwMS who were not tested or had a negative RT-PCR test but had the clinical symptoms and signs of the infection (cough, fever, shortness of breath, sudden onset of anosmia, ageusia, dysgeusia); positive radiological findings (ground-glass density on chest-CT) and close contact with the infected person and/or had positive serology.

All patients were either seen at the clinical setting or were interviewed by phone with follow-up calls and their data were recorded on the MuSC-19 website.

2.3. Assessed variables and end points

2.3.1. Statistical analysis

Sample size was not calculated since it was a retrospective collection of data and all the patients that met the selection criteria were included and analyzed. Missing baseline values were imputed by applying a multiple imputation method (MICE).

Baseline demographic and clinical characteristics were summarized as count and percentage, mean with range or median with interquartile range.

The association of baseline characteristics and MS therapies to a severe Covid-19 was assessed by univariate and multivariate ordinal logistic models. Severe outcome was defined as a 3-level factors: ICU or death, vs hospitalized, vs others. Age, sex, smoking, BMI, MS type, disease duration, MSSS, presence of comorbidities, previous use of methylprednisolone, and DMT classes were included in the multivariate models as independent variables, using a stepwise selection procedure.

The strength of the associations was expressed with adjusted Odds ratio (OR) and corresponding 95% confidence intervals (CI). All statistical tests were 2-sided and significance level was set at 0.05.

3. Results

3.1. Study population (patients characteristics)

309 patients were included in the study. 291 patients (94.2%) were confirmed Covid-19 on RT-PCR tests. The 18 patients (5.8%) who were negative on nasopharyngeal and nasal swabs, had a clinical, radiological or serologically defined diagnosis of Covid-19, as described above. Data were collected from every region of the country, with the majority being from large cities.

3.2. Demographics and clinical characteristics

The demographic data of the 309 patients included in this study are presented in Table 1. Two hundred nineteen (219) were females (70.9%). The mean age was 36.9, ranging from 18 to 66, 194 of them (62.8%) were under 40.

The number of healthcare workers (healthcare assistant, nurse and physician) was 31 (10.0%). As about habits, 66.7% out of patients had never smoked, 16.2% were active smokers. Thirty-six (11.7%) had a comorbid disease, hypertension was the most common (17 cases), followed by depression condition (8 cases). of these.

The demographic and clinical features of MS in the study cohort are shown in Table 2. The clinical phenotype was relapsing-remitting in 277 (89.6%) and progressive in 32 (10.4%). Disease duration ranged from 0.2 years to 31.4 years, with a mean of 6.6 (± 5.87) years. The median EDSS was 1.5, ranging from 0 to 8.5. The EDSS score was ≤ 1 in 134 (43%) of the patients. 91.6% of the patients were on a DMT, Fingolimod was the most frequently used drug (22.0%), followed by Interferon (20.1%). Thirty patients interrupted treatment due to Covid-19 infection.

The distribution of DMT use in the Covid-19 MS cohort is compared to the November 2020 MS Turkish Pharma Industry records in Fig. 1,

Table 1
Baseline demographic and clinical characteristics (N = 309).

Age categories	≤ 40 yrs	194 (62.8)
	41–59 yrs	110 (35.6)
	>60 yrs	4 (1.3)
	Missing data	1 (0.3)
Age, years		36.9 (18.0 – 66.0)
Sex	Female	219 (70.9)
Body Mass Index		24.4 (16.7 – 38.7)
Employment	Any/Not employed	139 (45.0)
	Office clerk & workman	86 (27.8)
	Other	66 (21.4)
	Student	18 (5.8)
Healthcare workers	No	278 (90.0)
	Yes	31 (10.0)
Smoking	Never smoked	206 (66.7)
	Current smoker	50 (16.2)
	Former smoker	46 (14.9)
	NA	7 (2.3)
Presence of at least one comorbidity		36 (11.7)
Comorbidities	Hypertension	17 (5.5)
	Major depressive disorder	8 (2.6)
	Hematological disease	3 (1.0)
	Coronary Heart Disease	3 (1.0)
	Diabetes	3 (1.0)
	HBV infection	2 (0.6)
	Cancer	2 (0.6)

Data are reported as mean (range) and n(%)

Table 2
MS history (N = 309).

Clinical phenotype	Relapsing remitting MS (RRMS)	277 (89.6)
	Secondary progressive MS (SPMS)	26 (8.4)
	Primary progressive MS (PPMS)	6 (1.9)
MS disease duration, years		5.0 (2.0 – 10.0)
Last available EDSS		1.5 (1.0 – 3.0)
Multiple Sclerosis Severity Scores (MSSS)	< 7	267 (86.4)
	≥ 7	42 (13.6)
In treatment		283 (91.6)
Treatment duration, months		19.0 (9.0 – 41.0)
Line of treatment	1st line	163 (52.8)
	2nd line	120 (38.8)
MS treatment	Fingolimod	68 (22.0)
	Interferon	62 (20.1)
	Ocrelizumab	43 (13.9)
	Teriflunomide	43 (13.9)
	Dimethyl fumarate	30 (9.7)
	Glatiramer acetate	27 (8.7)
	None	26 (8.4)
	Natalizumab	7 (2.4)
	Alemtuzumab	1 (0.3)
	Rituximab	1 (0.3)
Other	1 (0.3)	
Treatment interrupted		44/283 (15.5)
Reason for interruption	For Covid-19 infection	30/44 (68.2)
	Other/Not specified	6/44 (13.6)
	Patient's decision	5/44 (11.4)
	Other*	3/44 (6.8)
Use of methylprednisolone previous 1 month	Yes	30 (9.7)

Please note that data are reported as median (IQR) and n(%) within the table, whereas in the main manuscript data are reported with minimum and maximum values

* Adverse event / side effect, lack of efficacy, pregnancy or pregnancy planning

showing no major differences. Since the number of pwMS not receiving any DMT treatment in the Turkish MS population is unknown, the pwMS were not receiving treatment in the Covid-19 MS cohort were excluded and the comparison was made according to these modified rates.

The signs and symptoms of Covid-19 infection are summarized in Table 3. The most common symptoms were fatigue, fever and cough and the most common findings were swelling of the tonsils and sore throat. There were 37 (12%) MS patients who were and remained asymptomatic.

3.3. Risk factors for a severe Covid-19 outcome

Nine patients (2.9%) were admitted to an ICU, three of them died. Eighty-five (85) patients (27.5%) were only hospitalized (not-ICU), 81 cases of pneumonia were recorded Fig. 2. The lower class of Covid-19 severity included 215 patients (69.6%) not even hospitalized.

Patients' characteristics are shown in Table 4.

The rate of hospitalization was quite high in Turkey at the beginning of the pandemic. Because of unfamiliarity with the disease all detected cases were initially hospitalized, without taking into account the severity of the disease. Therefore, people with a positive RT-PCR swab test were hospitalized even if they had mild disease. This approach resulted a hospitalization rate of 40% in the beginning of the pandemic. This rate gradually decreased in the following months.

Older age, progressive MS type, high EDSS and high MSSS were found to be risk factors for severity of Covid-19 at univariate analysis.

Figure 1: Comparison of DMT Profile;
MS Covid-19 Cohort* vs National MS Cohort

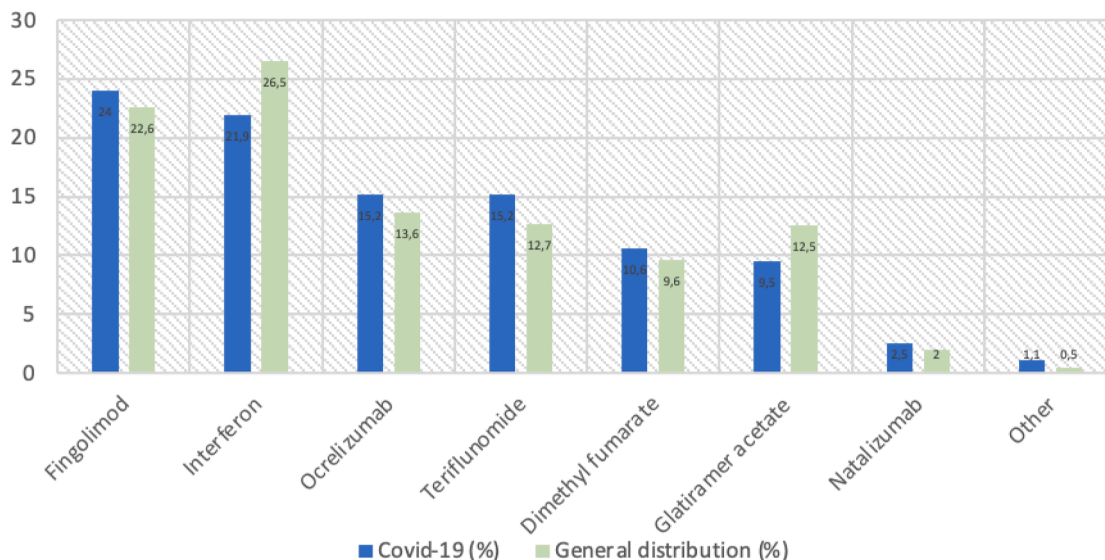


Fig. 1. *The differences in the frequencies of DMT use in the Covid-19 MS cohort in Table 2 and Fig. 1 is the result of excluding the untreated Covid-19 MS patients in Fig. 1 for being able to have a direct comparison with the general population, since the number of pwMS not receiving any DMT treatment in the Turkish MS population is unknown.

However, multivariable analysis confirmed only the role of high MSSS (OR = 2.13; 95%IC: 1.07 - 4.23; $p = 0.032$) and progressive forms of MS (OR = 2.36; 95%IC: 1.09 - 5.13; $p = 0.029$) as factors with a significant impact on Covid-19 severity. (Table 5).

The relationship between DMTs used by patients and Covid-19 disease severity was investigated. The fingolimod-natalizumab group, which has the highest number of patients, was taken as reference and analyzed accordingly. As a result, no DMT group, including B-cell depleting treatments, was found to be associated with Covid-19 disease severity. The low number of patients in the DMT groups may also have led to this result. (Table 5)

3.4. Death associated with Covid-19

Three patients in whom the infection was confirmed by a positive RT-PCR test for Covid-19 had died (lethality rate=0.9 %).

The first case is a 61-year-old female with hypertension, with secondary progressive MS (SPMS), untreated and with a EDSS = 8. The reported reason for death was pneumonia and a consequent septic shock.

The second case is referred to a 61-year-old male patient with SPMS, EDSS = 8.5, untreated, and presenting hypertension and coronary heart disease as comorbidity.

'The third case is a 38-year-old female with relapsing remitting MS and an EDSS score of 4, who was treated with fingolimod. She presented with a mild Covid-19 infection; for which she was started antiviral (favipiravir), antibacterial (clarithromycin) and hydroxychloroquine treatments. She had no known previous liver disease. During the one-year period of using fingolimod there was no impairment of liver functions. When Covid-19 symptoms had started her initial liver function tests were within normal limits and deteriorated after she was put on Covid-19 treatments. She was then diagnosed with toxic hepatitis along with multi-organ failure and aspiration pneumonia leading to death. Mortality data are shown in Table 6.'

At the time of this study submission of our study, there were 5 large MS&Covid-19 published series. We compared our findings to such

previous analyses in Table 7.

4. Discussion

A positive aspect of our study as compared to those previously published on the same topic is the high RT-PCR positivity rate (Sormani et al., 2021; Louapre et al., 2020; Loonstra et al., 2020; Parrotta et al., 2020; Zabalza et al., 2020). The few patients without a positive PCR test were confirmed with either diagnostic studies and/or later by positive serology for Covid-19. The likely explanation for the high rate of RT-PCR positivity in patients is an extensive screening program as well as repeated testing in suspected cases. An immediate observation from our national MS cohort with Covid-19 is that the majority of the Turkish pwMS had a very mild disease, as shown by the very low rate of ICU admission and death.

When comparing the Turkish MS-Covid-19 cohort with other national or regional studies, noticeably the Turkish cohort is younger, has a lower rate of disability and low rate of co-morbidities. The female/male ratio of the population of our study is 2.44 which is comparable to Turkish pwMS in MsBase's 'TurkMSBase' gender distribution sub-study, in which this ratio was 2.34, in 11596 patients ([https://www.msbase.org/sub-studies/\(Sub-studies\)](https://www.msbase.org/sub-studies/(Sub-studies))).

The rate of patients under the age of 40 is approximately two-third in our cohort. Mean age was found to be 36.9, whereas it is approximately 45 in previously published studies [Table 7]. However, this is representative of our national population. According to the 2020 Turkish national data 61.2% of the total population in under the age of 40 ([https://www.nufusu.com/turkiye-nufusu-yas-gruplari\(Turkiye Nufusu Yaş, 2020\)](https://www.nufusu.com/turkiye-nufusu-yas-gruplari(Turkiye Nufusu Yaş, 2020))). In our series, this ratio was 62.8%, consistent with the general national population. The rate of patients under the age of 40 was found to be 33.1% in the study of Sormani et al. (Sormani et al., 2021). It has been shown that one of the main factors for Covid-19 infection severity is age (Möhn et al., 2020), and since our cohort is younger this may be one other explanation for the better outcome observed in our cohort.

Another factor that determines the severity of Covid-19 infection is the presence of comorbidities. In our series, the comorbidity rate is

Figure 2: Monthly Rates of Death, Hospitalizations, and Pneumonia

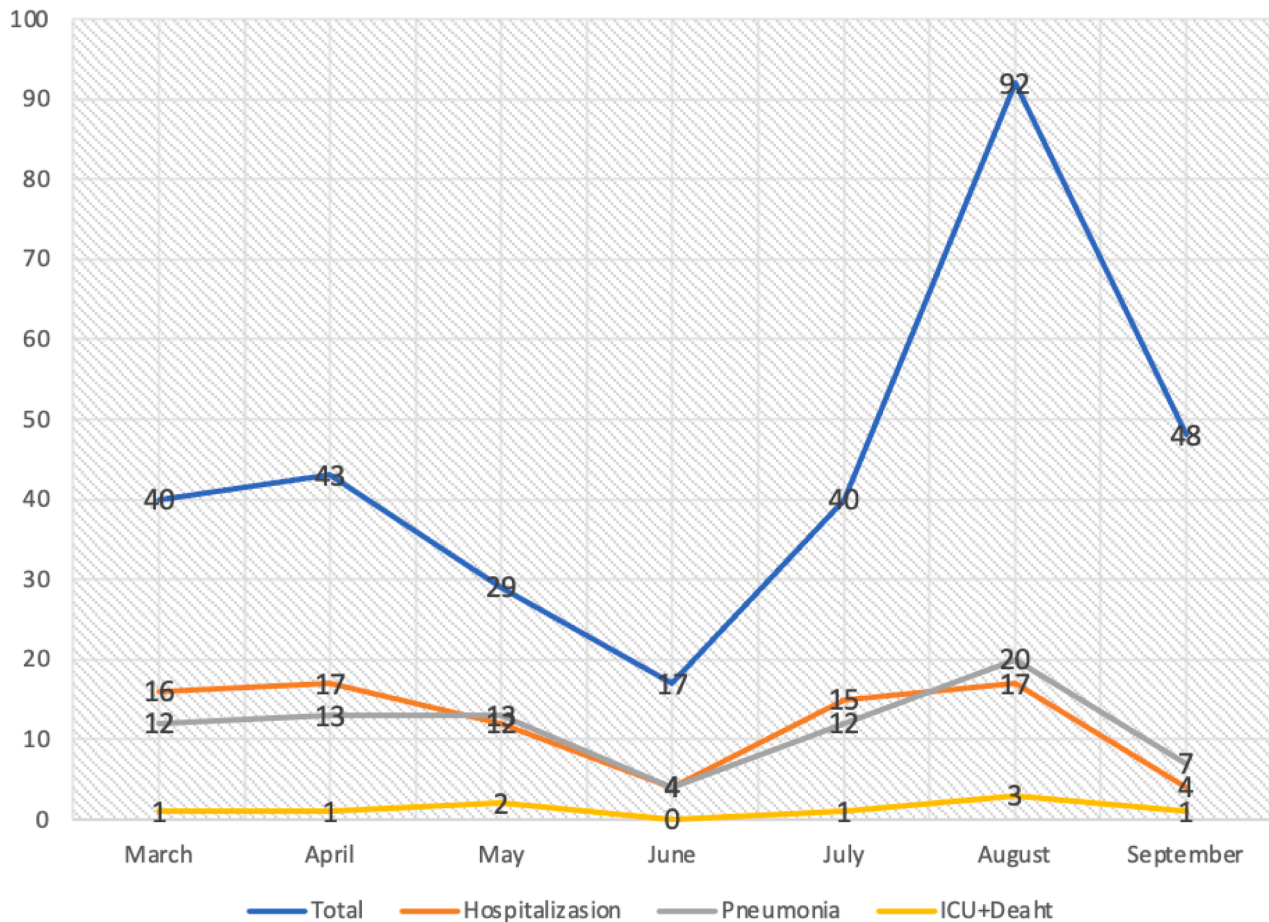


Fig. 2. It shows the monthly number of deaths, hospitalizations and pneumonia for the seven month period in which the study was conducted.

Table 3
Covid signs and symptoms (N = 309).

Asymptomatic		37 (12.0)
Symptomatic		272 (88.0)
Symptoms	Fatigue	168 (54.4)
	Fever	141 (45.6)
	Cough	132 (42.7)
	Headache	106 (34.3)
	Sore throat	90 (29.1)
	Bone joint	84 (27.2)
	Loss of smell	75 (24.3)
	Loss of taste	72 (23.3)
	Shortness of breath	42 (13.6)
	Nasal congestion	23 (7.4)
	Sputum production	18 (5.8)
	Chills	18 (5.8)
	Diarrhea	7 (2.3)
	Myalgia	5 (1.6)
	Other	14 (4.5)
Signs	Throat congestion	58 (18.8)
	Tonsils swelling	21 (6.8)
	Rash	6 (1.9)
	Other signs	5 (1.6)
	Lymph nodes enlargement	4 (1.3)

11.7%. The most important reason for the low rate of comorbidity can also be explained with the younger age of our patients. Since, in similar studies, the rate of comorbidity ranged from 22% to 46%, (Sormani

Table 4
Patients' characteristics.

	ICU or death (N = 9)	Hospitalized (N = 85)	Others (N = 215)
Age mean (range)	45.3 (19.0 - 66.0)	38.1 (18.0 - 63.0)	36.1 (18.0 - 58.0)
Last EDSS median (IQR)	4.5 (3.0 - 6.5)	2.0 (1.0 - 3.5)	1.5 (1.0 - 2.0)
MSSS			
< 7	5 (55.6)	69 (81.2)	5 (55.6)
≥ 7	4 (44.4)	16 (18.8)	4 (44.4)
Clinical phenotype			
Relapsing	5 (55.6)	73 (85.9)	5 (55.6)
Remitting			
Progressive	4 (44.4)	12 (14.1)	4 (44.4)

Data are reported as n(%), mean (range), or median (IQR)

et al., 2021; Loupre et al., 2020; Loonstra et al., 2020; Parrotta et al., 2020; Zabalza et al., 2020) our low rate of comorbidity may be another explanation related to the low mortality seen in Turkish pwMS.

Long disease duration and increased disability are among the major variables associated with the worst outcome in pwMS (Degenhardt et al., 2009). In our cohort, as both disease duration and mean EDSS scores were low these findings may also be associated with low morbidity and mortality observed. The MSSS is a parameter that reveals the relationship of the disease with disability and disease duration in MS (Roxburgh et al., 2005). In our study, the severity of Covid-19 was found to be

Table 5
Univariable and multivariable regression models evaluating risk factors for severe Covid-19.

Variable	Univariable Analysis n=309		Multivariable Analysis n=309		Stepwise Multivariate Analysis n = 309	
	OR (95% C.I.)	p	OR (95% C.I.)	p	OR (95% C.I.)	OR (95% C.I.)
Age	1.03 (1.01 – 1.06)	0.016	1.02 (0.99 – 1.05)	0.21		
Sex (Male vs Female)	1.30 (0.77 – 2.18)	0.33	1.41 (0.80 – 2.47)	0.23		
Smoking (Current/former vs Never)	0.99 (0.59 – 1.67)	0.97	0.94 (0.54 – 1.65)	0.83		
MS type (Progressive vs RR)	2.93 (1.39 – 6.15)	0.005	1.97 (0.73 – 5.35)	0.18	2.36 (1.09 - 5.13)	0.029
EDSS	1.40 (1.21 – 1.62)	<0.001	/	/		
Disease duration (years)	1.01 (0.97 – 1.06)	0.57	/	/		
MSSS (≥ 7 vs <7)	2.57 (1.33 – 4.97)	0.005	2.17 (1.07 – 4.40)	0.031	2.13 (1.07 - 4.23)	0.032
BMI	0.99 (0.94 – 1.04)	0.58	0.99 (0.94 – 1.05)	0.74		
Presence of comorbidities	1.53 (0.74 – 3.19)	0.26	1.32 (0.58 - 2.99)	0.50		
Methylprednisolone with in 1 month prior to Covid-19 onset	1.28 (0.59 – 2.78)	0.53	1.26 (0.56 – 2.84)	0.58		
Disease modifying therapy						
Fingolimod / Natalizumab	Ref.		Ref.			
Interferon / Glatiramer acetate	0.57 (0.29 – 1.12)	0.11	0.64 (0.32 - 1.27)	0.20		
Teriflunomide / Dymethyl fumarate	0.73 (0.37 – 1.45)	0.37	0.76 (0.38 - 1.52)	0.44		
Ocrelizumab/Rituximab	1.17 (0.54 – 2.53)	0.69	0.64 (0.26 - 1.60)	0.34		
None	1.06 (0.42 – 2.70)	0.90	0.77 (0.28 - 2.11)	0.61		

OUTCOME = ICU/death vs Only hospitalized vs Others

Table 6
Characteristics of deceased patients.

Sex	Age	Sex	Type of MS	MS disease duration years	MS treatment	Treatment duration months	Last EDSS	MSSS	Comorbidity	Presence of pneumonia	Cause of death
Female	38	Female	RRMS	13.0	Fingolimod	12.0	4.0	4.38	Major depressive disorder	Yes*	Toxic hepatitis, multiple system failure, pneumonia*
Male	61	Male	SPMS	28.0	None	.	8.5	9.45	Coronary heart disease; Hypertension	Yes	Pneumonia
Female	61	Female	SPMS	6.0	None	.	8.0	9.81	Hypertension	Yes	Pneumonia, septic shock

* Aspiration pneumonia

Table 7
MS&Covid-19 relationship.

Reference	Data of Turkey	Sormani M.P. et al. (4)	Louapre C. et al. (6)	Loonstra FC. et al. (7)	Parrotta E. et al. (8)	Zabalza A. et al. (9)
Total number of cases	309	844	347	86	76	48
Age range	18-66	18-82	-	20-71	13-71	
Age mean	36.9	45	44.6	45.5	44.9	43.9
Comorbidity %	12.3	22.3	32	26.70	46.1	35.4
RRMS patient rate %	89.6	80.1	79.5	80.20	72.3	72.9
MS disease duration (years)	7.43	10.2	13.5	-	15.2	14.5
EDSS (mean)	1.5	2	2	3.00	-	2
Covid-19 PCR (+) rate %	94.2	33.1	55	50.00	48.7	45.8
Mortality %	0.9	1.54	3.5	4.70	7.9	4.2
Mortality number	3	13	12	4	6	2
pwMS on DMT %*	91.6	82.1	81.8	86	84.2	89.6

higher in the patient group with high MSSS score confirming earlier observations (Sormani et al., 2021; Louapre et al., 2020; Loonstra et al., 2020; Parrotta et al., 2020; Zabalza et al., 2020).

From the beginning of the pandemic individuals over the age of 65 were locked down and have been well isolated in Turkey. It's likely that pwMS with advanced age were less infected as well as pwMS with higher disability levels who due to social isolation were less exposed to Covid-19. Since these most vulnerable MS populations were better isolated, they were further protected from infection.

Impact of Covid-19 on MS has been investigated since the early days of the pandemic. Due to difficulties in reaching all patients, alternative methods were implicated. One such multinational project was the use of wearable devices and smartphone technology to explore the impact of Covid-19 among MS patients (Costa et al., 2020). Such studies may provide some information and shed light on this effect, however, the confirmed cases with this specific infection remain low in these

populations. So, it may be difficult to reach definite conclusions with this methodology at this stage.

Another fact that it would be of crucial importance is the impact of DMTs in pwMS with Covid-19. We were not able to detect any significant association of DMTs with Covid-19 severity. The question on whether some of the DMT are partly protective and some may be associated with Covid-19 is still controversial (Sormani et al., 2021; Louapre et al., 2020; Loonstra et al., 2020; Parrotta et al., 2020; Zabalza et al., 2020; Baker et al., 2020; Laroni et al., 2020; Zrzavy et al., 2020). Only B-cell depleting treatments were shown to increase the risk for a more severe Covid-19 infection. In general, the infections are likely to be associated with increased morbidity in patients receiving DMT treatments with immunosuppressive properties (Winkelmann et al., 2016). It is known that the frequency of herpes virus infections and opportunistic infections are increased with high efficacy treatments (Luna et al.). This risk of infections is associated with lymphopenia, especially suppression

of CD8 T cells for viral infections and/or hypogammaglobulinemia (Baker et al., 2020; Vollenhoven et al., 2015; Hauser et al., 2008). It can be speculated that the effect of DMTs on Covid-19 can be either protective or negative by increasing the severity of the infection based on their mode of action. However, in most studies such a negative effect couldn't be established, but the probability of a preventive effect on the multisystem inflammatory syndrome that is associated with Covid-19 severity had been proposed in some other studies in which similar immunosuppressive agents were used in people with various neurologic and systemic autoimmune diseases (Akiyama et al., 2020; Altobrando et al., 2020; Montero-Escribano et al., 2020; Kovvuru et al., 2021).

Two of the patients who died in our series were older patients who weren't on any DMT but had severe disability and comorbidities. The third patient's death was accepted to be due to indirect causes and not directly related to Covid-19. Our experience is mostly consistent with the previously reported large series showing that disease severity and fatality were mostly related to longer disease duration, high disability and older age (Sormani et al., 2021; Louapre et al., 2020; Loonstra et al., 2020; Parrotta et al., 2020; Zabalza et al., 2020). In our national cohort of pwMS none of the DMTs had a significant effect on the outcome of Covid-19 severity. Although a tendency for the B-cell depleting therapies for a more severe disease course was observed, this observation didn't reach statistical significance. Since the distribution of pwMS on DMTs is proportional to the national MS population treated [Fig. 1], it may be suggested that our observation may be representative of our national MS population as well. As our study population was younger with a lower disability level these features may explain the overall better outcome observed in our cohort. Since a number of variables and biases may have influenced the included pwMS in the reported cohorts and the sample size is too small to discriminate the effects of the different DMTs on the risk of severe Covid-19, we believe that the current study does not allow to reach a definite conclusion regarding whether any DMT carries a higher risk independent of other variables. Therefore, we agree with the statements that all approved disease-modifying therapies in pwMS should be continued unaltered and that risk management may be made on individual basis (Zrzavy et al., 2020; Korsukewitz et al., 2020).

5. Limitations

In our cohort, asymptomatic patients were not considered as a separate group, but were included together with the mild disease group. Separate analysis of this selected population may provide more information about the course of the disease, however since their number was limited, they weren't evaluated as a subgroup. Since from the beginning of the pandemic individuals over the age of 65 were locked down and have been well isolated in Turkey, it's likely that pwMS of advanced age were less infected and therefore are under-represented in our cohort. Lack of well documented data for people within the general population with Covid-19 infection didn't allow us to compare the outcomes on national basis. Only 10.2% of the patients in our study population had progressive MS. The most likely explanation for the lower rate of Covid-19 infected MS patients with the progressive forms of disease may be that this population was most carefully following public health guidelines, staying at home and being in less contact with infected people as they know that they are at higher risk and therefore were less likely to be infected. Further limitations were the lack of detailed laboratory and serologic testing for Covid-19-IgG since running such tests was not common practice at the time of our study conduction. Therefore, we cannot reach any conclusion on the immunological profiles of our MS Covid-19 cohort and outcomes.

6. Conclusion

The Turkish MS-Covid-19 study revealed that pwMS are not at a higher risk of Covid-19 severity according to the DMT used, while it confirmed that MS severity, assessed by the EDSS or by a progressive

course, was a significant risk factor. In addition, due to the young age and the low proportion of patients with comorbidities, the Turkish MS population had overall a mild Covid-19 course.

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Declaration of Competing Interest

S. Sen has received honoraria or consultancy fees for participating to advisory boards, giving educational lectures and/or travel and registration coverage for attending scientific congresses or symposia from F. Hoffmann-La Roche Ltd, Sanofi-Genzyme, Merck-Serono, Novartis, Teva, Biogen Idec/Gen Pharma.

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The rest of authors declare no conflict of interest with the study project.

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