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Impact of COVID-19 on Hospitalization and Mortality Rate in Multiple Sclerosis Patients

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ABSTRACT

Background and Objective: Although the COVID-19 pandemic has currently subsided, there is a concern that it may once again threaten human societies. Among those at higher risk are patients with multiple sclerosis (MS) due to medication use and their immune status. The present study aims to evaluate the rate of COVID-19 infection, hospitalization, and mortality in patients with multiple sclerosis.

Methods: In this cohort study, 288 MS patients who visited Besat Hospital in Hamedan during the years 2020 and 2021 were included through convenience sampling. Demographic characteristics, medication use, COVID-19 infection, hospitalization, duration of hospitalization, mortality, and disability severity based on the Expanded Disability Status Scale (EDSS) were collected from medical records or interviews.

Findings: Of 288 participants, 132 (45.8%) had contracted COVID-19 at least once. The hospitalization rate due to COVID-19 was 2.4%, which was not higher than the general population. Seven patients died due to COVID-19. The use of rituximab and ocrelizumab was associated with a higher hospitalization rate. Patients with higher EDSS scores had a higher incidence of COVID-19 ($p<0.001$).

Conclusion: The findings of this study indicate that the incidence of COVID-19 is higher in MS patients; however, the risk of hospitalization did not significantly increase. Patients on anti-CD20 medications were more likely to require hospitalization.

Keywords: *COVID-19, Multiple Sclerosis, Risk Factors, Mortality, Hospitalization*.

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Introduction

Multiple Sclerosis (MS) is the most common non-traumatic disabling disease among young adults (1). The prevalence and incidence of MS are increasing globally, although its underlying cause remains unknown (2). The treatment of MS includes the use of Disease Modifying Therapies (DMTs) specific to MS, alongside symptomatic treatments to alleviate symptoms resulting from nervous system dysfunction (3). These drugs target the inflammatory process of MS by modulating or suppressing the immune system. While these medications have been effective in reducing the frequency of disease relapses, a significant concern regarding their safety is the potential increased risk of infections (4, 5).

In March 2020, the World Health Organization (WHO) declared COVID-19 a pandemic. Studies conducted so far indicate that the mortality rate from COVID-19 in MS patients is relatively low, and DMTs themselves do not inherently increase the risk; rather, age, comorbidities, and the severity of the underlying disease are more critical factors (6). The fact that patients not receiving DMTs had a significant share in mortality rates may even suggest the protective effect of these drugs. Additionally, many MS patients require regular access to medical services (such as injections, physiotherapy, occupational therapy, and botulinum toxin injections for spasticity), which may be impacted by changes in healthcare delivery during the COVID-19 pandemic (7).

Although the COVID-19 pandemic has currently subsided, there is a concern that outbreaks may still threaten communities; therefore, its impact on MS patients may be greater than other population groups. This cohort study aims to investigate the impact of COVID-19 on the infection, hospitalization, and mortality rate in MS patients.

Methods

After approval by the Ethics Committee of Hamedan University of Medical Sciences with the code IR.UMSHA.REC.1401.797, this cohort study was conducted on 288 patients diagnosed with MS at Besat Hospital in Hamedan during the years 2020-2021. Written informed consent was obtained from all participants. Subjects were included in the study if they had MS according to the 2017 McDonald criteria (8), were receiving medication for MS, were over 18 years of age, were aware of their COVID-19 status, and were able to complete the questionnaire. If they did not consent to complete the questionnaire and did not return to the clinic for follow-up, they were excluded from the study.

Data were collected through interviews and medical records and they were recorded in a prepared checklist. This checklist included demographic variables, disease duration, disease type, medication use, COVID-19 infection, COVID-19 symptoms, COVID-19 vaccination, hospitalization, duration of hospitalization, and mortality due to COVID-19. Disability severity was assessed using the Expanded Disability Status Scale (EDSS), where scores range from 1 to 10 (death), with higher scores indicating greater disease severity and disability. COVID-19 infection was confirmed in patients using Polymerase Chain Reaction (PCR) testing and clinical symptoms. Severity of COVID-19 disease was assessed according to WHO guidelines. Patients with mild to moderate disease were defined as symptomatic patients not requiring oxygen therapy, and patients with severe to critical disease were defined as patients receiving oxygen support (9).

Considering the prevalence of hospitalization among MS patients due to COVID-19 (25%) as reported by Sahraian et al.(10), with an alpha of 0.05 and an error of 0.05 using G-power statistical software, the sample size for this study was calculated as 300 patients. Data analysis was performed using SPSS version 26. Data were described using descriptive statistics, with mean and standard deviation for quantitative

variables and ratio and percentage for qualitative variables. Chi-square test or Fisher's exact test was used to compare the relationship between qualitative variables and quantitative variables between two groups, and Mann-Whitney test was used to examine the relationship between study variables and COVID-19 infection. Odds ratio with a 95% confidence interval was used to assess the relationship between study variables and COVID-19 infection, and $p<0.05$ was considered significant.

Results

Out of 300 participants, 12 were excluded due to lack of follow-up, leaving 288 participants who completed the questionnaire. Among the respondents, 225 (78%) were women and 63 (22%) were men. There was no significant association between gender and COVID-19 infection. Among the participants, 58 (20%) had comorbidities, the most common being diabetes and hypertension. There was no significant association between COVID-19 infection and comorbidities or the type of comorbidities. However, a significant association was found between comorbidities and hospitalization due to COVID-19 infection ($p=0.003$). The most common phenotype among the study population was Relapsing-Remitting Multiple Sclerosis (RRMS), accounting for 230 participants (80%).

280 participants were on Disease Modifying Therapies (DMTs), while 8 were not receiving any medication (Figure 1). Rituximab was the most commonly used DMT (112 participants or 39.4%).

None of the medications used increased the risk of COVID-19 infection in MS patients (Table 1). Among those who contracted COVID-19, 28 (9.7%) were hospitalized. Patients receiving rituximab and ocrelizumab had a significantly higher likelihood of hospitalization due to COVID-19 (Table 2).

A total of 156 participants (54.2%) contracted COVID-19 at least once, while 132 (45.8%) never contracted the virus. There was no significant association between the medications used for MS treatment and COVID-19 infection. A significant association was found between COVID-19 infection and the EDSS score before COVID-19 infection ($p=0.035$), the EDSS score at the time of diagnosis ($p=0.027$), and the duration of MS ($p=0.009$) (Table 3). Among the participants who contracted COVID-19 (156), 90 had received the COVID-19 vaccine (Figure 2).

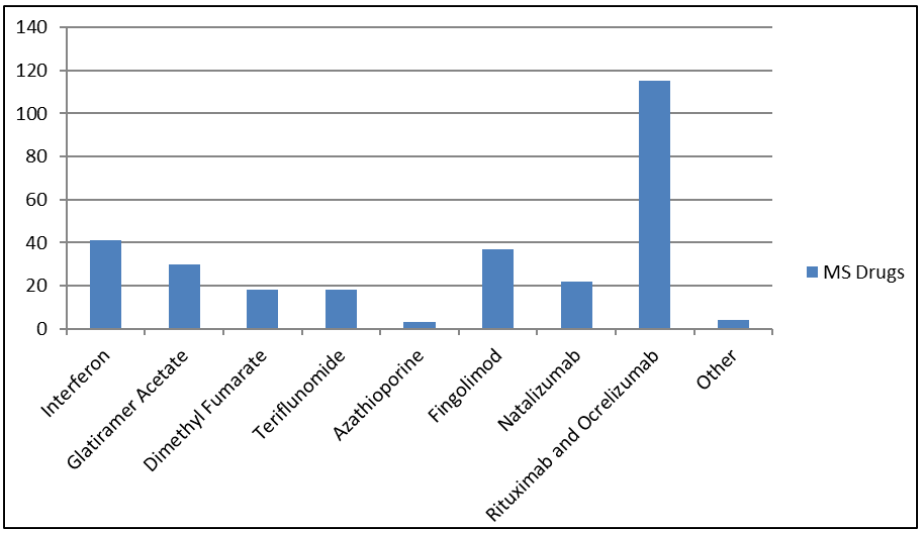


Figure 1. Frequency of medications in patients with MS

Table1. Frequency of COVID-19 in MS Patients by Type of MS Treatment

Medication	COVID-19 infection Yes (n=130) Number(%)	No (n=154) Number(%)	p-value	Odds Ratio	Lower	Upper
Interferon	16(11.1)	27(18.2)	0.18	0.56	0.23	1.33
Glatiramer Acetate	21(10)	16(11.7)	0.71	0.83	0.31	2.21
Dimethyl Fumarate	10(6.7)	5(5.2)	0.73	1.29	0.35	4.75
Teriflunomide	6(5.6)	10(6.5)	0.78	0.83	0.23	3.01
Rituximab & Ocrelizumab	62(43.3)	50(36.4)	0.38	1.31	0.71	2.44
Natalizumab	9(6.7)	9(9.1)	0.54	0.7	0.23	2.20
Fingolimod	20(13.3)	17(13)	0.96	1.02	0.42	2.07
Other	6(3.3)	-	0.11	1.03	0.99	1.07

Table 2. Frequency of hospitalization due to COVID-19 in MS patients

Medication	Hospitalized	Not Hospitalized	p-value
Interferon	2	16	0.001
Glatiramer Acetate	0	20	0.001
Dimethyl Fumarate	1	7	0.001
Teriflunomide	2	8	0.001
Rituximab & Ocrelizumab	22	37	0.001
Natalizumab	0	9	0.001
Fingolimod	1	16	0.001
Other	0	6	0.001

Table 3. Mean EDSS in MS patients with and without COVID-19

EDSS	COVID-19 infection Mean±SD	No COVID-19 infection Mean±SD	p-value
EDSS at diagnosis	1.66±1.99	1.40±1.55	0.427
After COVID-19 infection	1.98±2.21	0.33±0.58	0.073
Baseline	1.95±2.19	1.58±1.74	0.195

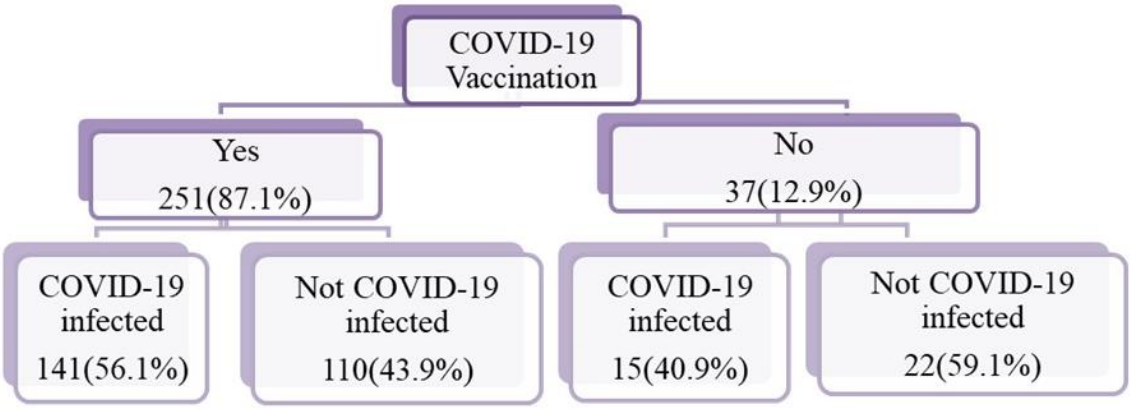


Figure 2. Frequency of patients with and without COVID-19 according to vaccination history

A total of 251 participants (87.1%) had completed COVID-19 vaccination. The frequency of COVID-19 infection did not significantly decrease among those who completed vaccination. Among the patients, 222 (77%) contracted COVID-19 after receiving at least one dose of the vaccine. Of those who experienced COVID-19 infection, 59 (20.5%) were hospitalized. There was no significant difference in hospitalization rates by gender. Participants who contracted COVID-19 were older. Overall, women were more likely to be infected than men (p=0.25).

There was no significant difference in EDSS scores between those who contracted COVID-19 and those who did not. However, the EDSS score assessed three months after COVID-19 infection was significantly higher (Table 3).

The results showed that patients with a longer duration of MS were more likely to contract COVID-19 (10.20±6.67 years vs. 7.28±4.72 years; p=0.008). Among patients hospitalized due to COVID-19, the mean duration of MS diagnosis was 11.05±8.66 years. Unfortunately, 7 participants (2.4%) died. Of these, 4 had received the COVID-19 vaccine. There was a significant association between death and receiving the COVID-19 vaccine (p=0.048). Five of the deceased patients had RRMS and two had secondary progressive MS (SPMS). Among these seven, one was on fingolimod, two on interferon, and four on rituximab. Although there was no statistically significant association between medications and death, most deceased patients were on rituximab. All seven were at a younger age at MS diagnosis (22 years vs. 31 years) and had a longer duration of MS (13 years vs. 8 years).

Discussion

The findings of this study showed that the prevalence of COVID-19 among the studied patients was 54.2%. This rate is higher than the COVID-19 infection rate in the general population (11, 12). However, previous studies have reported varying results. For example, Fan et al. reported no cases of COVID-19 among their study population of 1804 individuals (13). An Italian study assessing the impact of the pandemic on individuals with MS reported that although MS patients were more likely to be tested for COVID-19, their test positivity rate was similar to the general population. Although MS patients had a higher likelihood of hospitalization, ICU admission, and a slight increase in mortality, this increase was not statistically significant (14).

Previous studies have identified several risk factors for COVID-19 infection, including older age, male gender, and comorbidities such as hypertension, diabetes, and heart disease (15, 16). In the first multicenter study on MS patients with COVID-19 in Iran, most patients were women, in their mid-30s, had RRMS phenotype, and were in the early stages of MS (10). Montini and Sahraian also reported similar findings in their studies (10, 17).

The results of this study indicated that the use of interferon beta and glatiramer acetate was associated with a reduced risk of COVID-19 infection, while anti-CD20 therapies were associated with an increased risk of infection. Sahraian et al. reported no association between the type of medication used and hospitalization (10). Parrotta et al. reported a high hospitalization rate (26.4%) among patients on anti-CD20 therapies (15). In another study, Simpson et al. collected data from 28 countries (18). They concluded that compared to dimethyl fumarate and natalizumab, patients on rituximab had an increased risk of hospitalization, ICU admission, and mechanical ventilation. Ocrelizumab showed a similar pattern regarding hospitalization and ICU admission but not mechanical ventilation. Neither rituximab nor ocrelizumab was associated with an increased risk of mortality. They also found that older age, progressive MS phenotype, and greater disability were more common in those with severe COVID-19.

A Swedish study among 292 individuals with COVID-19 examined the association between DMT use and hospitalization risk. The study found that rituximab use in MS patients was associated with a 2.95-fold increased risk of hospitalization compared to other DMTs (19). Various DMTs with different mechanisms of action have been developed for MS patients, but they can also increase the risk of infections. This has been a major concern during the COVID-19 pandemic, leading to studies aimed at identifying risk factors for severe COVID-19 in MS patients. However, each study has chosen a specific drug as a reference for comparison, which is a limitation since these drugs, while similar in infection risk, have different mechanisms of action, particularly in their immunological response to SARS-CoV-2. Considering the results related to rituximab and ocrelizumab, differences in drug biology, such as affinity for CD20 proteins or differences in cytotoxicity, may explain the discrepancies between the studies mentioned (18).

Although we did not find a significant association between COVID-19 infection and EDSS, patients who contracted COVID-19 had higher EDSS scores post-infection. Several studies examining this relationship did not find an association between disability degree and COVID-19 infection (20). However, some studies did indicate a connection (21, 22). Montini et al. assessed the potential association between COVID-19 infection and disability worsening and other outcomes over an 18-24-month period after the infection (17). They concluded that COVID-19 infection did not impact disease progression or disability. In a similar study assessing the outcomes of COVID-19 infection in individuals with central nervous system demyelinating diseases, none of the patients reported worsening of their underlying disease after COVID-19 infection (23). In this study, the death of seven participant was reported. Statistically, there was no association between their medication or vaccination and death. Additionally, MS was not identified as a risk factor for death. An Italian study found that MS patients who contracted COVID-19 were at higher risk for hospitalization and ICU admission, but their mortality rate did not differ from the general population (14). Since most deceased patients in our study had the RRMS phenotype and were on rituximab, the MS phenotype and anti-CD20 medications can be considered risk factors for severe COVID-19 and adverse outcomes.

The findings of this study indicate that the incidence of COVID-19 is higher in MS patients; however, the risk of hospitalization did not significantly increase. Patients on anti-CD20 medications were more likely to require hospitalization.

Conflict of Interest: The authors declare no conflict of interest.

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