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.

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COVID-19 infection and hospitalization rate in Iranian multiple sclerosis patients: What we know by May 2021

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ABSTRACT

Background: : Despite investigations on the effect of disease modifying therapies (DMTs) used in multiple sclerosis (MS) on coronavirus disease 2019 (COVID-19); there are still controversies.
Objective: : We designed this study to evaluate the epidemiological features of covid-19 in a large sample of people with MS (pwMS) in Isfahan, Iran, as well as the association between DMTs, risk of COVID-19 infection and hospitalization.
Methods: : In an observational pwMS, we interviewed subjects on their MS and COVID-19 history.
Results: : 3050 subjects were included (74% female) with a mean age of 41.36. 423 (13.8%) had confirmed COVID-19 which shows that pwMS are at a higher risk of infection compared to the general population, No significant relationship was observed in COVID-19 infection when individual drugs. Dimethyl fumarate and rituximab had the lowest and the highest relative risks for hospitalization rate compared to other drugs, respectively.
Conclusion: : We found no evidence supporting a higher prevalence of COVID-19 in pwMS compared to the general population. However, our results show pwMS to be more prone to hospitalization compared to the general population, Therefore, it is advised to use safer treatment if possible until complete vaccination, and to postpone the use of rituximab.

1. Introduction

Multiple Sclerosis (MS) is demyelinating neurological disease which affects 2.8 million people estimated to be living with the condition globally (Walton et al., 2020) and it is one of the important causes of disability in early adulthood (Thompson et al., 2018). Different phenotypes have been described according to the course in which the symptoms are experienced: Clinically isolated syndrome (CIS) is the first episode of symptoms lasting for at least 24 h; the most common course, relapsing-remitting MS (RRMS), is defined by clear exacerbations and recovery periods; secondary progressive MS (SPMS) and primary progressive MS (PPMS) are characterized by progressive decline in neurologic function in people with and without prior RRMS, respectively (National Multiple Sclerosis Society, 2021).

Acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in January 2020 due to its causative role in coronavirus disease 2019 (COVID-19) (Carvalho et al., 2021). The disease, first reported in Wuhan in Hubei province of China alarmingly spread throughout the world, which led to the declaration of COVID-19 as a pandemic by the World health organization (WHO) on 11 March 2020(World Health Organization, 2020) As of June 9 2021 more than 186 million cases and 4 million deaths have been reported (WorldOMeter, 2021).

Immunocompromised patients seem to be at a higher risk of COVID-19 infection and also in danger of more severe forms of the disease. This was also suspected to be the case with people living with MS (pwMS) also, who have weaker immune systems due to the nature of the disease

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and the therapeutic strategies currently used: both disease modifying therapies (DMT) which are used to decrease the number of relapses and corticosteroids which are mainstays of treatment in acute attacks make patients immunocompromised and increases their infection risk (In, 2020; Youssef et al., 2016).

The results of various studies trying to address the issue of MS and the treatment implications for COVID-19, indicating a high risk for SARS-CoV-2 infection (Crescenzo et al., 2020) as well as more severe infection (Luna et al., 2020) in pwMS. Recent reviews however, have attributed such observations to older age and other comorbidities and do not consider MS or DMTs (with the exception of anti-CD20 therapies) as risk factors for severe COVID-19 (Chaudhry et al., 2021).

Despite the accumulated evidence on the subject, most investigations have reported being limited by small sample sizes and were conducted early in the pandemic when there was much less knowledge on COVID-19. We designed this study to evaluate the epidemiological features of covid-19 in a large sample of pwMS in Isfahan, Iran, as well as the association between DMT, disease course, and disability in this population with risk of COVID-19 infection and rate of hospitalization.

2. Methods

Study design: This was a cross-sectional observational study conducted on pwMS in Isfahan (an Iranian province with high MS prevalence (Saadatnia et al., 2007)). Study protocol was approved by the ethics committee of Isfahan University of medical sciences.

Participants: All pwMS 18 and older with definite MS according to McDonald's criteria (McDonald et al., 2001), who were registered at Kashani Comprehensive MS center (the main registered database in Isfahan) and were invited to receive the first dose of COVID-19 vaccine were included.

Data collection: pwMS were explained the process and aims of the study and nearly all of them agreed to be included. Those who chose to participate underwent a semi-structured medical interview before receiving the first dose of vaccine. The interview session consisted of medical history taking focused on demographic and disease characteristics (presenting symptoms, disease course Annual relapse rate (ARR), phenotype, current disability status according to Expanded Disability Status Scale EDSS), past and current treatment, and past history of COVID-19 infection. Those with a history of covid-19 infection completed another questionnaire detailing infection symptoms, diagnostic methods, and hospitalization history. Interview results were recorded on a coded form and then converted into an electronic format anonymously.

Variables: MS phenotype was classified as: RRMS or Progressive MS (including both SPMS and PPMS). Methods of diagnosing COVID-19 were categorized as either: 1. By positive PCR test for SARS-CoV-2, 2. Lung high-resolution computed tomography (HRCT) compatible with COVID-19, and 3. Via clinical judgment based on symptoms and contact tracing (without undergoing PCR testing or HRCT scanning).

Statistical analysis: Analysis was performed using IBM SPSS statistics software (Version 25.0. IBM Corp.). Frequency of qualitative variables data are presented via percentages, and for quantitative variables data are shown as mean ± SD (Standard deviation). To assess normal distribution of variables, Kolmogorov-Smirnov test was performed on the data. Mann-Whitney U test was used to compare differences between non-parametric variables when the dependent variable is either ordinal or continuous; for categorical variables Pearson's chi-square test was performed. In order to compare the risk of using DMTs and their effect on hospitalization risk, drugs were compared in pairs by Fisher's exact test and the relative risk (RR) was calculated with 95% confidence interval (CI).

3. Results

3.1. Population characteristics

3050 subjects were included in the study of which 2259 (74%) were female with a mean age of 41.36 ± 10.39 (SD). The average duration of MS was 10.54 ± 6.94 and the most prevalent phenotype was RRMS (56.7%) and 91.2% were on disease modifying therapies. 623 (20.4%) had a history of COVID-19 diagnosis of which 356 (57%) had been confirmed via a positive PCR, 67 (10.7%) via HRCT-scan findings (a total of 423 (13.8%) of the subjects having definite COVID-19 history) and the rest were diagnosed only by clinical judgment and contact tracing without further paraclinical evidence. There was no relation between ARR and risk of COVID-19 infection (*P*-value = 0.261). Further data on demographic characteristics, MS disease features and therapies and COVID-19 infection are presented in Table 1.

3.2. Sex differences

Comorbidity was present in 20.1% of women compared to 14.6% of men (*P-value* = 0.001). The most common comorbidities among women were hypothyroidism (6.3%) and hypertension (2.7%), and the one most commonly observed in men was diabetes (2.5%) as detailed in Table 1. Women had lower EDSS scores than men (2.03 ± 2.90 vs 2.39 ± 2.45; *P-value* < 0.001) and received more DMTs (92.8% vs. 87.65%; *P-value* <0.001).

Hospitalization rate due to COVID-19 infection was significantly lower in women compared to men (1.55% vs. 3.29%; *P-value* < 0.001) despite no significant difference in COVID-19 infection history (*P-value* = 0.089) Further differences between the sexes and are presented in Table 1.

3.3. DMTs and COVID-19 risk

Compared to pwMS on DMTs, those who did not take medication for MS were less likely develop COVID-19 infection (17.6% vs. 20.7%; *P-value* = 0.240), but had a significantly higher hospitalization rate (21.7% vs. 8.9%; *P-value* = 0.005). pwMS taking no drugs also had a significantly higher EDSS score (4.12 ± 5.37 vs. 1.94 ± 2.33; *P-value* <0.001).

No significant association was observed between different classes of DMTs and risk of having definite (supported by PCR or HRCT) (*P-value* = 0.068) or suspected (*P-value* = 0.025) COVID-19 infection. In terms of hospitalization risks, dimethyl fumarate had lowest relative risks compared to other widely used drugs, reaching a statistically significant difference when compared to rituximab (*P-value* <0.001; RR=0.159; CI = [0.04–0.61]), followed by both low dose and high dose interferons which showed lower risk compared to most of the other drugs. On the other hand, rituximab was associated with highest odd ratios, having statistically significant higher risks in comparison with low dose interferons (*P-value* <0.001; RR=1.740; CI = [1.45–2.08]) and dimethyl fumarate, as mentioned before. Further data on hospitalization risk of different DMTs is presented in Table 2.

4. Discussion

4.1. COVID-19 epidemiology

Out of 3050 pwMS, 20.4% had confirmed or suspected COVID-19 and a total of 356 (11.7%) had a positive PCR result. This is not very different than the general Iranian population which was reported to have a 14.2% prevalence of COVID-19 by Khalagi et al. (2021) Our results support the conclusion that pwMS are not in an increased risk of COVID-19 which has also been reached Fernandes et al. (2020), Kovvuru et al. (2021) and MorenoTorres et al. (2021) A previous study conducted in Iran reported a lower proportion of pwMS who had a

Table 1
population characteristics and sex differences.

		Total	Male	Female	*P-value*
Variables		(n = 3050) mean ± SD or n (%)	(n = 791) mean ± SD or n (%)	(n = 2259) mean ± SD or n (%)	
age		41.36 ± 10.39	42.33 ± 10.87	41.02 ± 10.21	0.01
gender Male		791 (25.9)			
Female		2259 (74.1)			
Duration of MS (year)		10.54 ± 6.94	10.00 ± 6.97	10.72 ± 6.92	0.004
Phenotype RR-MS		2384 (78.1)	586 (74.0)	1798 (79.5)	
SP/PP-MS		458 (15)	162 (20.5)	296 (13.1)	
missing		208 (6.8)	43 (5.4)	165 (7.3)	
Last cortisol pulse (year)		2.74 ± 3.81	2.60 ± 3.54	2.79 ± 3.89	0.953
Comorbidity	With comorbidity	568 (18.6)	115 (14.6)	453 (20.1)	0.001
	No comorbidity	2476 (81.2)	673 (85.4)	1803 (79.8)	
	Diabetes Mellitus	70 (2.3)	20 (2.5)	50 (2.2)	0.611
	Hypertension	74 (2.4)	12 (1.5)	62 (2.7)	0.054
	Hypothyroidism	153 (5.0)	11 (1.4)	142 (6.3)	<0.001
	Respiratory	26 (0.9)	9 (1.1)	17 (0.8)	0.311
	Other Cardiovascular	41 (1.3)	15 (1.9)	26 (1.2)	0.117
	Hyperlipidemia	12 (0.4)	1 (0.1)	11 (0.5)	0.163
	Major depressive disorder	14 (0.5)	3 (0.4)	11 (0.5)	0.700
EDSS		2.13 ± 2.79	2.39 ± 2.45	2.03 ± 2.90	<0.001
COVID-19 infection	Positive	623 (20.4)	145 (18.3)	478 (21.2)	0.089
	Negative	2427 (79.6)	646 (81.7)	1781 (78.8)	
COVID-19 diagnostic method	Not tested	2445 (80.2)	651 (82.3)	1794 (79.4)	
	PCR	356 (11.7)	96 (12.1)	260 (11.5)	
	CT-Scan	67 (2.2)	15 (1.9)	52 (2.3)	
	Clinical	178 (5.8)	27 (3.4)	151 (6.7)	
	Missing	4 (0.1)	2 (0.3)	2 (0.1)	
COVID-19 Hospitalization	No COVID-19	2427 (79.7)	646 (82.36)	1781 (78.87)	<0.001
	Hospitalized	61 (2.0)	26 (3.29)	35 (1.55)	
	Not-hospitalized	558 (18.3)	116 (14.72)	442 (19.57)	
MS drug	Not on DMT	261 (8.6)	98 (12.4)	163 (7.2)	<0.001
	On DMT	2789 (91.4)	693 (87.6)	2096 (92.8)	
	low dose interferon	469 (15.4)	93 (11.8)	376 (16.6)	
	high dose interferon	460 (15.1)	131 (16.6)	329 (14.6)	
	teriflunomide	209 (6.9)	36 (4.6)	173 (7.7)	
	natalizumab	30 (1.0)	5 (0.6)	25 (1.1)	
	rituximab	638 (20.9)	178 (22.5)	460 (20.4)	
	ocrelizumab	20 (0.7)	5 (0.6)	15 (0.7)	
	fingolimod	312 (10.2)	75 (9.5)	237 (10.5)	
	dimethyl fumarate	374 (12.3)	101 (12.8)	273 (12.1)	
	glatiramer acetate	180 (5.9)	44 (5.6)	136 (6.0)	
	alemtuzumab	1 (>0.00)	0 (0.0)	1 (>0.00)	
	two drugs	16 (0.5)	4 (0.5)	12 (0.5)	
	others	80 (2.6)	21 (2.7)	59 (2.6)	

Table 2
Drug comparison in hospitalization risk; Fisher-exact *P-value*; (RR) [95% CI].

	rituximab	low dose interferon	high dose interferon	Dimethyl fumarate	fingolimod	teriflunomide	glatiramer acetate
rituximab		<0.001 (1.740) [1.45–2.08]	0.002 (1.491) [1.25–1.76]	<0.001 (1.640) [1.39–1.92]	0.057 (1.270) [1.05–1.53]	0.049 (1.253) [1.05–1.48]	0.060 (1.243) [1.06–1.45]
low dose interferon	<0.001 (0.207) [0.07–0.61]		0.694 (0.852) [0.38–1.91]	1.000 (1.090) [0.52–2.25]	0.142 (0.578) [0.23–1.42]	0.220 (0.630) [0.26–1.49]	0.363 (0.704) [0.31–1.57]
high dose interferon	0.002 (0.252) [0.8–0.75]	0.694 (1.210) [0.53–2.74]		0.655 (1.296) [0.62–2.70]	0.465 (0.663) [0.26–1.64]	0.433 (0.714) [0.30–1.70]	0.670 (0.790) [0.35–1.78]
Dimethyl fumarate	<0.001 (0.159) [0.04–0.61]	1.000 (0.890) [0.30–2.63]	0.655 (0.745) [0.25–2.20]		0.126 (0.475) [0.14–1.54]	0.199 (0.525) [0.17–1.64]	0.338 (0.600) [0.20–1.78]
fingolimod	0.057 (0.466) [0.20–1.07]	0.142 (1.781) [0.99–3.17]	0.465 (1.439) [0.81–2.55]	0.126 (1.792) [1.07–2.99]		1.000 (1.038) [0.56–1.91]	1.000 (1.097) [0.62–1.93]
teriflunomide	0.049 (0.424) [0.16–1.09]	0.220 (1.789) [0.90–3.54]	0.433 (1.429) [0.72–2.81]	0.199 (1.826) [0.99–3.36]	1.000 (0.957) [0.44–2.04]		1.000 (1.068) [0.54–2.09]
glatiramer acetate	0.060 (0.363) [0.12–1.09]	0.363 (1.725) [0.74–4.00]	0.670 (1.362) [0.59–3.14]	0.338 (1.800) [0.84–3.84]	1.000 (0.872) [0.34–2.19]	1.000 (0.921) [0.38–2.23]	

history of COVID-19 infection: 1.46% had a positive PCR test or compatible CT-Scan results (Sahraian et al., 2020). The corresponding figure in our population was 13.8% the difference of which could be explained by the fact that our study conducted almost one year later into the pandemic when the country had endured two more waves of pandemic, both most tremendous in their size at their time.

It is of note that similar studies conducted in European countries and the USA tend to find a lower absolute history of positive COVID-19 in pwMS compared to our population. Two studies published in March 2021 by Reder et al. (2021) and Sepúlveda et al. (2021) report positive COVID-19 rates of 1.1% and 1.2% in the USA and Spain, respectively. It is not clear how the disparity between the results should be interpreted considering the difference in testing protocols used in different countries. As an example, the number of tests performed per million of

population, as of 11 March 2020, stands at 281,700 in Iran and at 1530, 771 and 1141,515 in the USA and Spain, respectively (WorldOMeter, 2021).

4.2. COVID-19 hospitalization risk

In terms of hospitalization, we observed 9.7% rate among those who had a positive COVID-19 diagnosis. While still higher than the rate of 4% expected in the general population (Clark et al., 2020), it is considerably lower than the 25% risk reported in the Iranian MS population reported by Sahraian et al. (2020). The reduction could be attributed to the fact that more people in Iran have been cooperating with mask mandates and physical distancing measures as reported by government (Islamic Repablic News Agency, 2020), a practice which has been shown to decrease hospitalization rates by Joo et al. (2020). It is also of note that in a report of Iranian pwMS, the subjects showed a relatively acceptable awareness on COVID-19 (Sahraian et al., 2020). While the decline could be seen optimistically as a sign of less severe COVID-19 in pwMS, hospitalization rate is still higher than the general population, an observation that has been reported in several studies (Louapre et al., 2020; Parrotta et al., 2020; Zabalza et al., 2020) and necessitates further efforts for vaccination and management strategies.

We also found that higher disability was associated with a higher likelihood of hospitalization, a finding which remains largely uncontroversial as the relationship between higher EDSS scores and severe COVID-19 has been observed by Louapre et al. and others (Louapre et al., 2020; Chaudhry et al., 2020; SharifianDorche et al., 2021).

EDSS and hospitalization risk was also higher in those who were taking no medication for their disease (likely due to progressive course of the disease and lack of response to treatment). It could be argued that their disability leads to a lack of community attendance and more adherence to health protocols, resulting in fewer infections, but this disability results in a more severe illness and need for hospitalization.

It is also of note that a significantly higher hospitalization risk seen in men, supporting the role of sex as a risk factor for severe COVID-19 which has been observed in numerous studies (Peckham et al., 2020; Booth et al., 2021; Rahman and Sathi, 2021). The lower hospitalization rate in women was observed despite their higher prevalence of comorbidities compared to men, This could be explained by the fact that the most prevalent comorbidity in our population (observed significantly more in women) was hypothyroidism which does not seem to affect COVID-19 severity (van Gerwen et al., 2020; Dworakowska and Grossman, 2020). The comorbidities suggested to be risk factors for severe COVID-19 as such for hypertension and diabetes mellitus (Booth et al., 2021; Rahman and Sathi, 2021) were not significantly different between the two sexes, despite being the second and third most prevalent comorbidities overall. In a study of COVID-19 in pwMS in the USA Reder et al. reported the most prevalent comorbidities to be hypertension and diabetes mellitus (Reder et al., 2021) and Sepúlveda et al. found the most prevalent comorbidity to be dyslipidemia, followed by hypertension and diabetes mellitus in a Spanish population (Sepúlveda et al., 2021). This shows a generally similar comorbidity profile in pwMS studies across countries.

4.3. DMT comparison

There was no significant relationship between the risk of having COVID-19 and the type of DMTs used. A finding that has been reported multiple times in different investigations since early on in the pandemic in research by Sormani (2020) and others (Fan et al., 2020; Crescenzo et al., 2020; Louapre et al., 2020; Chaudhry et al., 2020). It should be born in mind however that there have been different results: there have been reports of anit-CD20 therapies increasing infection risk by Reder et al. (2021) and Safavi et al. (2020) and interferons and glatiramer acetate lowering it by Reder et al. (2021).

Considering the relationship between individual drugs and hospitalization risk, drug classes with lowest relative risks were dimethyl fumarate and interferons and the highest relative risk was seen with rituximab. The topic of different DMT classes and their effect on COVID-19 course and hospitalization risk remains a controversial one. We found low dose interferons and dimethyl fumarate to have significantly lower relative risks in comparison with rituximab, findings that have been supported by other observations of high sample size in case of interferon by Sormani et al. (2021) and mechanistic predictions in case of dimethyl fumarate by Timpani and Rybalka (2020) and Safari et al. (2021). Although numerous studies and reviews have founds rituximab to have a worse effect on COVID-19 course compared to various DMTs (Chaudhry et al., 2021, Sormani et al., 2021, LangerGould et al., 2021, Safavi et al., 2020), a recent review by Sharifian-Dorche et al. does not support such an association (SharifianDorche et al., 2021) which shows the need for further studies and more thorough investigation of accumulated data.

It is of note that our data might be affected by a bias due to relying on people to recall their COVID-19 and MS history. It is of note however that nearly all of pwMS who met the inclusion criteria agreed to participate in the study.

5. Conclusions

We found no evidence supporting a higher prevalence of COVID-19 in pwMS compared to the general population. However, our results show pwMS to be more prone to hospitalization compared to the general population.

Although no relation was found between individual DMT drugs and risk of COVID-19 infection, rituximab had a significantly higher risk of hospitalization compared to other treatments and dimethyl fumarate had a lower risk. Therefore, it is advised to use safer treatment if possible until complete vaccination, and to postpone the use of immunosuppressive drugs such as rituximab.

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CRediT authorship contribution statement

Saba Naghavi: Investigation, Methodology, Data curation, Validation. **Aryan Kavosh:** Data curation, Writing – original draft, Writing – review & editing. **Iman Adibi:** Conceptualization, Methodology. **Vahid Shaygannejad:** Conceptualization, Resources. **Sina Arabi:** Formal analysis, Visualization. **Maryam Rahimi:** Resources. **Shahbanoo Mazaheri:** Resources. **Fereshteh Ashtari:** Project administration, Conceptualization, Methodology, Writing – review & editing, Funding acquisition, Data curation.

Conflict of interest

The authors declare no conflict of interest.

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