Journal of Vessels and Circulation
Qom University of Medical Sciences
Autumn 2022. Volume 3. Number 4

Research Paper

Investigation of the Risk Factors of COVID-19 Seropositivity and Symptomatic COVID-19 in Patients With Multiple Sclerosis

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Please cite this article as Hejazi SA, Aghaali M, Seyyedabadi SM, Paybast S. Investigation of the Risk Factors of COVID-19 Seropositivity and Symptomatic COVID-19 in Patients With Multiple Sclerosis. J Vessel Circ. 2022; 3(4):165-172. http://dx.doi.org/10.32598/JVC.3.4.74.3

doi: http://dx.doi.org/10.32598/JVC.3.4.74.3

Article info:
Received: 13 Mar 2023
Accepted: 17 Jul 2023
Publish: 31 May 2023

Keywords:
Multiple sclerosis, Seroprevalence, Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), COVID-19

ABSTRACT

Background and Aim: In the current situation of the COVID-19 pandemic, patients with multiple sclerosis (MS) represent a population of particular interest because they may be at higher risk of contracting COVID-19. The present study aims to determine the risk factors of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) seropositivity and symptomatic COVID-19 in MS patients, in Qom Province, Iran.

Materials and Methods: In this cross-sectional study, 486 patients diagnosed with MS were included in the study. First, the demographic characteristics of patients were collected. Then, the patients underwent serology tests for anti-SARS-CoV-2 immunoglobulin G (IgG) antibodies. Later, the risk factors for SARS-CoV-2 seropositivity and symptomatic COVID-19 were assessed. Finally, SPSS software, version 22 was used to analyze the data.

Results: Fifty-five patients (11.8%) were seropositive for SARS-CoV-2 immunoglobulin G (IgG), of whom 25% were symptomatic. The results showed a significant difference between the seropositive and seronegative groups in terms of MS type and comorbidity. Further, comorbidities, including hypertension and hypothyroidism were identified as the major risk factors for developing symptomatic disease. However, none of the variables were statistically associated with the severity of COVID-19.

Conclusion: The present study revealed a significantly lower seroprevalence of COVID-19 in MS patients than in the population. Based on the results, most seropositive patients were asymptomatic. Comorbidity was identified as the major risk factor for both SARS-CoV-2 seropositivity and symptomatic COVID-19. However, no relationship was observed between patients' characteristics and MS features with the severity of COVID-19, which reinforces the continuation of regular treatment during the COVID-19 pandemic.

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1. Introduction

Since the emergence of COVID-19 disease in Wuhan City, China, many attempts have been made to control the pandemic, of which massive vaccination has been of paramount importance. However, the pandemic persists and challenges the world's health systems [1]. In the current situation of the COVID-19 pandemic, patients with multiple sclerosis (MS) represent a population of particular interest because they may be at higher risk of infections due to immunosuppressive or immunemodulatory agents' administration [2]. Although the preliminary studies indicated that the patients with B-cell-depleting therapies were more likely to develop severe COVID-19, others did not support the negative association between the disease-modifying treatment (DMT) class and COVID-19 susceptibility [3-7]. Regarding the National MS Society guidelines, DMT decisions should be individualized and made collaboratively between the patient and the healthcare provider [8].

On the other hand, a large number of COVID-19-positive cases are asymptomatic or mildly symptomatic, making it difficult to estimate the confirmed prevalence of COVID-19. As the extent of circulating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remains unclear, serology tests may help determine whether a person has been exposed to SARS-CoV-2 in the past [9].

To the best of our knowledge, COVID-19 seroprevalence in the MS population is not reported, which may play a crucial role in identifying the risk factors for both symptomatic and asymptomatic COVID-19. Given the uncertainty about the risk factors of COVID-19 and its complications in MS patients, and the perpetual need to continue the DMTs, the present study was conducted to determine the seroprevalence of COVID-19 in MS patients in the pre-vaccination era, in Qom Province, Iran, with a focus on the predisposing factors for symptomatic COVID-19.

2. Materials and Methods

Study designs

This cross-sectional study was conducted at the MS Clinic of Qom Province, Iran, between July and August 2020. Additionally, all patients fulfilled the informed consent before they participated in this study.

Study population

All patients diagnosed with MS based on McDonald Criteria 2017, and aged over 18 years, who were referred to the MS clinic, were included in the study. Patients who were pregnant or in the postpartum period, patients who received COVID-19 vaccination, and those who did not consent to participate were excluded. Eventually, 468 patients met the eligibility criteria.

Data collection

First, in face-to-face interviews with patients, the following information was collected, demographic data, disease characteristics, including disease duration, type of MS, consumed DMT, clinical status based on the expanded disability severity scale score (EDSS), date of recent relapse and corticosteroid therapy. Then, the patients were divided into two groups, patients with a history of COVID-19 which was confirmed by polymerase chain reaction assays, and patients without a clear history of COVID-19. In the first group, the severity of COVID-19 was classified into mild, moderate, severe, and critical based on the recommendations of the World Health Organization (WHO).

Immunoassay for detection of SARS-CoV-2 immunoglobulin G (IgG)

All patients underwent serology tests for IgG antibodies against SARS-CoV-2 at the end of the interview. IgG levels were tested by chemiluminescent immunoassay (CLIA) Kits (Food and Drug Administration [FDA] approved), manufactured by Pishtaz Teb Company (Catalog No.Pt.Covid.100) in Tehran Province, Iran. The sensitivity and specificity of the kits were estimated to be 97% and 95%, respectively. The cut-off for positive IgG level was determined as >1.1 binding antibody units (BAU/mL).

Statistical analysis

Statistical analysis was performed using SPSS software, version 22. Data were expressed as Mean±SD for quantitative variables and counts (%) for categorical variables. One-sample Kolmogorov-Smirnov test, chi-square test, and Mann-Whitney U statistical test were used for data analysis, and an ordinal regression model was used to evaluate the relationship between the patient and disease characteristics, and severity of COVID-19.

3. Results

Patient population

In our cross-sectional study, 468 MS patients between July–August 2020 participated. A total of 373 patients (79.7%) were women with a mean age of 37.60±8.64 years. Most patients (77.6%) had an EDSS score ≤2(0 to 8 score) with a mean score of 1.61. Relapse remitting MS (RRMS) was found as the most frequent MS type in all patients (58.7%). The mean duration of the disease was (6.5±30.9) years. Approximately, 25% had one or more comorbidity, with hypothyroidism being the most frequently reported. Moreover, comorbidities were more common in elder patients.

Seroprevalence of SARS-CoV-2 IgG

Based on the results, 55 patients (11.8%) were seropositive for SARS-CoV-2 IgG as shown in Table 1. The patients in the seropositive and seronegative groups were similar in sex, age, history of recent corticosteroid therapy, and EDSS score (P=0.310, P=0.396, P=0.411, and P=0.823). While the mean age and disease duration were higher in the seropositive group, no significant relationship was observed between age and disease duration with SARS-CoV-2 IgG status (P=0.396 and P=0.919). Moreover, a considerable difference was observed between SARS-CoV-2 seropositive and seronegative groups in terms of MS type (P=0.04) and comorbidity (P=0.008). Secondary progressive MS (SPMS) and hypertensive patients were more susceptible to SARS-CoV-2 seropositivity.

Table 1. Clinical characteristics of seropositive and seronegative severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in patients with MS

Variables		Mean±SD/No. (%)		P
		SARS-CoV-2 IgG Level (BAU/mL)		
		Positive	Negative	
Age (y)		38.53±5.65	37.47±8.65	0.396†
Gender	Male	13(23.6)	82(19.9)	0.310‡
	Female	42(76.4)	331(80.1)	
Recent relapse or corticosteroid therapy	Yes	8(14.5)	70(16.9)	0.411‡
	No	47(85.5)	343(83.1)	
Type of MS course	CIS	1(1.8)	1(0.2)	0.044‡
	RRMS	41(74.5)	234(56.6)	
	SPMS	9(16.4)	131(31.7)	
	PPMS	4(7.3)	47(11.4)	
EDSS mean score ranges (0-8)		1.43	1.81	0.823‡
Disease duration (d)		9.38±5.92	9.29±5.98	0.919†
Comorbidity (HLP, DM, HTN, hypothyroidism)		14(25.5)	101(24.5)	0.008‡

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Abbreviations: SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; MS: Multiple sclerosis; CIS: Clinically isolated syndrome; RRMS: Relapse remitting multiple sclerosis; SPMS: Secondary progressive multiple sclerosis; PPMS: Primary progressive multiple sclerosis; EDSS: Expanded disability status scale; DM: Diabetes mellitus; HLP: Hyperlipidemia; HTN: Hypertension.

†Mann-Whitney U, ‡Chi-square.

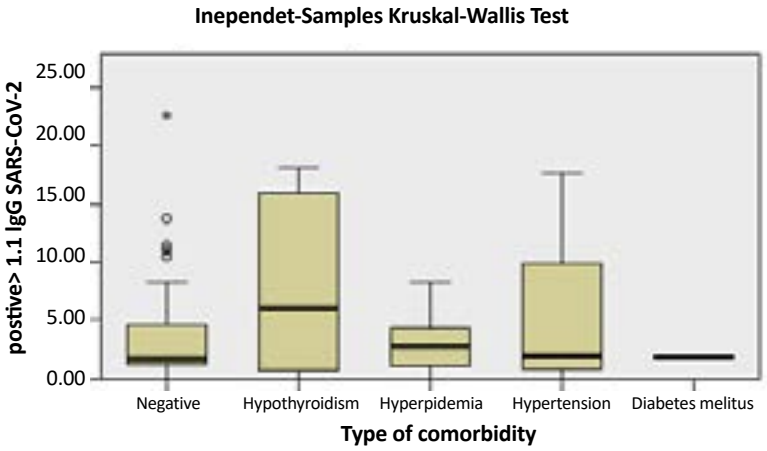

Figure 1. Distribution of comorbidities in seropositive MS patients for SARS-CoV-2

The frequency of distribution on the comorbidities is shown in independent–samples Kruskai Wallis test (Figure 1).

However, a difference in DMT type was seen in seropositive patients, as patients treated with interferon β (INF-β) exhibited lower levels of SARS-CoV-2 antibodies in independent–samples Kruskai Wallis test (Figure 2).

The Table 2 presents the medication history of patients. Of the overall sample, 449(95.94%) used DMT, the most common of which were INF-β (41.4%) and rituximab (20.1%), respectively. The type of DMT was not associated with SARS-CoV-2 seropositivity (P=0.283) (Table 2).

Risk factors of symptomatic COVID-19

The results indicated a 25% chance of being symptomatic in seropositive patients. Except for the pre-existing comorbidity (P=0.016), none of the variables included age (P=0.643), sex (P=0.238), MS type (P=0.510), EDSS score (P=0.319), and DMT type (P=0.754) were associated with an increased risk of symptomatic disease.

Severity of COVID-19

A sensitive analysis revealed that 113 patients had a history of symptomatic COVID-19, of whom 30 were SARS-CoV-2 seropositive. Most patients experienced

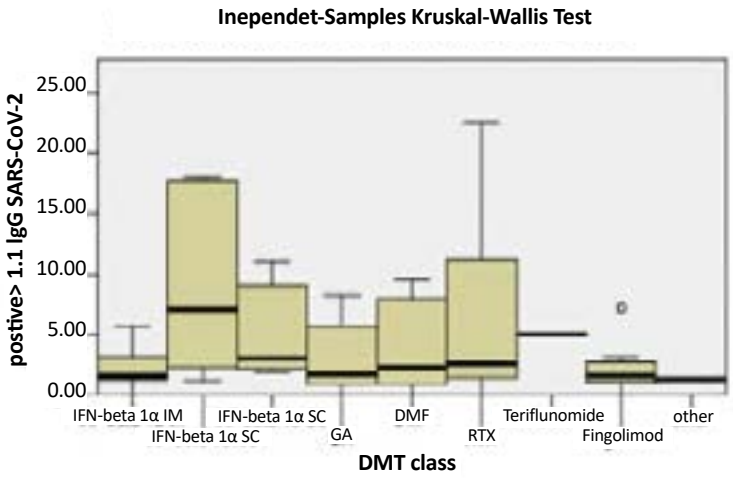

Figure 2. Distribution of DMT class in seropositive MS patients for SARS-CoV-2

Abbreviations: DMT: Disease-modifying treatment; MS: Multiple sclerosis; SARS CoV 2: Severe acute respiratory syndrome Cov2; IFN-beta 1α IM: Interferon-β 1α intramuscular; IFN-beta 1α SC: Subcutaneous; GA: Glatiramer acetate; DMF: Dimethyl fumarate; RTX: Rituximab.

Table 2. The DMT medication of MS patients and association between severe acute respiratory SARS-CoV-2, IgG level and DMT category (Ordinal regression model)

SARS-CoV 2 IgG Level	No. (%)											P
	Disease Modifying Treatment (DMT)											
	INF β 1a IM Injection	INF β 1a SC Injection	INF β 1b SC Injection	Glatiramer Acetate	DMF	Teriflunomide	Fingolimod	Natalizumab	Mitoxantrone	Rituximab	Ocrelizumab	
Positive (n=55)	15(27.27)	6(10.90)	4(7.27)	4(7.27)	5(9.09)	1(1.81)	8(14.54)	0	0	12(21.81)	0	0.283
Negative (n=413)	102(24.69)	55(13.31)	14(3.38)	51(12.34)	36(8.71)	7(1.69)	60(14.52)	1(0.24)	0	83(20.09)	0	

Abbreviations: DMT: Disease-modifying treatment; MS: Multiple sclerosis; SARS CoV 2: Severe acute respiratory syndrome Cov2; IFN-β 1α IM: Interferon-β 1α intramuscular; IFN-β 1α SC: Subcutaneous; DMF: Dimethyl fumarate.

mild to moderate COVID-19. Only three people had severe COVID-19, and one of them had critical COVID-19. Among patients with severe COVID-19, two men were with a mean age of 40 years old, and a mean EDSS score of 1.75. Two RRMS patients were treated with INF-β, and one PPMS patient was treated with rituximab. The person with critical COVID-19 was a 42-year-old man who was otherwise healthy and was being treated with INF-β. He was initially admitted to the intensive care unit (ICU) and received the standard of care for COVID-19 with mechanical ventilation for 10 days. Then, he was transferred to the infectious ward for 20 days to continue treatment. Although he did not develop a clinical relapse, his neurological status worsened with an increase in EDSS score from 2 to 4.5 at the time of discharge.

Moreover, all patients with mild and moderate COVID-19 underwent home quarantine and contacted their physicians to adjust their medications.

Based on the results, none of the variables, including age (P=0.972), sex (P=0.385), comorbidity (P=0.213), MS type (P=0.566), disease duration (0.190), recent corticosteroid therapy (P=0.649), EDSS score (P=0.138) and DMT category (P=0.421) were statistically associated with the severity of COVID-19 symptoms.

4. Discussion

Prevalence of COVID-19

The results of the present study indicated an estimated seroprevalence of 11.8% in MS patients which was significantly lower than the report of 58.5% in the population of Qom Province, Iran [10]. Similarly, another study demonstrated a significantly higher prevalence of SARS-CoV-2 antibodies in MS patients compared to high-risk populations (2.9% vs. 10.6%) [11, 12]. It is assumed that the difference in the values of our data may be related to the different serology tests used in these studies (chemiluminescent immunoassay [CLIA] compared to enzyme-linked immunosorbent assay [ELISA] and fluorescence immunoassays [FIA] methods). On the other hand, 25% of the seropositive patients developed symptomatic COVID-19, which was relatively comparable to the population, according to the previous reports [13, 14].

Previous studies have revealed that MS patients, regardless of their treatment, are theoretically at higher risk for infections than the population [15]. However, the lower prevalence of COVID-19 in our study may be covered by several factors. First, a substantial number of patients were women and young without serious comorbidities. Second, MS patients were more likely to adhere to strict quarantine and social distancing guidelines [4]. Third, most patients (41.6%) used INF-βs. The role of INFs in both an autocrine and paracrine manner has been shown to activate the Janus kinase signal transducer and activator of transcription signaling pathway, leading to downstream expression of IFN-stimulated genes, and as a result, contributes to control the viral infection. Moreover, INFs are well-recognized as crucial immunomodulatory cytokines for the development of the adaptive immune response to infection. Considering this and the promising results from several clinical trials on the beneficial effect of INFs on COVID-19 outcomes, the use of

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INF-βs in MS patients appears to have a fairly inhibitory role against some SARS-CoV- 2 products [15, 16].

Risk factors of COVID-19

Based on the results, comorbidity (P=0.008) and MS type (P=0.044) were identified as the risk factors for SARS-CoV-2 seropositivity. SPMS patients and hypertensive patients were more susceptible to SARS-CoV-2 seropositivity.

In a similar pattern, comorbidity was recognized as the major risk factor for symptomatic COVID-19. Comorbidity was identified as a risk factor for acquiring COVID-19, as epidemiological evidence has shown its role in both the incidence and severity of COVID-19 [13, 17]. We postulated that the lack of significant association between age and sex with COVID-19 may be related to the relatively younger age, and the predominant female gender in our participants, which both resulted in selection bias.

In addition, our results did not demonstrate a negative effect of the DMT type on both SARS-CoV-2 seropositivity and symptomatic COVID-19. However, patients treated with INF-β particularly have lower levels of SARS-CoV-2 antibodies, which may indicate an immunogenic role of INF-β. In some DMTs, it is well-known to be associated with an increased risk of infections, of which B-cell-depleting agents are of great importance. There are conflicting results in the literature on the role of B-cell-depleting agents in the development of COVID-19. While some studies reported a higher prevalence of COVID-19 in patients treated with B-cell-depleting agents [4, 6, 18], others did not support this negative association [3, 5, 19-21]. Noteworthy, recent meta-analyses did not demonstrate whether a specific DMT significantly modifies the progression of SARS-CoV-2 in the MS population [22, 23]. However, interpretation of our results should be made with extreme caution. Patients with mild to moderate COVID-19 participated more in this study. Consequently, the small number of patients with severe COVID-19 limited the possibility of accurate conclusions.

Severity of COVID-19

In the present study, most patients had mild COVID-19, and the rate of hospitalization was 7.27%, which was similar to the global statistics in the general population. However, reports indicated either a higher incidence of mild COVID-19 [3, 5, 20] or a lower incidence (70%-80%) [4, 6, 11]. Moreover, the results did not demonstrate a significant relationship between demographic and MS characteristics, and the DMT category with the severity of COVID-19 (P>0.05).

Inconsistent results for the prognosis of COVID-19 in the MS population may be related to factors, such as differences in the sample size, study design, endemic disease status, socioeconomic status, and health in different studies. Consistent with a recent meta-analysis [22], our data did not suggest a significant increase in the mortality of MS patients with COVID-19. In addition, our results did not identify an even poorer prognosis in patients treated with B-cell-depleting agents, which appears to be related to the small sample size of our severe COVID-19 patients.

5. Conclusion

The present study revealed that the seroprevalence of COVID-19 in MS patients was significantly lower than in the population in Qom Province, Iran. Moreover, a 25 % chance existed to developing symptomatic COVID-19 in seropositive patients. Comorbidity was identified as the major risk factor for both SARS-CoV-2 seropositivity and symptomatic COVID-19. However, neither demographic nor MS characteristics were associated with the COVID-19 outcome. This highlights the importance of continuing DMTs and adhering to health instructions during the COVID-19 pandemic.

Limitations and recommendations

The main limitation of our work was a healthy user bias. Patients with more severe diseases were less likely to participate in the study, leading to an improper impression of the COVID-19 patients. Further, the number of patients treated with high-efficacy DMTs was very small, which did not allow for a precise analysis of the association between DMT class and COVID-19.

The present study highlights the need for further epidemiological studies with particular attention to vaccinated patients to evaluate the humoral and cellular response to vaccination.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Qom University of Medical Sciences (Code: IR.MUQ.REC.1399.155). Additionally, all patients fulfilled the informed consent before they participated in this study.

Funding

This research was supported by Department of Neurology of Qom University of Medical Sciences.

Authors' contributions

All authors contributed to the design, running, and writing of all parts of the research.

Conflict of interest

The authors declared no conflict of interest.

Acknowledgments

The authors express their gratitude to the staff of the MS association of Qom University of Medical Sciences and also thank Fereshteh Shahrab and Payam Molavi, contributor the interview of patients, for their support in data collection.

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