Original Article

# Predictors of Catching COVID-19 Infection during Pandemic Stage in Patients with Multiple Sclerosis (MS)


## Abstract

**Background:** Patients with multiple sclerosis (MS) are considered at higher risk of COVID-19 infection due to treatment with immune modulators and immune-suppressive agents. The exact risk factors are not clear. So, we aimed to conduct a study to determine the predictors of catching COVID-19 infection during the pandemic stage in patients with multiple sclerosis (MS). **Methods:** We conducted a multicenter screening study and developed an online questionnaire to collect patients' self-reported demographic features along with MS-related and COVID-19–related information. The online questionnaire link was released by the Iran Multiple Sclerosis Society (IMSS) social media channel, accessible for 4160 MS patients totally and also was sent by WhatsApp for nonmember cases. **Results:** Totally, 1448 MS patients participated in our study. Twenty-five (1.7%) patients were diagnosed with COVID-19, from which 4 were hospitalized, 4 were treated with medical therapy, and 17 patients had home-quarantine. The patients with COVID-19 diagnosis were more frequently treated with rituximab (28% vs 24%, $P = 0.001$) than others, and cardiovascular comorbidity was more frequent in this group (8% vs 1.6%, $P = 0.01$). Regression analysis showed that cardiovascular disease was a significant positive predictor of COVID-19 infection (OR = 5.2, 95% CI: 1.1–23.7). **Conclusions:** Patients with MS who have cardiovascular disease should be more monitored for COVID-19 infection as they are at higher risk of infection.


**Keywords:** *COVID-19, Iran, multiple sclerosis, predictor*


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## Introduction

SARS-CoV-2 is a novel virus from the Coronaviridae family with high infection ability and considerable transmission potential.[1] The spread of coronavirus has reached to pandemic stage currently and many countries are affected worldwide.[2] The main routes of transmission are airborne droplets and infected surfaces.[3] Patients with diabetes, hypertension, pulmonary disorders, obesity, and who are receiving immunosuppressive agents are at higher risk of infection.[4] Therefore, patients with multiple sclerosis (MS) on treatment with immunosuppressive agents may be at higher risk to get infected with the coronavirus.[5]

Iran has high rates of SARS-CoV-2 infection with the reproduction estimation of 4.4–3.5 at the beginning and 1.55 after the implementation of social distancing.[6] As Iran is a country with a high prevalence of MS,[7] precise monitoring and determining the high-risk cases for COVID-19 is of particular importance.[8]

In a recent study, Sahraian *et al*. reported the prevalence of COVID-19 infection in MS patients as 1.46%.[9]

Here, we conducted this study to determine predictors of catching COVID-19 infection during the pandemic stage in patients with multiple sclerosis (MS).

## Methods

This is a cross-sectional study. We developed an online questionnaire to collect self-reported information of MS patients including demographic features (age, sex, blood group, and medical history), MS-related data (duration of the disease, type of MS, current medication, and history of vitamin D consumption), and COVID-19–related information (symptoms, adherence to the rules of quarantine, family support in the implementation of quarantine, consuming immune-boosting supplements before COVID-19 pandemic, wearing masks and gloves in public places, social distancing performance, a definite diagnosis of COVID-19, and measures taken after

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diagnosis). This is part of a large study which has been approved by ethics committee of TUMS IN March 2020.

Inclusion criteria were: Inclusion criteria were confirmed diagnosis of MS based on McDonald 2017 criteria, and age more than 18.

The online questionnaire link was released by the Iran Multiple Sclerosis Society (IMSS) social media channel, accessible for 4160 MS patients totally and also was sent by WhatsApp for nonmember cases in June 2020.

At the beginning of the questionnaire, patients were asked to answer questions only if they consented to participate in this program. The answers were blinded, and we had no access to the patient's personal information.

The data were gathered and analyzed using SPSS software version 22 (SPSS Inc., Chicago, IL, USA), and presented as mean ± SD for continuous variables and as frequencies for categorical variables. Chi-square test was used for comparing categorical variables. Univariate logistic regression analysis was applied to determine the predictors of COVID-19 diagnosis. We considered rituximab and ocrelizumab as B-cell depleting agents.

*P* value less than 0.05 was considered significant.

## Results

Of the 4160 people for whom the questionnaire was accessible, 3874 patients viewed the link, whereas 1448 answered the questions. Patients' mean age and mean MS disease duration were 37.5 ± 9.3 and 10.4 ± 5.9, respectively. The most frequent medications used were interferons (34.6%) followed by rituximab (24.8%).

Demographic, clinical, and COVID-19–related information are reported in Table 1.

Twenty-five (1.7%) patients were diagnosed with COVID-19, from which 4 were hospitalized, 4 were treated with medical therapy, and 17 patients had home-quarantine. The characteristic features of these patients are summarized in Table 2.

As compared to MS patients without COVID-19 diagnosis, MS patients diagnosed with COVID-19 were more frequently treated with rituximab (28% vs 24%, $P = 0.001$); of those on rituximab, three were hospitalized, three had home-quarantine, and one patient had medical therapy. Furthermore, cardiovascular comorbidity was more frequent in patients diagnosed with COVID-19 compared to patients without this diagnosis (8% vs 1.6%, $P = 0.01$).

Multivariate logistic regression analysis by considering COVID-19 as dependent and other variables an independent variable, showed that cardiovascular disease was a significant positive predictor of COVID-19 infection (OR = 5.2, 95% CI: 1.1–23.7) [Table 3].

**Table 1: Demographic, clinical, and COVID-19 related information**

| Variables | Findings |
|---|---|
| Age (Mean±SD) (Year) | 34.7±8.7 |
| Disease duration (Mean±SD) (Year) | 10.4±5.9 |
| Sex *n* (%) | |
| Female | 1155 (79.8%) |
| Male | 293 (20.2%) |
| Type of MS *n* (%) | |
| Relapsing Remitting | 1195 (82.5%) |
| Progressive Forms [*progressive* relapsing (PR), primary progressive (PP), secondary progressive (SP)] | 253 (17.5%) |
| Current medication *n* (%) | |
| INFs | 501 (34.6%) |
| Glatiramer acetate (GA) | 95 (6.6%) |
| Dimethyl fumarate (DMF) | 113 (7.8%) |
| Triflunomide | 69 (4.8%) |
| Ocrelizumab | 10 (0.7%) |
| Rituximab | 359 (24.8%) |
| Natalizumab | 12 (0.8%) |
| Azathioprine | 7 (0.5%) |
| Fingolimod | 185 (12.8%) |
| No current medication *n* (%) | 97 (6.7%) |
| Blood group *n* (%) | |
| A | 422 (29.1%) |
| B | 268 (19.8%) |
| AB | 164 (11.3%) |
| O | 576 (39.8%) |
| Vitamin D consumption. *n* (%) | |
| Daily | 65 (4.5%) |
| Weekly | 310 (21.4%) |
| Every two weeks | 609 (42.1%) |
| Monthly | 291 (20.1%) |
| None | 173 (11.9%) |
| Co-morbidities | |
| Diabetes | 29 (2%) |
| Hypertension | 81 (5.6%) |
| Cardiovascular disease | 25 (1.7%) |
| Hypothyroidism | 160 (11%) |
| Asthma/allergy | 107 (7.4%) |
| Living alone (yes). *n* (%) | 74 (5.1%) |
| Wearing masks and gloves in public places *n* (%) | 1184 (81.8%) |
| Implementation of social distancing *n* (%) | 1326 (91.6%) |
| Implementation of home-quarantine *n* (%) | 1312 (90.6%) |
| Family support in the implementation of quarantine *n* (%) | 1269 (87.6%) |
| Consuming immune-boosting supplements before pandemic *n* (%) | 794 (48%) |

## Discussion

Based on our knowledge, this is the first nationwide screening of MS patients for COVID-19 to determine predictors of catching the infection in Iranian patients during the pandemic stage. One thousand and forty-eight

**Table 2: Characteristics of COVID-19 confirmed cases**

| Variables | Findings |
|---|---|
| Age (Mean±SD)(Year) | 37.5±9.3 |
| Sex *n* (%) | |
| Female | 20 (80%) |
| Male | 5 (20%) |
| Type of MS. *n* (%) | |
| Relapsing-Remitting | 20 (80%) |
| Progressive Forms (PR, PP, SP) | 5 (20%) |
| Current medication *n* (%) | |
| INFs | 0 |
| GA | 2 (8%) |
| Triflunomide | 2 (8%) |
| Rituximab | 5 (20%) |
| No medication | 4 (16%) |
| Blood group *n* (%) | |
| A | 6 (24%) |
| B | 4 (16%) |
| AB | 2 (8%) |
| O | 13 (52%) |
| Vitamin D consumption *n* (%) | |
| Yes | 23 (92%) |
| No | 2 (8%) |
| Comorbidities *n* (%) | |
| Diabetes | 0 |
| Hypertension | 2 (8%) |
| Cardiovascular disease | 2 (8%) |
| Hypothyroidism | 5 (20%) |
| Asthma/allergy | 4 (16%) |
| Living alone *n* (%) | 2 (85%) |
| Wearing masks and gloves in public places *n* (%) | 18 (72%) |
| Implementation of social distancing *n* (%) | 22 (88%) |
| Implementation of home-quarantine *n* (%) | 24 (96%) |
| Symptoms *n* (%) | |
| Fever | 22 (88%) |
| Cough | 21 (84%) |
| Shortness of the breath | 14 (56%) |
| Diarrhea | 3 (12%) |
| Nausea/vomiting | 5 (20%) |
| Hyposmia | 5 (20%) |
| Hypogeusia | 3 (12%) |
| Headache/vertigo | 13 (52%) |

patients participated, of which 25 patients had confirmed diagnosis of COVID-19. Four patients were hospitalized, whereas none of them needed intensive care unit (ICU) admission.

The majority of patients with COVID-19 diagnosis were females (80%), and the most frequent medication used was rituximab (28%), which was significantly higher in patients with COVID-19 diagnosis. We also found that odds of catching COVID-19 are near five times higher than cases without cardiovascular comorbidity. We also found that blood groups and vitamin D consumption were not significantly different between cases with and without COVID- 19.

It is suggested that ABO blood group and cardiovascular diseases are prognostic factors of COVID-19 severity, whereas they are not predisposing factors of getting SARS-CoV-2 infection risk.[10]

The other risk factor of catching COVID-19 during the pandemic stage in MS patients was considered the type of medication.

B-cell depleting agents such as rituximab and ocrelizumab are now widely used in autoimmune diseases such as MS, and they are related to an increased risk of infection.[11] Seven out of 25 patients in this study who had COVID-19 infection were treated with rituximab, whereas none of them needed ICU admission. None of the COVID-19 patients were treated with ocrelizumab in this study.

Reports which are published up to now showed that MS patients who received ocrelizumab had mild COVID-19[12,13] as it was shown previously that patients who were treated with ocrelizumab are not at higher risk of viral infections.[14]

In a previous single-center study in Iran, receiving B-cell depleting therapies increased the risk of COVID-19 suggestive symptoms to 2.6 fold,[15] whereas we found no increased risk (OR = 1.2, 95% CI: 0.46–3.4).

In a study of 60 MS patients who were treated with rituximab or ocrelizumab, Montero-Escribano reported COVID-19 diagnosis in 9 patients, of which, 7 cases were treated with rituximab, and 2 with ocrelizumab.[16] Similar to our findings, they reported fever and cough as the most frequent symptoms. They observed anosmia and ageusia in 33% of their patients, whereas hyposmia and hypogeusia were present in 20% and 12% of our patients, respectively.

As the results show, none of the COVID-19 patients were treated with fingolimod although Foerch *et al*. reported severe COVID-19 in an MS patient under treatment with fingolimod.[17]

During the pandemic stage of COVID-19, medications such as fingolimod, siponimod, ozanimod, ponesimod, and cladribine are considered as medications with intermediate risk of infection, whereas natalizumab and dimethylfumarate are considered as low-risk medications.[18] Although interferons (INFs) and glatiramer acetate are considered as very low-risk medications,[18] 9 out of 25 patients in our survey were treated with these medications, but none of them developed severe disease.

One of the immune-modulator factors which down-regulates proinflammatory cytokines and has a role

**Table 3: Predictors of COVID-19 diagnosis at univariate logistic regression analysis**

| | OR | 95%CI |
|---|---|---|
| Sex | 0.98 | (0.36-2.6) |
| Type of MS | 0.84 | (0.31-2.2) |
| Blood group | 0.84 | (0.61-1.16) |
| Vitamin D consumption | 1.5 | (0.36-6.7) |
| Cardiovascular disease | 5.2 | (1.1-23.7) |
| Hypothyroidism | 2 | (0.75-5.5) |
| Hypertension | 1.4 | (0.34-6.3) |
| Asthma/allergy | 2.4 | (0.82-7.2) |
| Current medication | | |
| B-cell depleting agents | 1.2 | (0.46-3.4) |
| Others | | |

in developing autoimmune diseases is vitamin D.[19] It has been shown to have preventive effects on interstitial pneumonia and decrease the risk of infection.[20,21]Hence, it is supposed that a prophylactic vitamin D supplement may reduce COVID-19 severity as well as acute respiratory distress syndrome (ARDS).[22] As vitamin D deficiency is a risk factor of developing MS and its supplementation may ameliorate the inflammation during the relapse phase and attenuate disease progression, MS patients are recommended to use vitamin D regularly.[23] Based on this, MS patients receiving vitamin D supplementation might develop milder forms of diseases with lower hospitalization rates. In our survey, 11.9% of all MS patients and 8% of MS patients with COVID-19 diagnosis were not receiving vitamin D supplements, and we found no significant association between lack of vitamin D intake and increased risk of COVID-19 infection.

Our findings also showed that most patients, who considered themselves at higher risk of infection, were more serious in performing preventive rules, implementation of home-quarantine and social distancing, and they used masks and gloves in public places, which contributes to lower risk of getting infected with COVID-19.

This study had some strengths. First, our sample size is high and patients from all over Iran had an opportunity to participate. Second, we collected data regarding patient's characteristics, disease, and COVID-19 related factors and determined predictors of infection in MS patients.

## Conclusions

Patients with MS who have cardiovascular disease should be more monitored for COVID-19 infection as they are at higher risk of infection.

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### Conflicts of interest

There are no conflicts of interest.

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