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Original Article

The Severity of SARS-CoV-2 Infection among Patients with Multiple Sclerosis

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ABSTRACT

Background: Neurological disability associated with multiple sclerosis and immunosuppressive or immunomodulatory therapy which is administered for it may increase the risk of SARS-CoV-2 infection and its morbidity/mortality.

In this study, we evaluated the severity of SARS-CoV-2 infection in patients with multiple sclerosis based on their demographic and disease data.

Methods: A total of 1361 multiple sclerosis patients from Fars province were interviewed by phone from April 3 to June 20, 2020. Basic demographic data, information about their disease and any symptoms or laboratory results relevant to COVID-19 were gathered.

Results: Among the studied patients, 68 ones (5%) were COVID-19 suspected cases and 8 ones (0.58%) were in the confirmed group. Five cases in the confirmed group needed hospitalization. Two patients died while both of them were taking rituximab. The frequency rate of suspected cases with RRMS was 57 (87.7%), followed by 5 (7.7%) PPMS and 2 (3.1%) CIS. In the confirmed group, 25% used corticosteroid drug and 50% were on rituximab; moreover, 62.5% of the confirmed cases had a high disability level and needed assistance to walk. In whole, 36.8% of the suspected and 25% of the confirmed cases were on IFN-β1; eventually, all of them recovered well from COVID-19 infection.

Conclusion: In the present study, the rate of developing COVID-19 in multiple sclerosis patients was similar to the general population and most of patients with multiple sclerosis recovered from COVID-19 without referral to a medical specialist.

Keywords: COVID-19, Immunosuppressive, Multiple sclerosis, General population, Immunomodulatory therapy

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Introduction

The management of patients who need to receive immunosuppressive or immunomodulatory drugs should be rapidly changed during the current coronavirus disease 2019 (COVID-19) pandemic. Multiple sclerosis (MS) is a chronic autoimmune inflammatory disorder in which the immune system attacks the myelin and causes progressive disabilities by disruption of neuronal signal propagation (1). Approximately, up to 70% of people with MS receive disease-modifying therapies (DMTs) that influence the immune response. There is also evidence that DMTs second line therapies significantly increase the incidence rate of infection in MS patients compared to the general population (2-4). It seems that immunosuppression therapy combined with neurological disability in MS increases the risk of severe COVID-19 disease and the associated death (5). Treatment with type 1 interferons in MS patients has shown a lower risk of pneumonia (3) and a few published studies have supported the role of type 1 interferons in the potential therapy of COVID-19 infection (6-9). Hence, evaluating not only the risk of Covid-19 but also the severity of the infection in MS patients is an important issue in global healthcare system. Therefore, the demand for data to describe the frequency, morbidity, mortality and, in a word, the evolution of COVID-19 infection in MS patients grows rapidly around the world (10). Some studies have investigated the severity and outcomes of COVID- 19 infection in MS patients (11-14). However, few epidemiological studies with high number of population are now available; accordingly, larger and better-characterized data in population-based studies with sufficient sample size are needed for better interpretation of the results. In the present study, we designed a cross-sectional study on a large group of MS patients to pick up the cases with confirmed or suspected COVID-19 infection and evaluate the effects of that on this particular population compared with normal people. The aim of this cross-sectional study was to determine the severity of COVID- 19 infection in MS patients of southern Iran. Due to the fact that Iran is a country with high prevalence of MS which is rising over time (15) and is high in the number of infection rate or deaths due to COVID- 19 (16, 17), it is hoped that the obtained results from this population-based study will contribute to a deeper understanding of the severity of COVID-19 in MS patients.

Material and Method

This cross-sectional study was approved by Iran National Committee for Ethics in Biomedical Research with the registration number IR.SUMS.REC.1399.26. A total of 1700 patients were contacted by phone from April 3 to June 20, 2020 and 1361 patients agreed to participate in our study. All patients were from Fars province, one of the most affected areas of Iran by covid-19 pandemic. Patients or caregivers answered the questions of the checklist used in this study.

The data included age, sex, city, job, type of MS, the type of current DMT (or no DMT), duration of taking the current DMT, information about comorbidities, history of medications other than DMT, disability level based on a self-defined scoring scale (score =1- 6), history of close contact with a confirmed COVID-19 case or with someone who had respiratory symptoms during the past 14 days. Additional information was also taken into account including (a) confirmed infection by positive real-time reverse transcription polymerase chain reaction (rRT-PCR) checked by oropharyngeal swab or a positive chest computed tomographic (CT) scan; (b) suspected infection by showing one of the clinical signs of covid-19 infection after the February 20, 2020, such as cough, fever, shortness of breath, loss of taste or smell or one of these signs plus another symptom such as sore throat, dyspnea, body pain, headache, muscle pain, or diarrhea; and (c) severity of disease by duration of symptoms, referral or non-referral to a medical specialist, hospitalization in ward or intensive care unit ICU), and patient death.

We considered MS patients in three case groups: 1- Suspected COVID-19 case [any patient meeting the clinical symptoms without diagnostic imaging or laboratory criteria (rRT-PCR)]; 2- Confirmed COVID-19 case (any patient meeting the clinical symptoms plus confirmed rRT-PCR- or a positive (CT) scan); and 3- Healthy case (any patient without any clinical symptoms of COVID-19 infection). We estimated the occupational risk factors of MS patients for COVID-19 infection based on the frontline published on April 15, 2020 by Marcus Lu (18). The patient's job was categorized into three groups of low, intermediate, and high risk jobs.

Because we had to determine the degree of disability of the patients by phone, it was not possible to use the Extended Disability Status Scale (EDSS). We categorized the MS patients according to self-defined scoring into the following groups: 1= Able to walk more than 500 meters without aid, 2= Able to walk less than 500 meters, 3= Restricted to stick, 4= Restricted to walker, 5= Restricted to wheelchair, and 6= Restricted to bed. MS patients with a score of three or higher, which require assistance to walk, were considered in another group.

Statistical package for social sciences (SPSS Inc., Chicago, IL, USA), version 22, was used for data analysis and $P < 0.05$ was considered as statistical significance. One-way ANOVA and Chi-square were used for detection of significant differences in the clinical characteristics, demographic features, and the frequency of COVID-19 symptoms among the healthy, suspected and confirmed cases.

Results

A total of 1361 MS patients participated in this research (Table 1) of whom, 77% were female with a mean age and SD of 38.48 ± 9.40 year. From all, 1171 (86.6%) patients were from Shiraz and 190 (14 %) were from other provincial cities. Most patients (95.1%) had a job with low risk for COVID-19 and 1.6% had a high-risk job, based on what was described in the method section. In whole, 85.5% of MS patients had RRMS and 87.6% of all the respondents received one of the DMTs. The frequency of the prescribed DMTs was as follows: rituximab 27.7%, IFN-β 26.9%, fingolimod 12.3%, dimethyl fumarate (DMF) 9.0%, GA 7.2%, teriflunomide 1.8%, natalizumab 1.2%, and 74.5% of patients had been treated for more than three months. The most frequency of comorbidity in MS patients was hypothyroid disease (6.31%) followed by hypertension (4%) and cardiovascular diseases (3%), respectively. The frequency of the prescribed drugs other than DMT was as follows: levothyroxine 4.84%, corticosteroid 3.7% and antihypertensive 3.8%. In terms of disability, 89.8% of all respondents had a disability scale less than 3 that required no assistance to walk.

The following flowchart shows the severity of COVID-19 infection in MS patients with clinical presentation of mild, moderate, and sever forms of coronavirus disease.

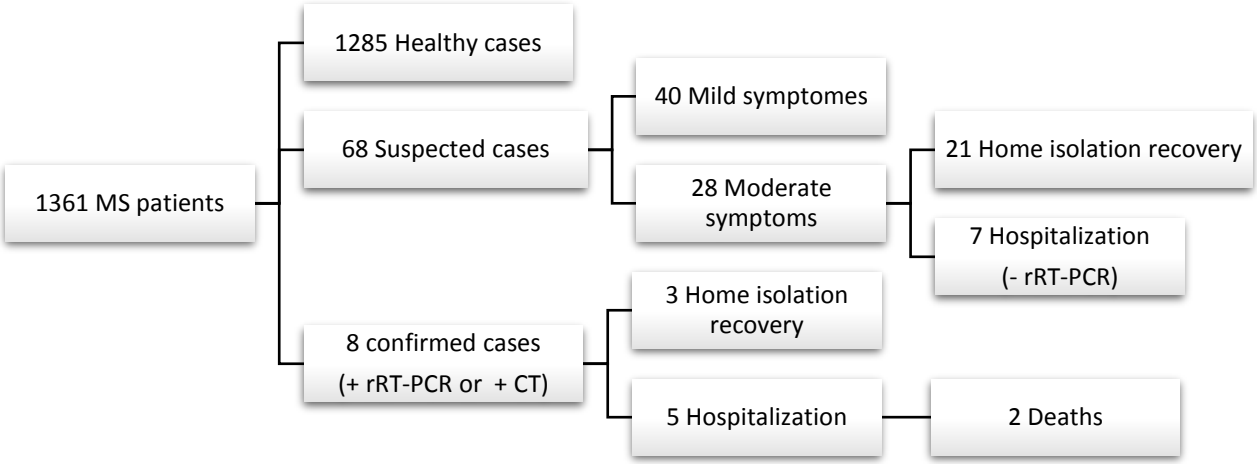

Figure 1. Flowchart of the clinical presentation of mild, moderate, and sever forms of coronavirus disease in the study population

As it is seen in Fig.1, out of 1361 patients, 68 (5%) were suspected cases; these patients were qualified by at least two reported defining symptoms of COVID-19 infection, and 8 ones (0.58%) of all MS patients with positive RT-PCR or chest CT were in the confirmed group. Forty out of 68 patients improved by staying home without medical attention and 28 patients referred to the physician due to their pulmonary symptoms, 21 were recommended to stay home and monitor the severity of the symptoms, and 7 patients showed severe clinical symptoms that required hospital admission with negative test and were discharged after 3 days of hospitalization. Three cases had positive PCR test without hospitalization; however, 5 cases

had positive RT-PCR or CT results and needed hospitalization due to the severity of pulmonary symptoms and shortness of breath, and 3 of them did not require ICU care or intubation and were eventually discharged from the hospital. In addition, 2 of the confirmed cases died, while both of them were female and had PPMS with relatively high disability score; one was bed-restricted and the other one had history of diabetes and hypertension. She was able to walk without assistance no more than 500 meters. In both patients, the administered DMT was rituximab.

The demographic, clinical, and disease characteristics of COVID-19-suspected, confirmed, and healthy cases are summarized in Table 1. We observed a significant difference ($p < 0.001$) in the frequency rate of MS types between the groups. The frequency rate of the suspected cases was 57 RRMS (87.7%), followed by 5 PPMS (7.7%) and 2 CIS (3.1%) respectively. In the confirmed group, 3 (37.5%) had relapsing remitting multiple sclerosis (RRMS) and 4 (50%) had primary progressive multiple sclerosis (PPMS).

Table 1. Demographic, clinical characteristics and COVID-19 symptoms of all MS patients, suspected, confirmed, and healthy cases

		All MS patients 1361	**COVID-suspected cases N=68**	**COVID-confirmed cases N=8**	**Healthy cases N=1285**	**P**
Demographic	Age	38.48±9.40	37.43±7.90	43.62±7.90	38.49±9.44	0.20
	Sex (Female)	1048 (77.0%)	48 (70.6%)	5 (62.5%)	995 (77.4%)	0.26
City	Shiraz	1171(86.0%)	55 (80.9%)	5 (62.5%)	1111 (86.5%)	0.068
	Another City	190 (14.0%)	13 (19.1%)	3 (37.5%)	174 (13.5%)	
Job	Low Risk	1177 (95.1%)	60 (96.8%)	4 (50.0%)	1113 (95.0%)	0.86
	Intermediate Risk	41 (3.3%)	2 (3.2%)	0	39 (3.3%)	
	High Risk	20 (1.6%)	0	0	20 (1.7%)	
MS type	RRMS	1157 (85.5%)	57 (87.7%)	3 (37.5%)	1097 (85.6%)	<0.001*
	SPMS	80 (5.9%)	1 (1.5%)	0	79 (6.2%)	
	PPMS	84 (6.2%)	5 (7.7%)	4 (50.0%)	75 (5.9%)	
	Cis	9 (0.7%)	2 (3.1%)	0	7 (0.5%)	
	Unknown or not Reported	24 (1.8%)	3 (4.4%)	1 (12.5%)	23 (1.8%)	
DMT, n (%)	Interferon Beta-1	366 (26.9%)	25 (36.8%)	2 (25.0%)	339 (26.4%)	0.16
	Glatiramer Acetate	98 (7.2%)	5 (7.4%)	0	93 (7.2%)	0.73
	Dimethyl Fumarate	122 (9.0%)	8 (11.8%)	0	114 (8.9%)	0.48
	Teriflunomide	25 (1.8%)	1 (1.5%)	0	24 (1.9%)	0.90
	Rituximab	377 (27.7%)	8 (11.8%)	4(50.0%)	365 (28.4%)	0.004*
	Natalizumab	17 (1.2%)	0	0	17 (1.3%)	0.60
	Fingolimod	168 (12.3%)	11 (16.2%)	0	157 (12.2%)	0.35
	No DMT	166 (12.4%)	10 (14.7%)	2 (25%)	158 (12.5%)	
Drug Duration	Longer Than 3 months	1014 (74.5%)	48 (70.6%)	4 (50.0%)	962 (74.9%)	0.33
	Shorter Than 3 months	57 (4.2%)	3 (4.4%)	0	54 (4.2%)	
	Not on DMT or Not Answered	290 (21.3%)	17 (25.0%)	4 (50.0%)	269 (20.9%)	
Comorbidities	Hypertension	54 (4.0%)	4 (5.9%)	1 (12.5%)	50 (3.9%)	0.34
	Diabetes	23 (1.7%)	1 (1.5%)	1 (12.5%)	22 (1.7%)	0.068
	Hypothyroidism	86 (6.31%)	6 (9.4%)	0	80 (6.4%)	0.017*
	Hyperthyroidism	4 (0.3%)	2 (2.9%)	0	2 (0.2%)	<0.001*
	Pulmonary disease	16 (1.2%)	3 (4.4%)	0	13 (1.0%)	0.038*
	Cardiovascular	41 (3.0%)	6 (8.8%)	1 (12.5%)	34 (2.6%)	0.004*
	Malignancy	4 (0.3%)	0	0	4 (0.3%)	0.88
Other Drugs	Antihypertensive	52 (3.8%)	4 (5.9%)	0	48 (3.7%)	0.56
	Corticosteroids	50 (3.7%)	2 (2.9%)	2 (25.0%)	46 (3.6%)	0.005*
	Cardiovascular	47 (3.5%)	6 (8.8%)	0	41 (3.2%)	0.040*
	Immunosuppressant	17 (1.3%)	0	0	17 (1.3%)	0.60
	Antihyperglycemic	20 (1.5%)	1 (1.5%)	0	19 (1.5%)	0.94
	Propranolol	19 (1.4%)	5 (7.35%)	0	14 (1.1%)	0.001*
	Bisoprolol	1 (0.07%)	0	0	1 (0.07%)	0.97
	Atorvastatin	13 (0.95%)	0	0	13 (1.01%)	0.67
	Metoprolol	3 (0.22%)	0	0	3 (0.25%)	0.91
	ASA	11 (0.80%)	0	0	11 (0.9%)	0.72

Table 1. Demographic, clinical characteristics and COVID-19 symptoms of all MS patients, suspected, confirmed, and healthy cases

	Nitrocontin	1 (0.07%)	0	0	1 (0.07%)	0.97
	Clopidogrel	1 (0.07%)	0	0	1 (0.07%)	0.97
	Carvedilol	1 (0.07%)	0	0	1 (0.07%)	0.97
	Warfarin	2 (0.14%)	1 (1.5%)	0	1 (0.07%)	0.014*
	Gemfibrozil	2 (0.14%)	0	0	2 (0.15%)	0.94
	Rosuvastatin	1 (0.07%)	0	0	1 (0.07%)	0.97
	levothyroxine	66 (4.84%)	2 (2.95%)	0	64 (5%)	0.60
	Methimazole	2 (0.14%)	0	0	2 (0.15%)	0.94
	Prednisolone	47 (3.50%)	2 (2.95%)	1(25%)	12 (1.1%)	0.003*
	Hydrocortisone	1 (0.07%)	0	0	1 (0.07%)	0.97
	Dexamethasone	1 (0.07%)	0	0	1 (0.07%)	0.97
	Betamethasone	2 (0.14%)	0	0	12 (1.1%)	0.94
Disability	6= Bed -restricted	15 (1.1%)	1 (1.6%)	2 (25.0%)	12 (0.9%)	<0.001*
	5= Wheelchair-	30 (2.2%)	0	3(37.5%)	27 (2.1%)	
	4= Walker-	37 (2.7%)	1 (1.6%)	0	36 (2.8%)	
	3= Stick-	59 (4.4%)	2 (3.2%)	0	57 (4.5%)	
	2= Walk less than 500 m	253 (18.8%)	11(17.5%)	0	242 (19.0%)	
	1= Walk more than 500 m	952 (70.6%)	48 (76.2%)	3 (37.5%)	901 (70.6%)	
	3 or more	84 (6.2%)	4 (6.4%)	5 (62.5%)	77 (6.0%)	
	Less than 3	1264 (93.8%)	59 (93.6%)	3 (37.5%)	1200 (94.0%)	
	Fever	28 (2.1%)	24 (35.3%)	4 (50.0%)	0	<0.001*
	Chills	17 (1.2%)	15 (22.1%)	2 (25.0%)	0	<0.001
	Dry Cough	30 (2.2%)	27 (39.7%)	2 (25.0%)	1(0.1%)	<0.001
	Sore Throat	30 (2.2%)	28 (43.8%)	2 (25.0%)	0	<0.001
	Dyspnea	21 (1.5%)	15 (22.1%)	5 (62.5%)	1(0.1%)	<0.001
	Body Pain	21 (1.5%)	19 (27.9%)	2 (25.0%)	0	<0.001
COVID-19	Headache	10 (0.7%)	10 (15.6%)	0	0	<0.001
Symptoms	Muscle Pain	9 (0.7%)	6 (8.8%)	2 (25.0%)	1(0.1%)	<0.001
	Diarrhea	2 (0.1%)	2 (2.9%)	0	0	<0.001
	Loss of Taste	1 (0.1%)	1(1.6%)	0	0	<0.001
	Loss of Smell	1(0.1%)	1 (1.6%)	0	0	<0.001
	Decreased LOC	4 (0.3%)	3 (4.4%)	1(12.5%)	0	<0.001
	History of contacts	4 (0.3%)	3 (4.4%)	1(12.5%)	0	<0.001*

MS: multiple sclerosis, RRMS: Relapsing-remitting multiple sclerosis, SPMS: Secondary-progressive multiple sclerosis, PPMS: primary progressive multiple sclerosis, CIS: clinically isolated syndrome, DMT: disease-modifying treatment, LOC: loss of consciousness. Chi-square and ANOVA tests.

Additionally, we found significant differences in the frequency rate of MS patients' comorbid condition such as hypo- and hyper-thyroidism, cardiovascular, and pulmonary diseases among the 3 groups. Moreover, we found that in the confirmed group, MS patients with a history of high blood pressure, diabetes, and CVD had the same frequency rate (12.5%).

Another significant difference was detected in the frequency rate of MS patients who used corticosteroid and CVD drugs in the 3 groups ($p= 0.005$ and $p = 0.04$, respectively). In whole, 25% of the patients in the confirmed group had used corticosteroid drug.

Moreover, 62.5% of the confirmed cases had disability score of 3 or more that required assistance to walk. Moreover, bed-ridden or wheelchair-bound cases increased significantly in the confirmed group (25% and 37.5%, respectively).

There were no significant differences between healthy, suspected, and confirmed cases in demographic information, DMT types, and duration of treatment. In regard to sex, 62.5% of the patients in the confirmed group and 70.6% in the suspected group were female. The mean age of MS patients in the confirmed group was higher than that in the healthy and suspected groups, but it was not statistically significant ($p=0.2$). In addition, our results showed that most of the patients (36.8%) in the suspected group were on IFN β-1a, while patients treated with teriflunomide had the lowest chance of being in the COVID-19 suspected group (1.5%) and 50% of the confirmed cases were treated with rituximab.

Additional results showed that 50% of the confirmed cases and 35.3% of the suspected cases had fever ($p < 0.001$), and most patients in the suspected group reported sore throat (43.8%) or dry cough (39.7%). History of contact with a case with fever or cough or shortness of breath showed a significant difference in the 3 groups ($p < 0.001$).

Discussion

In this study, we evaluated the severity of COVID-19 among MS patients in Fars province. According to the prior reports, the incidence rate of respiratory infections in MS patients may be higher than that in the normal population. In addition, second line therapies showed a higher rate of infection compared to the injectable first line medications (2, 3, 19). It is probable that the prevalence of COVID-19 in MS patients be more than that in the normal population. However, the recent studies showed that the frequency rate of COVID-19 infection in MS patients was not different from the incidence of COVID-19 in the general population. In our study, only 5% of all respondents showed signs of the COVID-19 infection that was similar to the prevalence of COVID-19 reported in the general population (20).Two of our studied patients were in a critical situation in ICU and eventually died. Sormani *et al*. in a study on COVID-19 infection in Italian MS patients categorized the symptomatic MS patients as mild (96%), severe (2%), and critical (3%) with one of the critical patients being recovered and five deaths (12). Fan *et al.* reported 1804 MS patients with DMT; none had COVID-19 infection (13). An Iranian study group in Tehran reported mild to moderate output of COVID-19 infection in MS patients. Only two cases needed hospitalization without ICU care and they showed that the susceptibility might increase in patients who were on B-cell depleting agents (11). In Sahraian *et al.* study, the frequency rate of COVID-19 infection in MS patients was not higher compared to the general population; however, 25% of the confirmed cases needed to be hospitalized, which is far more than the hospitalization rate in the general population (21).

Most of MS patients in our study were relatively young females who had low risk job for covid-19 infection (95%). Data collected from many countries suggested a higher risk of severe illness and death in men (22). As it was reported in the other study, we think the self-isolation and social distancing guidelines are stringently followed by MS patients and they have a good knowledge about this viral infection and its prevalence. Therefore, this experience caused a lower incidence of COVID-19 infection in this group compared to the general population (23).

In the present study, 2 (100%) of the critical cases or 25% of the confirmed cases died. In Sormani *et al.* study, 5 (83.3%) of the critical cases or 8.77% of the confirmed cases in ICU died. However, the fatality rate of general population with positive test (n=440) in Fars province has been 13 cases (2.95%) during one month of the first pandemic wave (24). In this survey, the high rate of mortality in the confirmed MS patients may be related to some influencing factors like the low number of PCR tests performed on people and comorbid conditions like diabetes and hypertension. Previous studies suggested that the risk of hospitalization and mortality rate were higher in MS patients with comorbid conditions (25, 26).

In our study, two patients who died had PPMS and were on rituximab. One of them was bed-restricted and another could walk less than 500 meters. Results showed that patients who were on rituximab, as compared to patients on other DMTs, had a higher frequency for being categorized in the COVID-19 confirmed group (50%). In our study, two patients who needed ICU care and intubation were on rituximab and eventually died. In Safavi *et al.* (2020) study, only two suspected patients required hospitalizations, while both of them were on a B cell depleting agent (Rituximab, Ocrelizumab) and eventually both recovered (11). This result is in agreement with Sormani and Quinti's (2020) findings (12, 27). Increase in the risk of COVID-19 in patients receiving rituximab therapies has been also reported by Sahraian *et al.* (21). In the current study and Sahraian's report, two MS patients who died were rituximab users and also had underlying diseases. However, further studies are needed to understand the role of rituximab in the deaths of these patients. Rituximab and ocrelizumab can increase the risk of infections by elimination of a large portion of circulating B-cells and impairment of the humoral immune response (2). Therefore, MS patients treated with these agents might be more susceptible to COVID-19 infection.

According to a previous report, antiviral properties of IFN-β1 may diminish the severity of COVID-19 (28). It is possible that patients who were treated with IFN-β1 were protected from the infection. Our results showed that 36.8% of the suspected cases and 25% of the confirmed group were on IFN-β1 and eventually recovered well from COVID-19 infection.

The MS type was also detected to be associated with the risk of developing COVID-19, and its frequency rate was significantly higher among PPMS patients. Since these patients may not have normal physical activity

and their presence in the community is limited, it seems the frequent close contacts with symptomatic or confirmed patients was not the main cause of their infection. The high rate of comorbid condition, type of DMT, and corticosteroid therapy may increase the susceptibility to infection.

Strengths and Limitations

This study was performed with a large sample size in non-hospitalized MS patients which is a better indicator of the society. However, it has some limitations, such as (a) provision of the medical information of patients by phone which caused the possibility of intentional or inadvertent errors; (b) over- or under-estimations of the suspected cases due to the lack of PCR testing for COVID-19 infection in all of the suspected patients or those who have had symptoms for more than two weeks, or infection with very mild gastrointestinal symptoms and (c) impossibility of estimating the Expanded Disability Status Scale (EDSS) over the phone.

Conclusion

The present study showed that the rate of developing COVID-19 in MS patients was similar to the general population and most MS people were recovered from COVID-19 without referral to a medical specialist.

Conflict of interest

The authors have declared no conflict of interest.

Acknowledgment

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