The study of COVID-19 infection following vaccination in patients with multiple sclerosis

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ABSTRACT

Background: At this time vaccination against SARS-CoV2 is a global priority. Cases with multiple sclerosis (MS) were among the first vaccinated populations in Iran. We evaluated the change in the frequency of COVID-19 after vaccination and the associated factors with severe COVID-19 infection before and after full vaccination.
Methods: A questionnaire was validated to investigate the basic characteristics (age, gender, education, body mass index, smoking status, and comorbidities), MS disease and treatment status (MS type, MS duration, The Expanded Disability Status Scale (EDSS), disease modifying treatments) and the information about COVID-19 infection and severity.
Results: 692 (91.9%) of participants have received both doses of vaccines, of which Sinopharm appeared to be the most common type. Significant difference of COVID-19 infection prevalence was seen before vaccination and after full vaccination (difference: 0.16, 95% CI: 0.12–0.20) (p value < 0.001). The difference was not significant for severe cases (those who were admitted in the ward or ICU) relative to the COVID-19 cases or the whole participants. Of all the basic and disease factors, only EDSS showed a significant association with severe COVID-19 before vaccination. Severe COVID-19 in fully vaccinated cases did not show any significant relation to any of basic or disease characteristics except with prior history of severe allergic reactions (OR: 17.1, p value: 0.001).
Discussion: The decreased frequency of infection with SARS-CoV2 was predictable but the insignificant difference in cases with the severe forms of the disease raise concern. The only significant predictor was found to be severe allergic reactions. As there are debates on antiCD20 s association with severe COVID-19 and vaccine efficacy, we could not find such significant relation. The other noticeable point about the found relation of EDSS and critical COVID-19 before vaccination is the absence of such relation after full vaccination.

1. Introduction

To date, about 4701,438 lives have been lost due to the infection with the novel coronavirus https://www.worldometers.info/coronavirus/ (reached at 19 September 2021). To overcome this hard time, scientists around the world have done their best to provide effective vaccines to mankind. According to the last statistics declared by the world health organization (WHO) around 5634,533,040 doses of vaccines have been administered globally till 15 September 2021 https://www.who.int/emergencies/diseases/novel-coronavirus-2019 (reached at 19 September2021).

The vaccination process in Iran started from populations with specific diseases like multiple sclerosis (MS). There is evidence of a higher admission rate due to COVID-19 in this population (Moghadasi et al., 2021). The authorities initially suggested that some disease-modifying

treatments (DMTs) used for the management of the disease may alter the risk of infection with the novel coronavirus (Sharifian-Dorche et al., 2021). Besides, these cases with chronic diseases have to be followed up on a regular basis, that increases the risk of exposure to the general population. Another concern was that the infection, and even the anxiety about it, could trigger relapses in the patients (Barzegar et al., 2021). A recent review, although with caution, warned about the probable increased risk of death among MS cases (Prosperini et al., 2021). While COVID-19 vaccines seem safe (Achiron et al., 2021; Ali Sahraian et al., 2021), yet there are doubts about vaccine efficacy in this population (Wolf and Alvarez, 2021).

The prevalence of MS in Tehran, as the capital city of Iran, appears to be high (Almasi-Hashiani et al., 2020). An Iranian study reported a higher hospitalization rate due to COVID-19 among MS cases in the country relative to the general population (Sahraian et al., 2020). It has

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also been shown that the most of the Iranian MS cases approve vaccination (Ghadiri et al., 2021). Sinopharm BBIBP-CorV is the most used vaccine in this group. Although no official documentation has yet been generated on vaccination status, it appears that a substantial proportion of MS cases has been fully vaccinated. We evaluated the change in the frequency of COVID-19 after vaccination. We also studied the associated factors with severe COVID-19 infection before and after full vaccination. The results would be of help in redesigning vaccination protocols in the future.

2. Material and methods

2.1. Ethical issues

The study protocol was approved at the ethics committee of Tehran University of medical sciences by IRB code of "IR.TUMS.NI. REC.1400.012″.

2.2. Questionnaire

A questionnaire was developed to investigate the basic characteristics (age, gender, education, body mass index (BMI), smoking status, and comorbidities), MS disease and treatment status including MS type (clinically isolated syndrome (CIS), radiologically isolated syndrome (RIS), relapsing-remitting MS (RRMS), secondary progressive MS (SPMS), and primary progressive MS (PPMS)), MS duration, The Expanded Disability Status Scale (EDSS), DMT, and the information about COVID-19 infection and its severity. It was checked by three MS specialists and three MS patients. The link to the final google form was made available in Telegram groups of Iranian MS patients for one week, from 11 September 2021 to 18 September 2021. To ensure validity, patients were asked to enter their unique National MS Registry code (Shahin et al., 2019) in the form. The given data about MS (type, treatment, duration, and DMT) and COVID-19 (severity, admission information) were rechecked in the registry. The diagnosis of COVID-19 had to be confirmed by an internist who evaluated the patient's history, physical exam, lung CT and nasal swab PCR test results.

2.3. Analysis

Data was entered to a SPSS IBM version 26 dataset. Duplicate cases were deleted. Regarding debates about the role of anti CD20 monoclonal antibodies, drugs were categorized as anti CD20s or others. Those cases managed inpatient (ward or ICU) were considered as patients with severe COVID-19. Frequency and mean with standard deviation (SD) were calculated for qualitative and quantitative data respectively. Differences in the frequencies were evaluated by z statistics. As it is assumed vaccination could not increase the risk of COVID-19 infection, one tailed p value was checked. Those under 0.05 were considered significant. Logistic regression method was used to find associated factors with severe COVID-19 infection before and after full vaccination. All available variables (related to basic characteristics and MS disease and treatment status) were analyzed separately. The factors with p value under 0.2 in univariate analysis were entered in the multivariate regression model. Those with p value less than 0.05 in the final model were considered to have significant association with the dependent variables.

3. Results

After one week of link sharing, 753 participants were enrolled. The basic characteristics of the participants are summarized in Table 1. The majority of the cases were young (mean age: 36.7 ± 8.0), female (578, 78.0%), with an academic degree (549, 72.9%), with BMI under 25 (454, 60.3%), nonsmoker (646, 85.5%), and without any considerable comorbidity.

*In the right column, mean (SD) is shown for quantitative factors and

Table 1
Basic characteristics of the participants.

Variable	*
Age	36.7 (8.0)
Gender	
Female	587 (78.0)
Male	156 (20.7)
Education (N, %)	
Without academic degree	194 (25.8)
With academic degree	549 (72.9)
BMI (kg/m^2) (N, %)	
< 25	454 (60.3)
≥ 25	299 (39.7)
Nonsmoker (N, %)	646 (85.8)
Smoker	89 (11.8)
< 15 pack year	80 (90.0)
≥ 15 pack year	9 (10.0)
Comorbidities (N, %)	
Metabolic disease (hypertension, diabetes mellitus, hyperlipidemia)	51 (6.8)
Cardiopulmonary diseases	7 (0.9)
Current or previous history of cancer	5 (0.7)
Previous history of severe allergic reaction (asthma, anaphylaxis, any reaction leading to hospitalization)	18 (2.5)

number (%) is shown for qualitative factors.

RRMS was the most frequent MS type (540, 71.7%) and most patients had EDSS less than six (685, 91.0%) (Table 2).

Table 3 shows DMTs used by the participants. Anti CD20s were used by 250 (33.2%) patients.

As Table 4 indicates 692 (91.9%) of participants have received both doses of vaccines, of which Sinopharm appeared to be the most common type.

Information on COVID-19 infection and severity is available in Table 5.

The frequencies are calculated relative to the whole population at base (without vaccination) and to the participants with full vaccination for the second outcome measure.

A significant difference of COVID-19 infection prevalence was seen before vaccination and after full vaccination (difference: 0.16%, 95% CI: 0.12% - 0.20%) (Z test p value: < 0.001) (one-tailed).

In all patients that got severe COVID-19 after full vaccination, it was after two weeks following full vaccination.

The difference was not significant for severe cases (those who were admitted in the ward or ICU) relative to the COVID-19 cases or to the whole participants. Sensitivity analysis also showed the same results for ICU admission and hospitalization (in the ward) as separate outcome measures (*p* value > 0.05).

Of all the basic and disease factors (age, gender, BMI, smoking status,

Table 2
MS disease characteristics of the cases.

Variable	Number (%)
Disease type	
RIS	4 (0.5)
CIS	26 (3.5)
RRMS	540 (71.7)
SPMS	87 (11.6)
PPMS	38 (5)
Disease duration	9.2 (6.3)
EDSS	
< 6	685 (91.0)
≥ 6	56 (7.4)

Table 3
DMTs used by the participants.

Drug name	Number (%)	Drug name	Number (%)
No drug	26 (3.5)	Natalizumab	28 (3.7)
IFN beta-1a (IM)	96 (12.7)	Rituximab	229 (30.4)
IFN beta-1a (SC)	39 (5.2)	Ocrelizumab	21 (2.8)
IFN beta-1b	17 (2.3)	Cyclophosphamide	1 (0.1)
Glatiramer acetate	46 (6.1)	Mitoxantrone	2 (0.3)
Teriflunomide	16 (2.1)	Azathioprine	3 (0.4)
Dimethyl fumarate	99 (13.1)	Mycophenolate mofetil	1 (0.1)
Fingolimod	97 (12.9)	Missing	31 (4.3)

Table 4
Vaccination status of the study population.

Variable	Number (%)
Vaccination status	
None	16 (2.1)
One dose	37 (4.9)
Full	692 (91.9)
Vaccine type	
Sinopharm	695 (92.3)
AstraZeneca	15 (2)
Sputnik	9 (1.2)
Others (Bharat Biotech COVAXIN, Pfizer-BioNTech COVID-19 Vaccine)	7 (0.9)

Table 5
COVID-19 outcomes before and after full vaccination.

Variable	N (%)
COVID-19 infection before vaccination	
Outpatient	215 (27.6)
Inpatient	12 (1.6)
ICU admission	1 (0.1)
COVID-19 infection after full vaccination	
Outpatient	95 (12.6)
Inpatient	6 (0.8)
ICU admission	1 (0.1)

and comorbidities, MS type, MS duration, EDSS, and anti CD20s), gender (p value: 0.04) and EDSS (p value: 0.01) were found to have possible correlations with severe COVID-19 before vaccination. As shown in Table 5, finally only EDSS showed a significant association with severe COVID-19 before vaccination in the final model.

Severe COVID-19 in fully vaccinated cases did not show any significant relation to any of basic or disease characteristics except with prior history of a severe allergic reaction (OR: 17.1, 95% CI: 3.08 – 94.83, *p* value: 0.001) (Table 6)

Sensitivity analysis was performed comparing outcome measures (severe COVID before and after full vaccination) between all potential B cell depleting agents (antiCD20s, fingolimod, mitoxantrone, and cyclophosphamide) in one group and other drugs in the other group. No significant association was found (p value > 0.05). Table 7

Table 6
Outputs of logistic regression model investigating factors associated with severe COVID-19 before vaccination.

Variable	OR	95% CI	*p* value
Univariate analysis			
Gender	3.3	1.1– 10.3	0.04
EDSS	6.8	1.6 – 29	0.01
Multivariate analysis			
Gender	3.1	0.9 – 9.8	0.06
EDSS	6.2	1.4 – 27.5	0.02

Table 7
Outputs of logistic regression model investigating factors associated with severe COVID-19 after full vaccination.

Variable	OR	95% CI	p value
Univariate analysis			
History of severe allergic reactionsAnti	37.6	2.9 – 488.0	0.006
CD20	3.6	0.6 – 14.4	0.16
Multivariate analysis			
History of severe allergic reactions	28.0	1.7 – 458.9	0.02
Anti CD20	1.57	0.2 – 9.9	0.63

4. Discussion

This study reports the changes in the frequency of COVID-19 after full dose vaccination and also associated factors of severe COVID-19 after vaccination in MS patients. We found that while the frequency of COVID-19 infection was significantly reduced after vaccination, the change was insignificant for severe infection. EDSS was found to be significantly associated with severe COVID-19 infection before vaccination. On the other hand, history of severe allergic reactions (asthma, anaphylaxis, or any other reaction leading to hospitalization) is shown to be an associated factor of severe COVID after vaccination.

The decreased frequency of infection with SARS-CoV2 was predictable but the insignificant difference in cases with a severe form of the disease raises concern. However, small number of severe cases could explain this finding. The only significant predictor was found to be severe allergic reactions. Darabi et al. (2021) reported a protective effect of allergic comorbidities on the risk of disease severity in Iranian COVID-19 cases . Another study among pediatric population could not find any relation between history of allergic reactions and the risk of worse outcome COVID-19 (Du et al., 2021). In a review, Wakabayashi and colleagues suggested that respiratory allergic diseases could inhibit severe inflammatory responses in COVID-19 (Wakabayashi et al., 2021). On the other hand, in line with our study, a Korean cohort study found asthma and allergic rhinitis associated with severe COVID-19 (Yang et al., 2020). This incongruity can arise from differences in the study populations. As with our cases, treatment with disease modifying therapies may have a confounding effect on the immune system. Another point is the definition of allergic reaction. We just included those reactions that are considered as severe, needing prompt medical attention. However, further investigations on the subject could lead to a better understanding of the disease. Besides, it could shed light on the road to designing vaccination guidelines.

Anti CD20 monoclonal antibodies (rituximab and ocrelizumab) are considered to be associated with severe forms of COVID-19 (Cabreira et al., 2021; Esmaeili et al., 2021; Safavi et al., 2020). Although, some contradicting results are reported (Sharifian-Dorche et al., 2021). Some scientists suggest that as CD20 depleting agents act against B-cell mediated immune response, T-cell immunity and defense against viruses like the novel coronavirus are not that disturbed (Apostolidis et al., 2021; Brill et al., 2021; Gadani et al., 2021; Sabatino et al., 2021). Another hypothesis is the effect of these drugs in inhibition of the inflammatory storm could blunt the COVID-19 disease course (Novi et al., 2020). Besides, there have been initial concerns of immune response attenuation in patients on treatment with anti CD20s that could influence vaccination outcomes (Sharifian-Dorche et al., 2021; Sormani et al., 2021b). Some experts proposed individualized anti CD20s dose adjustment (Maarouf et al., 2020; van Lierop et al., 2021), special vaccination timeline regarding the treatment course, and post-vaccination serology examination in cases receiving these drugs (Cabreira et al., 2021). However, our study results indicate that severe COVID-19 infection after full vaccination, especially with the Sinopharm vaccine, is not related to treatment with this group of drugs. This may be an indicator of intact T-call response like what some other studies suggest (Asplund Hogelin et al., 2021; Jena et al., 2021; Klineova et al., 2021; Naser Moghadasi, 2021). Moreover, Apostolidis et al. found

robust CD8 T cell response even in the absence of receptor-binding domain IgG after vaccination (Apostolidis et al., 2021).

Various studies did not find any association between the degree of disability in MS cases and risk of severe COVID-19 (Alonso et al., 2021; Czarnowska et al., 2021; Sen et al., 2021), while other scientists high-light the possible relation (Klineova et al., 2021; Louapre et al., 2020; Sormani et al., 2021a). Our results are in line with the latter. The other noticeable point is the absence of the same relation after full vaccina-tion. This may encourage those with higher EDSS to get vaccinated.

Our work suffers the limitations of a cross sectional study and limited number of participants. Besides, there are no data on the mortality rate. Another caveat is that our study population bares lower risk of severe COVID infection, as the majority are young, with BMI under, nonsmoker, and without any considerable comorbidity. As discussed above, this could explain the absence of vaccine efficacy in controlling severe COVID-19. However, some studies suggest lower antibody titers are detected after inoculation with inactivated vaccines like Sinopharm, compared to mRNA vaccines (Lijeskic et al., 2021) while available data from Australia show the neutralizing titer could be predictive of SARS-CoV2 infection after vaccination (Khoury et al., 2021).

One could argue the effect of different mutations on vaccine efficacy, as there are debates over the Sinopharm protection against delta variant, although with no official evidence. Controlling for the virus variant was not applicable in our study, therefore further research is warranted. However, we expected more infection over time in the absence of vaccination but we observed that vaccines could curb the incidence.

Still the results could be of use to look into the mechanisms of COVID-19 pathogenicity, the effect of history of severe allergic reactions on vaccine response, and finding alternative options to increase the vaccine efficacy in preventing critical COVID-19 disease in MS patients.

CRediT authorship contribution statement

Fereshteh Ghadiri: Conceptualization, Data curation, Formal anal-ysis, Investigation, Writing – original draft, Writing – review & editing. **Mohammad Ali Sahraian:** Conceptualization, Project administration, Resources, Validation, Writing – review & editing. **Amirreza Azimi:** Conceptualization, Validation, Writing – review & editing. **Abdorreza Naser Moghadasi:** Conceptualization, Methodology, Data curation, Supervision, Investigation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare no conflict of interest.

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