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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 pandemic of the new type of corona virus infection 2019 [Covid-19] also affect people with Multiple Sclerosis.

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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 (Brownie 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 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 methyldaprisolone, 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 score was 1.5, ranging from 0 to 8.5. The EDSS score was ≤ 7 in 267 (86.4%) 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 score was < 7 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 (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 (43%) of the patients. 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.

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, showing no major differences. Since the number of pwMS not receiving any DMT treatment in the Turkish MS population is unknown, the pwMS who 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. 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.

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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 an 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).

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-grupları/Türkiye Nüfusu 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 (Mohn 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...
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 et al., 2021; Louapre 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

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**Table 3**

| Symptomatic Symptoms | Asymptomatic |
|----------------------|-------------|
| 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)   |

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**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)         |
| MSSS ≥ 7                    | 4 (44.4)             | 16 (18.8)             | 4 (44.4)         |
| Clinical phenotype          | Relapsing            | Remitting             | Progressive      |
| Age mean (range)            | 5 (55.6)             | 73 (85.9)             | 5 (55.6)         |
| Last EDSS median (IQR)      | 4.4 (4.4)            | 12 (14.1)             | 4 (4.4)          |

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

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

| Variable | Univariable Analysis n=309 | p | Multivariable Analysis n=309 | p | Stepwise Multivariate Analysis n – 309 |
|----------|---------------------------|---|-----------------------------|---|-------------------------------------|
| OR (95% C.I.) | 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 | Pneumonia, septic shock | 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 |
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 multisytem 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; Altorbrando 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 that were less infected and therefore are under-represented in our cohort. 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 conduct. 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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Credit author statement

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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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