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# Can pulse steroid therapy increase the risk of infection by COVID-19 in patients with multiple sclerosis?

Abdorreza Naser Moghadasi [a], Maryam Shabany [b], Hora Heidari [a], Sharareh Eskandarieh [a,*]

[a] Multiple Sclerosis Research Center, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran
[b] Brain and Spinal Cord Injury Research Center, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran

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ABSTRACT

*Background:* Iran is one of the countries with a high prevalence of multiple sclerosis (MS) and COVID-19.MS patients receiving the immunomodulatory or immunosuppressive therapy have a higher risk of infection. Due to the significance of determining the risk factors for getting COVID-19 among MS patients, the present study was designed to assess the risk of infection following the pulse steroid therapy.

*Methods:* This cross-sectional study included all MS patients that received corticosteroids in Tehran from December 2019 to August 2020 during the COVID-19 pandemic spread. The subjects' clinical records including their sex, age, the type of MS, the type of medication, the number of days using corticosteroids, the status of prednisolone intake, and the number of days receiving prednisolone after the corticosteroid therapy were obtained. Moreover, main outcomes such as COVID-19 infection and the occurrence of death were recorded by patient's visits and follow-up phone calls. COVID-19 infection was confirmed by physicians according to the clinical performance of RT-PCR, chest CT scan, and antibody tests.

*Results:* Totally, 133 MS cases participated in the study, and the pulse therapy was completed for 104 (78.2%) patients up to 5–7 days. 89 (66.9%) cases used the prednisolone tablet following the pulse therapy. Overall, the infection by Covid-19 was observed in 8 (6%) cases, among whom 5 (71.4%) cases received the pulse therapy for 5–7 days and 4 (57.1%) cases had a history of taking the prednisolone tablet. The age of less than 40 years (OR = 1.03; 95% CI (0.23–4.51)), male sex (OR = 0.35; 95% CI (0.03–3.34)), and the RRMS type (OR = 2.87; 95% CI (0.52–15.72)) had no effect on the risk of Covid-19 infection.

In addition, there was not statistically significant difference between subjects with the short-term pulse therapy duration (3–4 days) (OR 0.68 (0.12–3.74) and those with the long-term pulse therapy duration (5–7 days). Similarly, no statistically significant difference was observed between subjects taking prednisolone (OR = 1.62 (0.34–7.61) and those not taking prednisolone. Furthermore, there was no significant association between different medication groups and the risk of Covid-19 infection ($p < 0.05$). No death occurred due to Covid-19 infection among the subjects.

*Conclusion:* COVID-19 infection was more common among female and younger patients as well as patients with a longer duration of the pulse therapy and prednisolone intake. There was no significant association between the pulse steroid therapy in MS patients and the risk of infection by COVID-19 in the Iranian population.

## 1. Background

Since December 31, 2019, a number of patients with atypical pneumonia caused by a novel coronavirus (2019-nCoV) have been reported in Wuhan, China [1]. Twenty-five countries around the world have confirmed the outbreak of 2019-nCoV one month after the spread of the virus in China. The World Health Organization (WHO) has declared a public health emergency of international concern on February 1, 2020 [1,2].

With most countries reporting cases of the disease and infections that were rapidly spreading in some regions of the world including South Korea, Iran, and Italy, the WHO declared COVID-19 as a pandemic on March 11, 2020 [3].

Among the countries in the world, Iran ranks 13th in terms of the coronavirus infection [4].

1,212,481 patients with COVID- 19 have been identified in Iran on

* Corresponding author at: MS Research Center, Sina Hospital, Hassan Abad square, Tehran, Iran.
*E-mail address:* sh_eskandarieh@yahoo.com (S. Eskandarieh).

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December 30, 2020. Of the mentioned number of patients, 54,946 deaths occurred by the virus, and Tehran (the capital of Iran) was considered as a region with a high prevalenceof Covid-19 [4].

Everyone in the community is at risk of the virus. However, some people with neurological conditions such as multiple sclerosis (MS) may be at a higher risk of the disease [5].

As one of the most common demyelinating disorders, MS receives due attention at present [6]. MS affects patients' quality of life, social relationships, employment, and productivity especially among those with disease exacerbation [7]. MS relapse can be defined as "a monophasic clinical episode with patient-reported symptoms and objective findings typical of MS, reflecting a focal or multifocal inflammatory demyelinating event in the Central Nervous System (CNS), developing acutely or sub-acutely, with a duration of at least 24 h, with or without recovery, and in the absence of fever or infection" [8].

The main treatment for MS relapses is the corticosteroid therapy, and many studies have demonstrated that a short-term high-dose intravenous methylprednisolone pulse therapy (IVMP) ameliorates the neurological symptoms and signs of acute relapses in patients with relapsing-remitting MS (RRMS) [9,10]. Improvement of MS relapses accelerates with high-dose steroids; however, the ultimate degree of improvement is not affected by steroids [10].

Glucocorticoids can induce the elimination of the inflammatory reaction and impact cellular immune systems by the induction of apoptosis and the inhibition of immune cell migration. The mentioned point means that humoral immune systems are affected by steroids leading to the diminution of proinflammatory cytokines [interleukin (IL)-2, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α] [11]. The other mechanisms include the suppression of arachnoid acid metabolites, suppression of the degranulation of lysosome enzymes, vascular dilatation shrinkage, fibrin deposition, and recovery of the blood–brain barrier [12].

In comparison with the general population, MS patients have indicated an increased risk of infections that leads to an increasing rate of mortality and the necessity of more critical and urgent care services [13, 14]. Among patients with MS, infections are one of the leading causes of death [14]. Moreover, the risk of infections increases in the long-term use of glucocorticoids in spite of being a more anti-inflammatory rather than an immunosuppressive therapy [15].

The very aim of this study was to determine whether the pulse steroid therapy could increase the risk of COVID- 19 infection among MS patients.

## 2. Methods

### 2.1. Study design

The present cross-sectional study included all MS patients that referred to Sina Hospital (Neurology departments) in Tehran to receive corticosteroids during December 2019 to August 2020 that corresponded to two months before and six months after the Covid-19 spread in Iran.

Sina Hospital as the tertiary referral center has one MS specialist clinic and three units with neurology departments that provide inpatient care and treatment services for MS patients.

The diagnosis of MS for all patients was confirmed by neurologists using the McDonald criteria [16].

Regarding the pulse therapy, all cases received the intravenous (IV) therapy (1 g per day) for 5–7 days. At the end of the pulse therapy course, the patient was discharged with the necessary training, which included the use of prednisolone 50 mg tablets. The dose of the tablet was gradually reduced and finally discontinued [9].

### 2.2. Sampling and data collection

To determine the risk of coronavirus among MS patients after the corticosteroid therapy, the baseline characteristics and clinical records of all MS patients that referred to the neurology wards were reviewed.

Information extracted from patients' records including sex, date of birth (age), age at the MS onset, marital status, occupation, types of MS, type of medication used over the last year, number of days using corticosteroids, status of receiving prednisolone tablet after the corticosteroid therapy, and number of days receiving prednisolone were collected [17].

All treatment outcomes were evaluated as whether or not patients were infected with the corona virus, which was confirmed by physicians according to the clinical performance of RT-PCR, chest CT scan, and antibody tests. Patients' infection was specified by reviewing patients' records on their clinic and doctor's visit in case of patients' referral and on follow-up phone calls in case of patients' non-referred to the hospital [18].

### 2.3. Ethical consideration and analysis

The demographic characteristics of cases, means (SD), and significant P-values ($< 0.05$) were estimated based on two-tailed tests. Logistic regression analysis was applied to estimate the Odds Ratio (OR) at 95% confidence interval (CI) using SPSS software, version 23.

This study was approved by the Research Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.VCR.REC.1399.137) with the grant number of 99-1-235-47274.

## 3. Results

A total number of 133 MS cases including 126 (94.7%) females and 7 (5.3%) males participated in the present study. The mean age (SD) of cases was 36.33 (±9.16) years with the minimum and maximum age of 13 and 64 years, respectively. The mean age (SD) of the disease onset was estimated to be 30 (±8.62) years. The most common occupation was being housewife (87 (65.4%) cases). Majority of cases, i.e. 118 (88.7%), were diagnosed to have RRMS, while 15 (11.3%) cases had progressive MS.

Most patients, i.e. 76 (57.6%), received the infusion therapy, while the injection therapy was received by 21 (15.9%) cases. Moreover, 24 (18.2%) cases did not use any drugs (Table 1).

The pulse therapy was completed for 104 (78.2%) and 29 (21.8%) cases over 5–7 and 3–4 days, respectively. 89 (66.9%) cases used prednisolone tablets after the pulse therapy for the mean (SD) of 11.34 (±3.46) days.

Among all subjects, only 8 (6%) cases were infected by Covid-19 virus (Table 1).

As it is demonstrated in Table 2, the infection rate in 133 patients indicated 8 (6%) infected vs. 125 (94%) non-infected cases.

Most of the infected patients by Covid-19 were female, i.e. 7 (87.5%) cases. Moreover, 5 (62.5%) cases were under the age of 40 years, and 6 (75%) cases were recognized to have RRMS. The younger age groups (less than 40 years) (OR = 1.03; 95% CI (0.23–4.51), $p = 0.96$)), male sex (OR = 0.35; 95%CI (0.03–3.34), $p = 0.36$)), and RRMS type (OR = 2.87; 95% CI (0.52–15.72)), $p = 0.22$) had no effect on the risk of Covid-19 infection.

Most of the infected patients, i.e. 5 (71.4%), received the pulse therapy in hospital for 5–7 days. Four (57.1%) cases of the mentioned patients had a history of taking prednisolone tablet.

There was not a statistically significant difference between the study groups regarding their shorter time pulse therapy (3–4 days) (OR 0.68 (0.12–3.74)) and prednisolone usage (OR 1.62 (0.34–7.61)). Evaluation of the association of different medication groups with Covid-19 infection revealed no significant association ($p < 0.05$).

Among the patients participating in the study, no death occurred due to Covid-19 infection.

**Table 1**
Baseline characteristics of MS patients.

| Variables | N (%) |
|---|---|
| **Age** (mean ± SD) (year) | 36.33 ± 9.16 |
| Sex | |
| Female | 126 (94.7) |
| Male | 7 (5.3) |
| Marital status | |
| Single | 45 (33.8) |
| Married | 88 (66.2) |
| **Occupation** | |
| Housewife | 87 (65.4) |
| Employed | 21 (15.8) |
| Unemployed/Retired | 13 (9.8) |
| Student (College/High school) | 12 (9.0) |
| **Types of MS** | |
| RR | 118 (88.7) |
| Progressive (PP and SP) | 15 (11.3) |
| **Age at disease onset** (mean ± SD) (year) | 30 (±8.62) |
| **Type of Medication** | |
| Injection therapy 1 | 21 (15.9) |
| Oral therapy 2 | 7 (5.3) |
| Infusion therapy 3 | 76 (57.6) |
| Other treatments 4 | 4 (3) |
| No Drug | 24 (18.2) |
| **Pulse therapy (days)** | |
| 3–4 | 29 (21.8) |
| 5–7 | 104 (78.2) |
| **Prednisolone usage after pulse therapy** | |
| Yes | 89 (66.9) |
| No | 44 (33.1) |
| **Prednisolone usage duration** (mean ± SD) (Day) | 11.34 (±3.46) |
| **Covid-19 infection** | |
| Yes | 8 (6) |
| No | 125 (94) |

SD: standard deviation, PP: primary progressive, SP: secondary progressive.
1= (Interferon b or Glatiramer acetate), 2= (Dimethyl fumarate, Teriflunomide, Fingolimod), 3= Natalizumab, Ocrelizumab, Rituximab), 4= (Azathioprine, Cyclophosphamide, Intravenous immune globulin (IVIG), Mitoxantrone).

**Table 2**
Associations of Variables with Covid-19 Infection.

| Variables | Covid-19 infected N (%) 8 (6%) | Covid-19 non-infected N (%) 125 (94%) | OR (95% CI) | P-value |
|---|---|---|---|---|
| **Age (years)** | | | | 0.96 |
| Less than 40 | 5 (62.5) | 79 (63.2) | 1.03 (0.23–4.51) | |
| 40 and older | 3 (37.5) | 46 (59.4) | Reference | |
| **Sex** | | | | 0.36 |
| Male | 1 (14.3) | 7 (5.6) | 0.35 (0.03-3.34) | |
| Female | 7 (87.5) | 119 (94.4) | Reference | |
| **Marital status** | | | | 0.32 |
| Single | 4 (50) | 41 (32.8) | 0.48 (0.11–2.05) | |
| Married | 4 (50) | 84 (67.2) | Reference | |
| **Types of MS** | | | | 0.22 |
| RR | 6 (75) | 112 (89.6) | 2.87 (0.52–15.72) | |
| Progressive (PP and SP) | 2 (25) | 13 (10.4) | Reference | |
| **Pulse therapy (days)** | | | | 0.66 |
| 3–4 | 2 (28.6) | 27 (21.6) | 0.68 (0.12–3.74) | |
| 5–7 | 5 (71.4) | 98 (78.4) | Reference | |
| **Prednisolone usage** | | | | 0.54 |
| Yes | 4 (57.1) | 80 (68.4) | 1.62 (0.34–7.61) | |
| No | 3 (42.9) | 37 (31.6) | Reference | |

OR: Odds Ratio, CI: Confidence Interval, RR: Relapsing-Remitting, PP: Primary-Progressive.
SP: Secondary-Progressive.

## 4. Discussion

The present study did not figure out a significant association between the use of corticosteroids and the risk of developing COVID-19. There was also no association between the duration of taking corticosteroids and developing COVID-19. Moreover, none of the eight patients with COVID-19 died.

From the beginning of the outbreak of COVID-19 in December 2019, MS patients and their treatment in the current situation have been a topic of special interest to neurologists [19].This concern has been raised in several aspects. First, many patients with MS take immunosuppressive drugs, which have been previously shown to increase the risk of infections [20]. Therefore, the mentioned fact could be true for COVID-19 disease. Whether or not these patients should continue or discontinue their immunosuppressive drugs is also a serious issue for neurologists [21].

The next issue is the need to use corticosteroids in MS relapses. Corticosteroids are the first-line treatment in patients with MS relapse [22]. However, it has been shown that using corticosteroids can increase the risk of infection [23]. Moreover, studies have demonstrated that the use of high doses of corticosteroids can increase the mortality rate in patients with COVID-19 [24]. In fact, although the low-dose and short-term use of corticosteroids may improve the condition of patients, high doses of corticosteroids (i.e., the dose normally prescribed in MS relapses) can lead to a longer hospitalizationand viral shedding [25].

The effect of low-dose corticosteroids, especially dexamethasone, has been investigated in a number of studies. The findings have revealed that the use of dexamethasone can reduce the mortality rate in COVID-19 patients [26]. Therefore, the question is whether the use of corticosteroid can increase the risk of developing COVID-19 in MS patients.

This concern has been so serious that even some guidelines have recommended to avoid or prescribe corticosteroids at the lowest possible dose, especially in cases of mild relapses [27]. However, the high-dose corticosteroid injections as a standard treatment for MS attacks are often prescribed. Thus, the possibility of the increased risk of developing COVID-19 following the consumption of corticosteroids should be considered. Similarly, the present study revealed that the injection of corticosteroids did not increase the risk of developing COVID-19. In addition, it was not found to be associated with an increased risk of mortality in case of developing the disease.

The fact that the results obtained in this study were contrary to initial estimates can be justified considering several reasons. First, it has been indicated that the risk of developing COVID-19 was generally not higher in MS patients as compared to the normal healthy population [28].

In MS patients, younger age, fewer comorbidities, and female sex were all factors that reduced the risk of developing COVID-19 [29].

The MS patients' high awareness level regarding COVID-19and its risk factors is the next issue. Patients' knowledge and awareness can be effective in following healthcare recommendations in these patients [30], which is an important factor in reducing the risk of developing COVID-19. These explanations may justify the lack of an association between using corticosteroids and developing COVID-19 in MS patients despite the immunosuppressive effects of corticosteroids[31].

## 5. Conclusion

No association was identified between the pulse steroid therapy in MS patients and the risk of infection by the novel coronavirus, COVID-19. The present inquiry manifested a higher number of COVID-19 among females, which can be justified considering the higher prevalence rate of MS in women. Moreover, its association with RRMS can be due to the high incidence of relapses in these patients and the higher probability of their inclusion in similar studies. However, further studies with a larger sample size are required to obtain more comprehensive

results.

## Ethics approval and consent to participate

The study was approved ethically by the Institutional Review Board of Tehran University of Medical Sciences, Tehran, Iran.

An informed consent was obtained from each subject.

In the study, the privacy of the subjects was maintained.

## Consent for publication

Not Applicable.

## Availability of data and materials

The data sets used and analyzed during the study are available from the corresponding author on a reasonable request.

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The founder had no role in the design of the study; in the collection, analysis, and interpretation of data; and in the writing process of the manuscript.

## Authors' contribution

Sharareh Eskandarieh conceived and designed the study, Funding acquisition, data collection and data analysis Methodology, Project administration and supervision. The manuscript was original draft, Writing - review & editing by Abdorreza Naser Moghadasi, Maryam Shabany, Hora Heidari, Sharareh Eskandarieh and was then critically revised by them. All authors read and approved the final version of the manuscript.

## Declaration of Competing Interest

The authors report no declarations of interest.

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