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## Original article



## Characteristics of COVID-19 in patients with multiple sclerosis

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## ABSTRACT

**Background:** Regarding the high prevalence of multiple sclerosis (MS) and COVID-19 in Iran, a multicenter study of COVID-19 in Iranian MS patients with is carried out to address the concerns of this population.

**Methods:** Data on MS patients with COVID-19 from nine provinces of Iran were entered in a web-based registry system, between July 2020 and March 2021. Among the COVID-19 symptoms, dyspnea, altered mental status, or those resulting in hospital admission were considered severe.

**Results:** A total of 397 eligible patients were identified. In addition, 310 (78%) were female. The mean age was  $36.5 \pm 9.5$ . 294 (74%) patients had relapsing-remitting form. Also, four patients (1%) expired due to COVID-19 infection. The mean duration of admission in hospitalized patients was  $9 (\pm 5.3)$  days. MRI was performed on 111 (28%) patients after developing COVID-19. MRI changes were observed in 27 (24%) of these cases. MS drug was changed in 26 (6%) patients. Steroid use in the past three months (OR: 2.43, 95% CI: 1.003–5.88) ( $p$  value: 0.049) and antiCD20s (OR: 4.03, 95% CI: 2.41–6.68) ( $p$  value < 0.001) showed significant association with severe COVID-19 symptoms.

**Conclusion:** The death rate of COVID-19 among MS patients (1%) is lower than the overall death rate of the pandemic in Iran (3%). Those who received steroid in the past three months may be at increased risk of more severe forms of COVID-19. There are still doubts about the effect of anti CD20s on COVID-19 severity.

## 1. Introduction

Multiple sclerosis (MS) with an age-adjusted prevalence of 137.6 and incidence of 6.7 per 100,000 is a common neurologic disease in Iran (Almasi-Hashiani et al., 2020; Hosseinzadeh et al., 2019). A recent systematic review showed high and rising prevalence in the country (Azami et al., 2019). Apart from high rates of depression, studies have shown patients' concerns about the effect of the recent pandemic on

their disease and treatment (Ramezani et al., 2021; Rezaeimanesh et al., 2020; Zhang et al., 2021). Worried about becoming infected, many patients have postponed their usual medical care (Zhang et al., 2021). It was found that many Iranian MS patients were not informed about necessary changes in treatment protocols in case of infection with SARS-CoV2 (Ghajarzadeh et al., 2021). More clarification of the situation would help manage the distress. There are epidemiologic studies of COVID-19 on MS patients. A large cohort, of 42,899 MS cases, from the

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US reported the same infection rate in MS population relative to the general US population (Kovvuru et al., 2021). A unicentric study in Iran also showed the same incidence of COVID-19 in MS patients compared with the general Iranian population, but a higher risk of hospitalization in these patients (Sahraian et al., 2020). However, there are other reports with various, sometime contradicting, results (Sharifian-Dorche et al., 2021). As far as the authors are concerned, this study is the first multicenter report of COVID-19 on Iranian patients with MS, which attempted to address the disease characteristics, risk factors of severity, and differences with the general population.

## 2. Methods

### 2.1. Setting

The nationwide MS registry of Iran (NMSRI) was established in 2018. The validity and reliability of the MS questionnaire had been previously confirmed (Shahin et al., 2019). The study was carried out between July 2020 and March 2021. Several workshops were held to educate admins in nine provinces of Iran: East Azerbaijan, Fars, Guilan, Isfahan, Kermanshah, Khuzestan, Mazandaran, Qazvin, and Tehran. Admins had to enter the data from day clinics, private and public hospitals, and private offices.

### 2.2. Patients

MS was diagnosed, based on Mc Donald's criteria 2017, by neurologists (Carroll, 2018). COVID-19 infection was confirmed by an internist or infectious diseases specialist with reviewing clinical aspects, polymerase chain reaction (PCR), and/or lung CT scan. MS patients with COVID-19 were entered into the registry.

### 2.3. Variables

Identification data, demographic characteristics (age, gender, and place of residence), and information on MS and COVID-19 were collected. Patients were categorized into the two groups of older or younger than 50 years old. MS data included: type (clinically isolated syndrome (CIS), relapsing-remitting (RR), secondary progressive (SP), primary progressive (PP)), expanded disability scoring scale (EDSS), disease-modifying drug (DMD), and whether the patient had received steroid in the last three months. MS types were grouped as progressive versus non-progressive forms. Patients were also categorized to cases with EDSS lower or higher than three. As there were data on the effect of antiCD20s on the course of COVID-19, they were analyzed compared to other treatment choices, separately. Information on COVID-19 characteristics included: symptoms, PCR and CT results, drugs, and admission information. The symptoms of COVID-19 were categorized into more severe ones (dyspnea, altered mental status, or those symptoms resulting in hospital admission) and less severe symptoms (others). This categorization was based on the results of studies evaluating symptoms and prognosis (Tenforde et al., 2020; Attia et al., 2021), and also the protocols in clinical management of Iranian COVID patients.

Admins were responsible to check for errors in data entry and solve any problem during follow ups. Finally, files with incomplete key information were excluded. Duplication was checked by national code number.

### 2.4. Ethical issues

To ensure the privacy of the patients, limited access to the registry was defined for each registrar. Study details, and goals were explained to the patients. Enrollment was optional. The project protocol has been approved by ethical committee of Tehran University of Medical Sciences (IR.TUMS.NI.REC.1400.030).

## 2.5. Analyses

Q-Q plots and Kolmogorov-Smirnov (K-S) tests were run to check for normality. Descriptive analysis included frequency for qualitative variables, mean  $\pm$  standard deviation (SD) for quantitative variables, and median (interquartile range (IQR)) for categorical ones like EDSS. Univariate analysis was applied to find factors with significant association with the outcome measures ( $p$  value  $<$  0.2). After entering the found factors to the final multivariate regression models, those with  $p$  value  $<$  0.05 were considered significant. IBM® SPSS® version 26 was used.

## 3. Results

During the study period, 397 eligible patients were identified and none was excluded. The basic characteristics of the patients are summarized in Table 1.

Characteristics of the COVID-19 are summarized in Table 2.

Of all the patients, four (1%) expired during the study period due to COVID-19 infection. The mean duration of admission in hospitalized patients was 9 (SD: 5.3) days.

MRI was performed on 111 (28%) patients after developing COVID-19. The reason for imaging was either routine MS follow up or post-COVID neurologic symptoms that could be attributable to pseudo-attacks. MRI changes were observed in 27 (24%) of these cases. Two patients showed new enhancing lesions. The presence of any change in the MRI was not associated with age group, gender, antiCD20, steroid use, or MS type. It did not correlate with hospitalization either ( $p$  value  $>$  0.05). MS drug prescription was changed in 26 (6%) patients (dose reduction in 10 and switch in 16 patients).

In univariate analysis, studying associated factors to more severe COVID-19 symptoms, age group, MS type, EDSS group, consumption of steroid three months before the covid-19 infection, history of asthma, and anti CD20 treatment showed significant relation. Entering them in the final model, only steroid use in the past three months (OR: 2.43, 95% CI: 1.003–5.88) ( $p$  value: 0.049) and antiCD20s (OR: 4.03, 95% CI: 2.41–6.68) ( $p$  value  $<$  0.001) remained significant.

Fifteen patients (4%) showed false-negative PCR results. It did not correlate with age group, MS type, use of anti CD20, or steroid use ( $p$  value  $>$  0.05). Consumption of vitamin D did not show any association with admission variables or symptoms. Also, COVID-19 medications did not show any association with the admission results.

## 4. Discussion

This is the first multicentric report on Iranian MS patients infected with COVID-19 from NMSRI. The majority were female patients, in their mid-thirties, with RR type of MS, and in the earlier stages of the disease. Most of the patients took vitamin D as a supplement. Body pains, malaise, and fever were the most common complaints.

The death rate from COVID-19 approximated those of previous reports from Iran and other countries (Sahraian et al., 2020; Sormani et al., 2021a). It is obviously lower than the overall death rate from the pandemic in Iran (3%), officially announced by the ministry of health <https://www.worldometers.info/coronavirus/country/iran/>. The admission rate was lower compared to the previous unicentric Iranian study (18% in our study versus 25%) (Sahraian et al., 2020). The risk of infection with SARS-CoV2 and its severe course in MS patients was not higher compared to general population in other cohorts, either (Moreno-Torres et al., 2021; Stastna et al., 2021). However, the data from the United States is in a different direction (Salter et al., 2021b; Sormani et al., 2021b). No exact data on the rate of ICU admission was available in our registry.

About the relation between MS and COVID-19, there are notable debates. Our study revealed the association of anti CD20s with more severe forms of COVID-19 including severe symptoms like altered mental status or dyspnea, and more hospitalization rates. This is in line

**Table 1**  
Basic information of the patients.

Variables	N (%)
Gender	
Female	310 (78)
Male	87 (22)
Mean age	36.5 (± 9.5)
Age > 50	36 (9)
Age ≤ 50	350 (88)
Province of residence	
Isfahan	108 (27)
Tehran	74 (19)
Guilan	40 (10)
Mazandaran	38 (10)
Qazvin	35 (9)
Khuzestan	34 (9)
East Azerbaijan	33 (8)
Fars	27 (7)
Kermanshah	8 (2)
MS type	
RR	298 (75)
SP	32 (8.1)
CIS	22 (5.5)
PP	15 (3.8)
Median EDSS (IQR)	1.5 (1–3)
EDSS ≤ 3	279 (70)
EDSS > 3	118 (30)
MS drug	
No drug	18 (4.5)
Injectable (Glatiramer acetate, Interferon beta-1a, Interferon beta-1b)	113 (28.4)
Dimethyl fumarate	41 (10.3)
Teriflunomide	18 (4.5)
Fingolimod	36 (9.1)
Fingolimod	6 (1.5)
Natalizumab	139 (35.0)
Rituximab	3 (0.8)
Ocrelizumab	3 (0.8)
Azathioprine	
Steroid in the last three months before covid-19 infection	
Negative	364 (92)
Positive	33 (8)
Supplementary drugs	
Vitamin D	339 (85)
Vitamin C	111 (28)
Zinc	71 (18)
NSAID	8 (2)
ACE inhibitors	2 (0.5)
Chronic comorbidities	
Hypertension	19 (5)
Diabetes mellitus	14 (4)
Asthma	5 (1)
Chronic obstructive pulmonary disease (COPD)	1 (0.3)
Respiratory allergy	8 (2)
Previous pneumonia	4 (1)
Cancer	1 (0.3)
Pregnancy	1 (0.3)
Others	40 (10)

N: number, SD: standard deviation, RR: relapsing- remitting, SP: secondary progressive, CIS: clinically isolated syndrome, PP: primary progressive, EDSS: Expanded Disability Status Scale, NSAID: non-steroidal anti-inflammatory drugs, ACE: angiotensin-converting enzyme

with some of the previous studies (Luna et al., 2020; Safavi et al., 2020; Sharifian-Dorche et al., 2021; Sormani et al., 2021a). The proposed mechanism is the manipulation of the immune system with depleting B-cell lineage. Nevertheless, some scholars argue for the role of B-cells in the antiviral immune response (Giovannoni, 2020; Montero-Escribano et al., 2020). Some even suggest that reduced B-cell-related cytokine responses (e.g., interleukin 6) may play a favorable role in limiting the inflammatory phase of COVID-19 (Novi et al., 2020). The obvious point is the need for further research on the subject.

There is data on neurologists' attitude towards treatment changes during the pandemic (Mateen et al., 2020). In spite of the concerns, a minor change in the treatment protocols was reported in our database.

**Table 2**  
COVID-19 related data.

Variables	N (%)
COVID-19 symptoms	
Body pain	238 (60)
Malaise	232 (58)
Fever	217 (55)
Loss of smell	200 (50)
Loss of taste	187 (47)
Dry cough	161 (41)
Headache	155 (39)
Dyspnea	123 (31)
Nasal discharge	55 (14)
Productive cough	49 (12)
Altered mental status	12 (3)
COVID PCR	
Not done	126 (32)
Positive	256 (64)
Negative	15 (4)
Lung CT results	
Not done	291 (73)
Normal	16 (4)
Ground glass	87 (22)
Consolidation	14 (3)
ARDS	1 (0.3)
COVID drugs	
Naproxen	64 (16.1)
Hydroxychloroquine	58 (14.6)
Kaletra	7 (1.8)
Tamiflu	7 (1.8)
Salbutamol	3 (0.8)
Tocilizumab	1 (0.3)
Others	106 (26.7)
Admission status	
Not admitted	325 (82)
Discharged	68 (17)
Death	4 (1)

Regarding other aspects of MS disease, Louapre et al. (2020) demonstrated age, EDSS, and obesity as independent risk factors for COVID-19 severity in MS patients. In another study in New York, age, presence of comorbidities, progressive disease, and a nonambulatory status were found to be related to more severe diseases (Parrotta et al., 2020). Also, a recently published study showed increased disability, older age, black race, cardiovascular comorbidities, and recent treatment with corticosteroids could be associated with more clinical severity (Salter et al., 2021a). The association of steroids and anti CD20s with severe course is found in some other studies, as well (Sormani et al., 2021b; Stastna et al., 2021). Our findings agree in some aspects with previously mentioned studies whereas a strong association with DMT type was found.

No association was found between baseline use of supplements (e.g., vitamin D) and COVID-19 severity. Nevertheless, as some studies seem to contradict these results (Lordan et al., 2021; Pinnawala et al., 2021), more investigations are required in the future.

Apart from low dose steroids (2021), most drugs listed here as COVID drugs are proven to be ineffective (Sanders et al., 2020; Tang et al., 2020), <https://www.covid19treatmentguidelines.nih.gov/outpatient-management/>, however as the data was gathered over the last year, they were included in the study. Our data confirmed many of the previous mentioned results (Sanders et al., 2020; Tang et al., 2020).

As growing evidence shows, chronic diseases like diabetes mellitus and hypertension may alter the prognosis in COVID-19 patients (Abu-Farha et al., 2020; Alyammahi et al., 2021). Lack of such correlation in our study (except for asthma that is predictable to cause more dyspnea) may be due to the younger age of our study population and the low prevalence of such diseases.

## Conclusion

Despite substantial studies about COVID-19 in MS patients, the discrepancy in the literature is still of note. There are even concerns about the long-term effects of COVID-19 on MS patients (Di Stadio et al., 2020). Thereafter, more extensive data registries may be of help to depict a clearer viewpoint on the matter.

## Supplementary material

English Certificate.pdf

## CRediT authorship contribution statement

**Fereshteh Ghadiri:** Formal analysis, Writing – original draft, Writing – review & editing, Visualization, Funding acquisition. **Mohammad Ali Sahraian:** Conceptualization, Investigation, Validation, Resources, Supervision. **Vahid Shayannejad:** Investigation. **Fereshteh Ashtari:** Investigation. **Hamidreza Ghalyanchi Langroodi:** Investigation. **Seyed Mohammad Baghbanian:** Investigation. **Hossein Mozhdehipanah:** Investigation. **Nastaran Majdi-Nasab:** Investigation. **Samaneh Hosseini:** Investigation. **Maryam Poursadeghfard:** Investigation. **Nahid Beladimoghadam:** Investigation. **Nazanin Razazian:** Investigation. **Saeideh Ayoubi:** Investigation, Software, Data curation. **Nasim Rezaeimanesh:** Investigation, Software, Writing – review & editing. **Sharareh Eskandarieh:** Conceptualization, Methodology, Validation, Data curation, Writing – review & editing, Project administration. **Abdorrezza Naser Moghadasi:** Conceptualization, Validation, Resources, Supervision, Project administration.

## Declarations of Competing Interest

None

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2021.103437.

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