Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Multiple Sclerosis and Related Disorders 67 (2022) 104067

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Association between disease-modifying therapies and adverse clinical outcomes in multiple sclerosis patients with COVID-19 infection

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ARTICLE INFO

Keywords:
Multiple sclerosis
COVID-19
Mortality
Disease-modifying therapies
Immunosuppressive

ABSTRACT

Background: This study aimed to consider the main risk factors related to adverse clinical outcomes in MS patients with COVID-19.

Methods: Using the electronic health records systems, this is a cross-sectional study of two years of hospital admissions in terms of COVID-19 in Iran from March 2019 to August 2021. The severities of COVID-19 outcomes were admitted to ICU, hospitalization days, and in-hospital mortality.

Results: A total of 1634 hospitalized MS patients with a definite diagnosis of COVID-19 based on PCR were recorded in the electronic health systems. MS patients had a 7% increased risk for longer hospitalization, a 3% increased risk for the need to the ICU, and no increased risk of mortality compared with the general population. MS patients who were taking immunosuppressive (IS)-disease modifying therapies (DMT) had longer hospitalization (adjusted OR=2.06, 95%CI: 1.48, 2.86) and higher mortality risk (adjusted OR=2.05, 95%CI: 1.52, 6.29) compared to patients were under the immunomodulatory (IM)-DMT. There was not any significant association between the types of DMT and ICU (12.2% vs. 12.7%). Besides, MS patients who were vaccinated against COVID-19 before admission had shorter hospitalization (adjusted OR=0.40, 95% CI: 0.18, 0.92).

Conclusions: The current data suggest that MS healthcare providers should consider specific risks of severe COVID-19 infection before starting IS-DMT.

1. Introduction

During the last two years, COVID-19 was one of the major leading causes of death in the most affected countries and territories around the world based on the average number of daily deaths (Adam, 2022), 754 per million people died in terms of being exposed by COVID-19 until 17 Feb 2022 (https://www.worldometers.info/coronavirus/). COVID-19 can affect anyone, and the disease can cause symptoms ranging from mild to very severe. Because they have qualities or medical problems that raise their risk, some persons are more likely to experience severe disease than others (Fang et al., 2020). Adults aged ≥ 65 years, male gender, and with one or more underlying illnesses such as hypertension and diabetes mellitus had the greatest death rates (Fathi et al., 2021). Furthermore, underlying immunosuppression was one of the most risk factors strongly associated with severe COVID-19 (Li et al., 2021).

Multiple sclerosis (MS) is a chronic inflammatory, and demyelinating disease of the central nervous system (CNS), and immunomodulatory therapies are used as the main strategy to manage MS (Gajofatto and Benedetti, 2015).

In our study, we investigated the relative risk (RR) of adverse outcomes of COVID-19 in MS patients compared with a total population affected by COVID-19 based on data from the national health system of Iran. Besides, we aimed to consider the prevalence of adverse clinical outcomes of COVID-19 in MS patients based on different underlying types of disease-modifying therapies (DMT).

Abbreviations: IM-DMT, the immunomodulatory- disease-modifying therapies; IS-DMT, immunosuppressive-disease modifying therapies.

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https://doi.org/10.1016/j.msard.2022.104067
Received 6 March 2022; Received in revised form 18 June 2022; Accepted 21 July 2022
Available online 22 July 2022

2. Methods and analysis

2.1. Study design and data source

This is a cross-sectional research of COVID-19-related hospital admissions in Iran from March 2019 to August 2021, conducted utilizing electronic health records systems named Medical Care Monitoring Center (MCMC) and Hospitals' Information System (HIS). Both nationwide health information systems were established by Information Technology (IT) and the Statistics Department of the Ministry of Health. MS patients' ID was used to extract data of MCMC and HIS.

2.2. Data collection

MCMC records the data of patients who are admitted to the hospital in terms of COVID-19. The data were (1) demographic information (age, sex, and body mass index), (2) smoking habit, (3) medical history, (4) principal clinical symptoms, (5) real-time polymerase chain reaction results, (6) radiological findings, (7) comorbidities, (8) needing intensive care (ICU), (9) hospitalization days, (10) in-hospital mortality.

HIS records demographic information, admission and discharge dates, initial and final diagnoses, hospital inpatient services, including all drugs, admitted wards (ICU, isolation, and other wards), procedures (mechanical ventilation), comorbidity, and hospital mortality. The international classification of diseases 10 (ICD-10) was used as the diagnostic codes for COVID-19; U07.1, and U07.2.

The date of vaccination (each dose) was collected from the **SALAMAT** System. Patients, who received at least one dose of the COVID-19 vaccine before the date of hospital admission, were recorded in the data.

All MS patients were recalled for quality control, and a questionnaire was filled out with information on their MS diagnosis, MS medications at the time of COVID-19 admission, history of other chronic illnesses, and history of smoking at the time of COVID-19 admission, and height and weight. The Expanded Disability Status Scale (EDSS) of MS patients was available in 938 patients on the electronic medical records who were visited by a neurologist during the three months before their hospital admission.

To consider the role of living in a populated city, we selected the top 10 cities with the higher population as follows; Tehran, Karaj, Esfahan, Mashhad, Shiraz, Tabriz, Qom, Kermanshah, and Oromia.

3. Ethics

The study was conducted based on the Declaration of Helsinki and Ethical Committee of Neuroscience Institute of Tehran University of Medical Sciences approved human experiments (IR.TUMS.NI.REC.1400.007).

The data from the general population was coded anonymously, and informed permission was not required. In the case of MS patients, each participant or their close relatives of those who died gave verbal informed permission.

3.1. Statistical analysis

Data were analyzed by SPSS statistical software (version 20). Data analyses were performed on MS patients based on the disease course and medications. Ocrelizumab, rituximab, fingolimod, and azathioprine were defined as immunosuppressive (IS)- disease-modifying therapies (DMT). Interferon, glatiramer acetate, dimethyl fumarate, teriflunomide, and natalizumab were defined as immunomodulatory (IM)-DMT. Treatment with IS- DMT in MS patients was investigated using multivariable logistic regression models to see whether it was a risk factor for poor results. Adjusting covariates were selected based on the parameters associated with severe outcomes, including age, sex, body mass index (BMI), living in populated cities, smoking status, at least one chronic disorder (e.g. hypertension, diabetes, heart disorders, malignancy, chronic kidney disease (CKD), lung disorders, asthma, and immunodeficiency), MS duration, MS type (RRMS vs. progressive) and EDSS score ≥ 5. If *P*-value was less than 0.2 (P-value < 0.2), it was adjusted in multivariable logistic regression analyses.

A total of COVID-19 patients admitted to a hospital throughout Iran were used as a reference group to compare COVID-19 outcome severity in MS patients to the general population. Age, sex, comorbidities, and COVID-19 severity outcomes were all accessible data for the general population. The relative risk of adverse clinical outcomes of COVID-19; the length of hospitalization higher than 5 days, ICU admissions, and the hospital mortality rate was calculated by a $\chi 2$ test. The data analyses were performed in each sex, and each age group ($>$ 30, 30–39, 40–49, 50–59, 60–69, 70–79, 80–89, $\geq$ 90). To adjust age, sex, and comorbidity, the logistic regression model was used to address the RR of COVID-19 clinical outcomes.

All tests were two-sided, and a *P*-value of less than 0.05 was defined as statistically significant.

4. Results

4.1. Demographic and clinical characteristics of MS patients

The MCMC system documented a total of 2859 MS patients who were hospitalized with COVID-19. The data study includes 1634 patients with a definitive diagnosis of COVID-19 and a positive real-time polymerase chain reaction (PCR), 45.7 percent ($N = 747$) of laboratory-confirmed patients resided in populous cities. The demographic characteristics of included MS patients with COVID-19 were provided in Table 1 based on sex classification. The mean age of all patients was 42 ± 10 years; while men ($N = 472$) were older than women ($N = 1162$) (mean difference (years) ± SE: −1.2 ± 0.5). There were not any significant differences in terms of disease course, undergoing MS medications, and history of any chronic disorders except heart disorders ($p = 0.02$) between two subgroups; men and women with MS. Totally, 27.6% ($n = 451$) of MS patients had at least a history of one chronic disorder.

Regarding smoking status, among available data, the smoking habit was above two times more common in men patients than in women patients with COVID-19 ($p = 0.000$). The prevalence of obesity (BMI greater than 30 kg/m2) was higher among women than men, although the difference was not statistically significant (19.8% vs. 16.8%, $p = 0.3$).

4.2. COVID-19 clinical symptoms and outcomes in MS patients

The most common symptom was cough (53.7%), followed by fever (47.7%) and myalgia (33.0%) (Table 2). The median length of the hospitalization was 5 days with a wide range; of 1–62 days with no significant difference in men and women ($p = 0.4$) even after adjusting for age and EDSS ($p = 0.15$). In the case of ICU, 12.4% of MS patients were admitted to the ICU, without any significant difference between women and men ($p = 0.2$) even after adjusting for age and EDSS ($p = 0.2$). The prevalence of patients who required mechanical ventilation was 6.7% with the same proportion in men ($p = 0.7$) and women even after adjusting for age and EDSS ($p = 0.8$).

4.3. In-hospital mortality rate

In general, the hospital mortality rate in MS patients was 9.4%. Patients who died were older (mean difference= 4.15, 95% CI: 0.84, 2.5–5.8; $p = 0.000$), had a history of comorbidity (39.2% vs. 26.4%, $p = 0.001$) which had the severe MS type (progressive MS types/RRMS 73.7%, vs. 64.4% $p = 0.017$). There was no statistically significant difference in sex (F/M) (71.2% vs. 70.6%, $p = 0.8$) or disease duration (8 (9.25) vs. 7(8.75) years; $p = 0.07$) between survivors and non-survivors.

Moreover, the mortality rate statistically was similar in populated cities compared with other cities (8.5% vs. 10.4%, $p = 0.17$). In the case

Table 1
The demographic data of hospitalized MS patients to be infected with COVID-19.

	N* (F/M)	Female (*N* = 1162)	Male (*N* = 472)	Total (1634)	*P*-value
Demographic characteristics					
Age, years	1160/471	42 ± 10.0	43 ± 10	42 ± 10	0.03
BMI, kg/m^2	524/211	26.0 ± 4.7	25.8 ± 4.4	26.0 ± 4.7	0.3
Smoking status	488/210	13.1% (64)	30.0% (63)	18.2% (123)	0.000
MS-duration	1122/452	7(4-12)	7(3-12)	7(3-12)	0.6
MS classification					
RRMS		66.1% (768)	60.6% (286)	64.5% (1054)	0.2**
SPMS		11.5 (134)	14.4% (68)	11.8% (202)	
PPMS		11.5% (134)	14.4% (68)	12.4% (202)	
CIS		2.4% (28)	1.7% (8)	2.2% (36)	
Unknown		8.2% (95)	8.6% (41)	8.8% (136)	
MS treatment, no. (%)	1634				
Ocrelizumab/ Rituximab		38.3% (445)	38.3% (181)	38.3.0% (626)	0.7
Interferon		27.1% (315)	26.7% (126)	27.0% (441)	
Fingolimod		6.3% (73)	6.4% (30)	6.3% (103)	
Glatiramer Acetate		5.7% (66)	4.9% (23)	5.4% (89)	
Dimethyl fumarate		3.8% (44)	3.4% (16)	3.7% (60)	
Teriflunomide		1.7% (20)	1.1% (5)	1.5% (25)	
Natalizumab		0.9% (11)	1.1% (5)	1.5%(16)	
Azathioprine		0.2% (2)	0.8% (4)	0.4% (6)	
Unknown		10.7% (124)	11.2% (53)	10.8% (177)	
None		5.3% (62)	6.1% (29)	5.6% (91)	
History of chronic disorders	1634				
Diabetes		5.2% (61)	5.7% (27)	5.2% (88)	0.7
Hypertension		5.2% (61)	6.1% (29)	5.5% (90)	0.4
Kidney disorders		0.5% (6)	1.3% (6)	0.7% (12)	0.1
Liver disorders		0.1% (1)	0.6% (3)	0.2% (4)	0.07**
Lung disorders		1.3% (15)	1.3% (6)	1.3% (21)	0.9
Heart disorders		2.3% (27)	4.4% (21)	2.9% (48)	0.02
Cancer		0.9% (11)	1.3% (6)	1.0% (17)	0.5
Hematology disorder		1.0% (12)	0.2% (1)	0.8% (13)	0.09
Coronavirus vaccination before hospital admission	1634	5.1% (59)	3.8% (18)	4.7% (77)	0.3
EDSS score≥5	938	20.8% (141)	30.8% (80)	23.6% (221)	0.001

* *N*=available data, F/M= Female/Male.
** Fisher exact test.
Numerical variables were expressed as the mean ± SD or median (lower-upper IQR). Categorical variables were presented as percentages.

of first computed tomography (CT) scan findings at the time of admission, 73.9% (1207) of MS patients had positive CT (moderate or severe), and there was no significant association between pulmonary involvement and mortality risk (p = 9.2% vs. 9.8%, with and without positive CT, respectively, $p = 0.6$).

After adjusting for confounding factors in the logistic regression model, in MS patients, only older age (OR=1.03, 95% CI: 1.01, 1.05) and comorbidities (OR=1.8, 95% CI: 1.1, 2.9) had a significant association with risk of mortality. Of note, 52.3% (80 out of 153) of patients who

Table 2
COVID-19 clinical symptoms at the time of admission and the severity outcomes in MS patients.

	N*	Female (*N* = 1162)	Male (*N* = 472)	Total (*N* = 1634)	*P*-value
Symptom at the time of admitted					
Cough	1634	54.6% (635)	51.5% (243)	53.7% (878)	0.24
Fever	1634	46.4% (539)	51.1% (241)	47.7% (780)	0.08
Chest pain	1577	5.5% (61)	4.1% (19)	5.1% (80)	0.26
Dyspnea	1634	16.9% (196)	18.0% (85)	17.2% (291)	0.58
Anorexia	1478	12.2% (128)	7.6% (33)	10.9%(161)	0.009
Myalgia	1634	33.6% (390)	31.8% (150)	33.0% (540)	0.48
Vertigo	1576	5.1% (57)	4.3% (20)	4.9% (77)	0.52
Gastrointestinal symptoms	1590	13.3% (150)	10.7% (50)	12.6% (200)	0.15
Outcomes					
Hospitalization days	1554	5 (1–62)	5 (1–42)	5 (1–62)	0.46
ICU admission	1634	13.0% (151)	10.8% (51)	12.4% (202)	0.22
Mechanical ventilation	1634	6.5% (75)	7.0% (33)	6.7% (109)	0.74
Mortality	1634	9.3% (108)	9.5% (45)	9.4% (153)	0.88

* *N*=available data.
Numerical variables were expressed as the median (lower-upper IQR). Categorical variables were presented as percentages.

died were admitted to an ICU. There were no significant differences in the cases of age, sex, the MS course (severity of MS, EDSS score, and MS duration), and the mortality rate ($p > 0.05$).

4.4. COVID-19 clinical characteristics based on treatment with various types of DMT

Among studied patients, 5.6% ($N = 91$) did not receive any DMT at the time of SARS-CoV-2 infection and 10.8% were unknown ($N = 177$). The rest of the patients (83.6%) were consuming DMT; 38.6% were IM-DMT, and 45% were IS-DMT.

Patients on IS-DMT therapies had a severe kind of MS, a higher EDSS, and were more vaccinated against COVID-19 before hospital admission ($p < 0.05$) (Table 3). The patients receiving IS-DMT had a longer hospital stay (median (IQR) of 6 (4–9) days) than patients receiving IM-DMT (median (IQR) of 5 (3–7) days) ($p = 0.000$).

In the multivariate logistic regression model, after adjusting for age, sex, BMI, comorbidity, living in a populated city, smoking status, MS duration, EDSS score, disease course, and coronavirus vaccination (prior to admission), there was an independent significant association between using IS-DMT medication and longer hospitalization duration (adjusted OR=2.06 95%CI: 1.48, 2.86) in the (Table 4).

In terms of mortality, patients treated with IS-DMT had a higher mortality rate than patients who were treated with IM-DMT (10.7% vs. 8.6%); but the difference was not statistically significant ($p = 0.17$). In the logistic regression model, after adjusting for confounding factors, there were significant associations between IS-DMT (adjusted OR=2.05, 95% CI: 1.52, 6.29) ($p = 0.002$) and comorbidity (adjusted OR= 1.81, 95% CI: 1.06, 3.10) ($p = 0.03$) and risk of mortality .

Regarding the requirement for ICU, there was not any significant difference between patients treated with IS-DMT or IM-DMT (12.2% vs. 12.7%, $p = 0.79$).

The comorbidity was the independent common risk factor associated with severity outcomes, including longer hospitalization (> 5 days) (adjusted OR = 1.39, 95% CI: 1.07, 1.79), and mortality (adjusted OR =

Table 3
The demographic and clinical data of hospitalized MS patients to be infected with COVID-19 based on different MS medications.

	N*	N-DMT (N=91)	IM-DMT (N=631)	IS-DMT (N=735)	*P*-value
Age, years	1454	44 ± 9	42.5 ± 10.5	42 ± 9	0.06
BMI, kg/m^2	666	24.5 ± 4.8	26.8 ± 4.5	25.8 ± 4.5	0.002
Smoking status	664	18.4% (7)	22.7% (45)	15.2% (65)	0.000
MS-duration	1442	8(4–14)	7(4–11)	7(3–12)	0.7
Type MS.RRMS	1378	55.0 (44)	81.6% (492)	68.9% (479)	0.000
EDSS≥5	841	36.1% (22)	13.8(36)	26.3% (137)	0.000
Comorbidity (at least one)	1457	23.1% (21)	26.7% (168)	27.4% (202)	0.7
Coronavirus Vaccination before the admission	1457	3.3% (3)	3.7% (23)	6% (44)	0.1
COVID-19 outcome					
hospitalization days	1457	5(3–9)	5(3–7)[a]	6 (4–9)[a]	0.000**
ICU	1457	9.9% (9)	12.7% (80)	12.2% (179)	0.74
Mortality	1457	5.5% (5)	8.6% (54)	10.7% (79)	0.16
Mechanical ventilation	1457	6.6% (6)	6.2% (39)	7.2% (53)	0.75

*N=available data. Numerical variables were expressed as the mean ± SD or median (lower-upper IQR). Categorical variables were presented as percentages.
[a] The patients receiving IS-DMT had a longer hospital stay than patients receiving IM-DMT ($p = 0.000$).

Table 4
Adverse COVID-19 outcomes in MS patients based on using IS-DMT.

	Hospitalization more than 5 days	ICU	Death
Odds Ratio, 95% CI (lower, upper)*	1.71 (1.37, 2.13)	0.96 (0.69, 1.32)	1.28 (0.89, 1.84)
Odds Ratio, 95% CI (lower, upper)**	2.06 (1.48, 2.86)	1.14(0.70, 1.96)	2.05 (1.52, 6.29)

* Un-adjusted data.
** Adjusting for age, sex, BMI, comorbidity, smoking status (at the time of admission), MS duration, EDSS, the disease course, and coronavirus vaccination before admission.

1.81, 95% CI: 1.06, 3.1), but not with the need for ICU admission (adjusted OR = 1.4, 95% CI: 0.85, 2.29).

In terms of the vaccination's favorable impact on severe COVID-19 outcomes, after correcting for the aforesaid confounding variables, patients who were immunized against COVID-19 prior to admission had a shorter stay regardless of DMT therapies (adjusted OR=0.40, 95% CI: 0.16, 0.96). There was no significant association between being vaccinated against COVID-19 before admission and mortality ($p = 0.1$) or admissions to ICU ($p = 0.8$).

4.5. COVID-19 outcome severity in MS patients versus the general population

The general population was a total of adult patients (≥ 18 years) with COVID-19 who were admitted to a hospital all over Iran ($N = 735{,}336$) at the same study time of data collection for MS patients (Table S1).

MS patients were younger than the general population with COVID-19 who were admitted to the hospital (Table S2) ($p = 0.000$). In general, 33.7% of the general population was older than 64 years compared with 1.7% ($N = 27$) of those MS patients ($p = 0.000$). Patients with MS were primarily less than 30 (42.7%), and the percentages of the rest of the age groups were as follows: 30–39 (33.5%), 40–49 (33.4%), 50–59 (19.2%), and 60–69 (3.9%) years of age.

Fig. 1 represents the COVID-19 clinical outcomes in different age groups of MS patients and the general population.

The proportion of men was 50.5% in the general population compared with 28.9% in MS patients ($p = 0.000$). The data analyses were adjusted based on age and sex (Table S2). After controlling for age and sex, MS patients had a longer hospital stay and fewer ICU admissions than the general population. The death rate in the two groups, the general population, and MS patients, did not vary significantly ($p = 0.2$). As a difference in the prevalence of comorbidity, it was added to the adjusting model. In the multivariate logistic regression model, after adjusting for age, sex, and history of comorbidity, there was an overall higher risk for longer hospitalization duration (adjusted-RR =1.03) and the need for ICU admission (adjusted-RR =1.15) than in the general population. In the adjusted model, the mortality rate was higher in the MS patients than in the general population, but not significantly (Table 5).

5. Discussion

One of the biggest challenges for physicians is whether MS patients are more likely to have worse COVID-19 results, longer hospital stays, more ICU hospitalizations, and a higher death rate. To address this problem, we studied the complete population of people with and without MS who were PCR positive and admitted to hospitals throughout Iran for roughly two years. In comparison to the overall population, MS patients were younger and mostly female. In comparison to 33.7% of the overall population, just 1.7% of MS patients were over 64 years old. Compared to MS patients, a history of chronic disorders was more prevalent in the general population in terms of a higher number of elderly people. A total of 34.0% of the general population had at least one medical disorder, including hypertension, diabetes, chronic hematology, heart, lung, kidney, and liver disorders, neurological (except MS) disorders, and cancers. In the general population, people with comorbidity were twice as at risk of mortality compared to healthy people (20.4% vs. 10.4%).

As a result, it is vital to remember that the MS population differs from the general population in terms of age, sex, and the prevalence of comorbidities (The Multiple Sclerosis International Federation, 2020). The multivariable logistic regression model was used to control the effect of age, sex, and comorbidity. In this model, our data revealed MS patients had a 7% increased risk for longer hospitalization and a 3% increased risk for need the intensive care (ICU). In consistence to our study, it has been highlighted immunocompromised patients infected with SARS-CoV-2, especially those with comorbidities, may have a higher risk for severe outcomes than the general population(Ciotti et al., 2020; Clark et al., 2020; Gianfrancesco et al., 2020; Wei et al., 2020). However, when it came to mortality rates, our data revealed that MS patients did not have a higher risk than the general population. Based on some MS registry systems, the mortality rate attributed to COVID-19 was estimated at 1.6%−3.6% in the total MS patients (Salter et al., 2021; Sormani et al., 2021). Because we only investigated the death rate among hospitalized MS patients, our research revealed a higher fatality rate of roughly 9%. Most MS patients who are hospitalized to a hospital have more significant COVID-19 and/or are more likely to have severe MS disease courses. To consider the role of severity of COVID-19 on the mortality rate, MS patients were classified based on COVID-19 severity via positive chest scan findings compatible with COVID-19 at the time of admission. Overall, 73.9% of MS patients had positive CT, and there was no significant association between pulmonary involvement and mortality risk.

However, because of the medical history of MS, it is more likely the admission rate of MS patients with lower severity of COVID-19 was higher than that of healthy people. To investigate the role of MS disease course, we re-analyzed data from MS patients based on their EDSS score, type of MS, and illness duration. MS patients who died had progressive

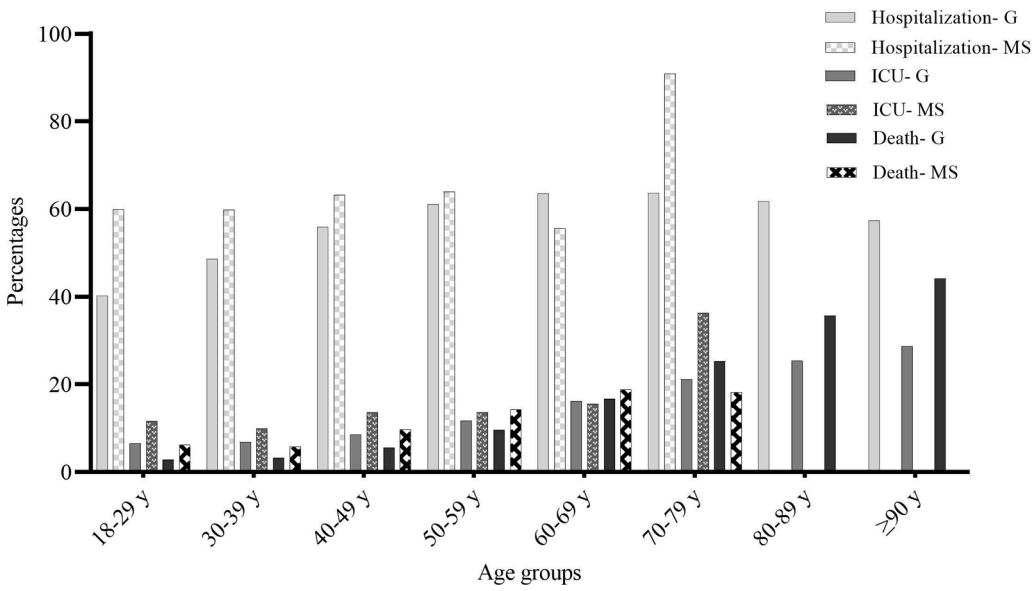

Fig. 1. COVID-19 outcome severity in MS patients versus the general population: The bar chart presents the COVID-19 clinical outcomes in different age groups of MS patients and the general population. The horizontal (x) axis represents the different age groups (18–29, 30–39, 40–49, 50–59, 60–69, 70–79, 80–89, and ≥ 90 years); the vertical (y) axis represents the severity of COVID-19 outcomes. In the figure, the values are percentages of each of the outcomes in two groups: MS and the general population.

Table 5
The relative risk of COVID-19 clinical outcomes in MS patients compared to the general population.

RR	Hospitalization more than 5 days	ICU	Death
RR, 95% CI (lower, upper)*	1.07(1.03–1.11)	0.88 (0.78–1.01)	0.66 (0.57–0.77)
RR, 95% CI (lower, upper)**	1.03 (1.02–1.02)	1.15 (1.02–1.31)	1.74 (0.93, 1.25)

* The relative risk (RR) of un-adjusted data.
** The relative risk (RR) of adjusted data with age, sex, and comorbidity.

kinds of MS, a history of comorbidity, and were older than surviving patients. Concerning the severity of outcomes of COVID-19, one of the main issues in MS patients is receiving immunosuppressed therapies (Safavi et al., 2020; Sahraian et al., 2020). Using IS-DMT is a double-edged sword. Such DMT agents inhibit the exaggerated immune response that prevents relapse or progression of disability. However, the potentially serious side effect of these drugs in MS is the increased risk of different types of infections (Hauser et al., 2017; Hemmer and Muhlau, 2017; Luna et al., 2020; Montalban et al., 2017). A nationwide Swedish cohort revealed that the COVID-19 infection risk was higher in MS patients who were under DMT therapies, particularly rituximab, which was associated with the highest rate of serious infections (Luna et al., 2020).

According to our findings, MS patients receiving IS-DMT were two times more likely to stay in the hospital longer, 1.15 times more likely to need critical care, and 1.74 times more likely to die in the hospital. Patients using IS-DMT seem to have a greater chance of severe COVID-19 outcomes than those receiving other treatments. Recently, an Italian study observed an increased frequency of severe COVID-19 in people who were treated with anti-CD20 therapies like rituximab or ocrelizumab. The severity of COVID-19 outcomes was related to the duration of antiCD-20 therapy. The patients who were under anti-CD20 therapy for over one year had a higher risk of severe COVID-19 outcome with OR02.9 (death, ICU admission, pneumonia, or hospitalization). The duration of using ant-CD20 had a direct correlation with the severity of COVID-19 (Sormani et al., 2022).

Some limitations in our study are worth noting. Firstly, in our data, only patients with positive results from PCR were included. Patients with CT positive but negative results and also patients with unknown PCR results were excluded from the data analysis. During the initial COVID-19 pandemic, a small number of patients admitted to hospitals were tested, and admission and treatment decisions were made based on CT scan findings and severity of symptoms. As a result, our data analyses were most certainly overestimated. Second, our data analyses for COVID-19 outcomes were based on electronic data registries. The accuracy of HIS and MCMC was ascertained through a pilot study that compared the electronic registry data with the data directly extracted from the medical records of the Sina Hospital in Tehran during the study period.

In general, MS patients were at higher risk of longer hospitalization compared to the general population suffering from COVID-19. Besides, this study shows MS patients who are under IS-DMT have a higher risk of COVID-19 adverse outcomes, including longer hospitalization, more admissions to intensive care, and a higher hospital mortality rate. During the COVID-19 pandemic, professionals who treat MS patients should weigh additional possible advantages against potentially significant side effects to make better decisions.

CRediT authorship contribution statement

Zhila Maghbooli: Conceptualization, Methodology, Formal analysis, Writing – original draft. **Hesham Hosseinpour:** Software, Data curation, Validation, Writing – review & editing. **Mohammad Reza Fattahi:** Investigation, Writing – review & editing. **Tarlan Varzandi:** Investigation, Validation, Writing – review & editing. **Sara Hamtaeigashi:** Investigation, Writing – review & editing. **Sara Mohammadnabi:** Investigation, Writing – review & editing. **Yasaman Aghababaei:** Validation, Writing – review & editing. **Mohammad Ali Sahraian:** Supervision, Writing – review & editing.

Declaration of Competing Interest

The Authors declare that there is no conflict of interest.

Acknowledgment

We are indebted to the deputy of research and technology of the multiple sclerosis research center affiliated with the Tehran University of Medical Sciences, the Iranian Multiple Sclerosis Society, and the Information Technology (IT) and Statistics department of the Ministry of Health for their support.

Funding

This work was supported by the Neuroscience Institute of Tehran University of Medical Sciences (Grant No: 52878-233-1-1400).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2022.104067.

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