

# Implementing coronavirus disease 2019 scale-up registry protocol in national multiple sclerosis registry system of Iran

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## Keywords

COVID-19; Multiple Sclerosis; Registry System; Database; Iran

## Abstract

**Background:** The national multiple sclerosis (MS) registry is aimed at monitoring and improving quality of care and providing feedback to improve health outcomes by systematic recording of data. In 2018, the nationwide MS registry of Iran (NMSRI) was initiated for collecting epidemiological data and information on health care provision for patients with MS. The aim of the current study was to introduce the role of implementing coronavirus disease 2019 (COVID-19) scale-up registry protocol in NMSRI and arrange the national MS generality with information obtained during the COVID-19 pandemic.

**Methods:** The NMSRI group set up a program with crucial elements to collect the data of patients with MS who developed COVID-19. All MS cases with confirmed diagnosis of COVID-19 were enrolled in this study. New elements were considered to be added into the dataset, including demographic characteristics, definite diagnosis of COVID-19 and its

symptoms, history of comorbidities, history of medications and hospitalization, changes in magnetic resonance imaging (MRI), and infection outcomes.

**Results:** The COVID-19 data collection program was designed in NMSRI to collect data of MS cases with COVID-19 infection. The data collection protocol was explained to neurologists through an online training workshop. To the date of the study, 21 centers from 17 provinces of Iran were involved in the COVID-19 databases promoting NMSRI and 612 participants were registered successfully.

**Conclusion:** We extended an agreement on data collection and developed it in NMSRI with various contributors to discover a critical need for COVID-19 awareness and monitor clinical training in MS.

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## Introduction

On February 19, 2020, Iran reported its first

confirmed cases of the coronavirus disease 2019 (COVID-19) infection. The total number of patients with COVID-19 and the total number of deaths caused by this disease reached respectively 388810 and 22,410 cases by September 8, 2020 in the country; these figures were expected to increase dramatically.<sup>1</sup>

The COVID-19 infection caused significant concerns in a population with chronic neurological disabilities such as multiple sclerosis (MS) in the absence of valid data.<sup>2</sup>

Everyone in the community was at risk of the infection, however some people with neurological conditions such as MS were at a higher risk, which increased the concern among people with MS.<sup>2,3</sup>

On the basis of the results of several studies, patients with MS are at increased risk for infection in comparison to the healthy population. This infection can cause relapses, worsening of neurologic symptoms, and morbidity.<sup>4,5</sup> On the other hand, patients with MS who are treated with immunosuppressive therapies, might be more at risk and need more protection against the COVID-19 infection.<sup>6</sup>

However, some disease-modifying therapies (DMTs) for MS treatment may have effects on increasing the risk of infection during the COVID-19 pandemic, therefore it is of utmost importance to understand how DMTs affect a patient's immune response against the novel coronavirus.<sup>7</sup>

Moreover, it is critical to consider the effect of DMTs on the risk of developing COVID-19 in patients with MS as well as the morbidity and severity of the COVID-19 infection developed due to DMT or treatment approaches.<sup>3</sup>

There are inadequate information about patients with MS infected by COVID-19, while there is a crucial requirement to detect patient baseline characteristics and disease outcomes among this population.<sup>8,9</sup> In this regard, collecting data to estimate the association between MS and COVID-19 and implementing suitable protective strategies in care and treatment are of great concern.<sup>8</sup>

It is now important to conduct some evidence-based research on MS cases for prevention, care, and treatment of COVID-19.<sup>8</sup>

The national disease registries play an important role in providing a higher quality of care services and better patient clinical outcomes leading to more effective management processes.<sup>10,11</sup>

The nationwide MS registry of Iran (NMSRI) was established in 2018 using standardized minimum data set to determine MS distribution,

investigate the effect of MS on patients' life, and enlighten the use of pharmacological treatments and their side effects by recording the patient data along with the annual follow-up data.<sup>12</sup>

Beside NMSRI, we decided to design a dynamic registry of MS cases with COVID-19 infection in Iran.<sup>8</sup>

We are recording clinical outcomes and symptoms, diagnostic tests, provided treatments, and hospitalization rate to identify the risk factors for developing this infection and improve quality of care among patients with MS in regional and national levels.

The aim of this study was to introduce the role of implementing COVID-19 registry protocol in NMSRI.

## Materials and Methods

**Project Design and Setting:** The Multiple Sclerosis COVID-19 registry system is a prospective and ongoing clinical and hospital-based registry project on patients with MS who have been diagnosed with COVID-19 infection.

This MS registry system was planned to be a dynamic, follow-up based registry as a supplementary to NMSRI. The resources were all MS referral hospitals and clinics in Iran. The scientific team of the Multiple Sclerosis Research Center, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran supervised the database of NMSRI under the sponsorship of Ministry of Health and Medical Education (MOHME) of Iran.

Each neurologist has limited access to the information recorded in the center he/she is working. In fact, an administrator in each province has access to the information of the province under his/her coverage. However, the main director of NMSRI has access to all the information according to the legal contract with MOHME.

The NMSRI is a national registry and according to the rules governing the Iranian MS registration systems, all neurologists can access the system and register their patients if they wish. So far, more than 300 trials have been made to register patients with MS in Iran.

On the other hand, all physicians and researchers can have access to registration information by submitting a research proposal and receiving approval from the Scientific and Executive Committee of the registration system.

A group of national multidisciplinary MS researchers cooperated to define and expand an evidence-based standard set of data elements of COVID-19 to be incorporated into the NMSRI,

which is a group specific COVID-19 registry during the epidemic.

Diagnosis of all patients with MS was performed by neurologists based on the latest McDonald criteria in neurological departments in Iran and neurologists filled out the database in their settings.<sup>13</sup>

The national MS registry dataset was implemented in 2018 in Iran covering six domains including patient identification, family history of MS, clinical diagnosis, disease course, disability status, and medications and their side effects. To prevent repeated data input in NMSRI, the registration is performed using patients' individual identification number (ID).

The data collection in registry system is intended, based on the neurologists' interview with the patients and the clinical examination in each visit.<sup>12</sup> The neurologist adds new events and other required information into the dataset in each visit and updates the Expanded Disability Status Scale (EDSS) and any medicine changes.

This study included patients with MS who were infected by corona virus after February 2020 during the COVID-19 epidemic in Iran. This supplementary registry system was planned in agreement with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and the Declaration of Helsinki (DoH) principles.<sup>14,15</sup>

**Ethical Consideration:** This study was approved by the "Research Ethics Committee" of Tehran University of Medical Sciences (IR.TUMS.NI.REC.1399.028).

**Data collection methods and measures:** Patients with MS of any age with confirmed identification of COVID-19 along with the attached documents, including a definitive diagnosis by chest computed tomography (CT) scan, well-matched with COVID-19 infection and/or confident diagnosis of the COVID-19 infection with real-time polymerase chain reaction (PCR) were involved in the study.<sup>16,17</sup>

## Results

In addition to MS registration data, we added the following items in 2 phases: 1) Further investigations on COVID-19 infection among patients with MS including corticosteroid use in 3 months before being infected by the coronavirus, symptoms of infection, COVID-19 treatment drugs, blood test and CT scan result, prescribed drugs before and after developing the infection,

history of chronic diseases, and history of hospitalization or intensive care unit (ICU) course and the outcomes (Table 1).<sup>17</sup>

2) Further investigations on MS disease after COVID-19 infection, including MRI, gadolinium enhancing lesions and new T2 numbers, MS drug changes, and EDSS (Table 2).

Until December 3, 2021, 612 cases were registered successfully and screened for any repeated data by the patients' IDs.

All data was recorded on separate predesigned District Health Information Software 2 (DHIS2) by trained neurologists.<sup>18</sup>

**Bias reduction and quality assurance:** The retrospective data collection from medical registers may impose some bias in the prospective registry system. However, due to the unidentified general outcomes of COVID-19, the rules might be changed and updated through the study. Therefore, a scientific committee was regularly monitoring the international and national recommendations of data collection.

To prevent incorrect data entry into the DHIS2, validation rules were defined and implemented including syntactic and semantic rules and rules for acceptable value range.

## Discussion

NMSRI-COV19 is a continuing registration of patients with MS with confirmed COVID-19 in Iran, which is considered to evaluate patients' demographic characteristics, hospital outcomes, findings, etc.

During the COVID-19 pandemic, initiatives to reduce the risks of COVID-19 infection and its prevention are particularly important for people with chronic diseases.

Worldwide, Iran ranks 8<sup>th</sup> in terms of developing COVID-19 infection. By December, 3, 2021, 6129199 patients with COVID-19 were identified in Iran, of who 130066 were died due to the infection.

Healthcare professionals need urgent evidence for challenging with clinical decisions.

The threat of COVID-19 in patients with MS during the pandemic has motivated clinicians to look for an approach to provide a registry system for data gathering across the country, preventing infection, and supporting qualified investigation of treatment outcomes.<sup>19</sup>

An Italian program of the COVID-19 infection in patients with MS collected data of 232 patients from 38 centers and continues to monitor the patients throughout the pandemic.

**Table 1.** Further investigations of coronavirus disease-2019 (COVID-19) on patients with multiple sclerosis (MS)

| Variables                                                                                                                                                                                          | Findings                                                                            |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Baseline characteristics                                                                                                                                                                           | Number                                                                              |
| Occupation                                                                                                                                                                                         |                                                                                     |
| Family members living with the patient                                                                                                                                                             |                                                                                     |
| Corticosteroid use                                                                                                                                                                                 | Yes/No                                                                              |
| History of use (3 months before COVID-19)                                                                                                                                                          | Year/month/day                                                                      |
| Date of use                                                                                                                                                                                        | Pulse therapy (3 or 5 days), Dexamethasone, Betamethasone, ACTH, Prednisolone, etc. |
| Type and amount of corticosteroid use                                                                                                                                                              | Had/did not have                                                                    |
| Symptoms                                                                                                                                                                                           |                                                                                     |
| Cough, fever, shortness of breath, runny nose, muscle ache, diarrhea, headache, fatigue, dizziness, nausea/vomiting, loss of taste and smell, weakness and lethargy, decreased consciousness, etc. |                                                                                     |
| Blood test                                                                                                                                                                                         | Test answers                                                                        |
| White blood cells, hemoglobin, neutrophil, lymphocyte, CRP, PCR                                                                                                                                    |                                                                                     |
| CT scan of the lungs                                                                                                                                                                               | Unilateral or bilateral                                                             |
| Ground glass opacity                                                                                                                                                                               | Unilateral or bilateral                                                             |
| Consolidation                                                                                                                                                                                      | Uploading CT scan                                                                   |
| ARDS                                                                                                                                                                                               |                                                                                     |
| COVID-19 test                                                                                                                                                                                      | Positive or negative                                                                |
| Hospitalization                                                                                                                                                                                    | Yes (days) /No                                                                      |
| Outcomes                                                                                                                                                                                           | Hospital discharge/Death                                                            |
| Prescription drugs                                                                                                                                                                                 | Amounts                                                                             |
| Hydroxychloroquine, Tamiflu, Antibiotique, Ribavirin, Salbutamol, Naproxen, Tocilizumab, Kaletra, etc.                                                                                             |                                                                                     |
| History of chronic comorbidities                                                                                                                                                                   | Yes/No                                                                              |
| Hypertension, DM, asthma, COPD, allergy, lung infection, cancer                                                                                                                                    |                                                                                     |
| Patients' medications during COVID-19 infection                                                                                                                                                    | Name of drugs                                                                       |
| Patients' medications before COVID-19 infection                                                                                                                                                    | Yes/No                                                                              |
| Vitamin D, Vitamin C, Zinc, NASID <sup>2</sup>                                                                                                                                                     |                                                                                     |

COVID-19: Coronavirus disease-2019; ACTH: Adrenocorticotrophic hormone; PCR: Polymerase chain reaction; CRP: C-reactive protein; CT: Computed tomography; ARDS: Acute respiratory distress syndrome; DM: Diabetes mellitus; COPD: Chronic obstructive pulmonary disease; NASID: Nonsteroidal anti-inflammatory drugs

**Table 2.** Further investigations on multiple sclerosis (MS) disease after coronavirus disease-2019 (COVID-19) infection

| Variables                    | Detection       |
|------------------------------|-----------------|
| Changes in the main drug     | Yes (dosage)/No |
| Changes in MRI               | Yes/No          |
| Gadolinium enhancing lesions | Numbers         |
| New T2 Lesions               | Numbers         |
| EDSS                         | Numbers         |

MRI: Magnetic resonance imaging; EDSS: Expanded Disability Status Scale

During a mean follow-up of 12 days, there was not enough information to speculate about any susceptibility to protection from COVID-19 afforded by DMTs.<sup>8</sup>

Moreover, according to the baseline characteristics and clinical outcomes of 347 patients with COVID-19 and MS in French MS registry, 73 (21.0%) patients had severe COVID-19 and 12 (3.5%) died of COVID-19. Totally, 284 (81.8%) patients received DMT and there was a higher percentage of cases with a COVID-19 severity score among patients without DMT in comparison to cases who received

DMTs (46.0% vs 15.5%;  $P < 0.001$ ).<sup>20</sup>

The registry collects longitudinal data, thus neurologists and practitioners can sign into the registry via a survey access code and update information and outcomes of MS cases and download their own patients' data to complete their records or establish case reports.<sup>21</sup> As a result, this complementary and COVID-19 support registry can be a critical tool for breaking down information polarization.<sup>21</sup>

On the other hand, we motivated several stakeholders in the specialized field of MS in different provinces of the country (specialized neurologists, researchers, etc.) to join the NMSRI-COV19 registry for data collection from clinicians, patients, and nurses.<sup>19</sup>

The results of this study would deliver valuable and novel epidemiological information on Iranian patients with MS who were affected by the COVID-19 infection. These outcomes could be used for 1) identifying patients' demographic characteristics, comorbidities, symptoms, and risk factors; 2) estimating disease outcomes in patients

with MS and gaining information on risk factors related with harmful events; 3) evaluating variations in laboratory results of COVID-19 patients and their relationship with outcomes; 4) assessing diverse treatment policies and their potential safety and efficacy; and 5) arranging a system for leading upcoming evidence-based studies and beneficial clinical trials.

We included 22 centers from 17 provinces of Iran in NMSRI-COV19 and strongly encouraged a multidisciplinary approach for data collection and collaboration to increase the coverage of the centers included across various provinces involved in the care of patients with MS in Iran.<sup>22</sup>

We would like to include other centers to participate in NMSRI-COV19. To allow a quick set-up of the registry for centers willing to contribute, we established a selection of resources including the registry protocol, patient information form, and distance education by holding workshops and compiling an educational file for entering and managing information.<sup>22</sup>

However, there is an urgent need for neurologists to help the NMSRI-COV19 in collecting these important clinical data.<sup>6</sup>

This registry could prove lifesaving during the current COVID-19 pandemic and be responsive in next challenging virus that might follow the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).<sup>21</sup>

## Conclusion

We implemented COVID-19 scale-up registry protocol in NMSRI with various partners to address a critical need for disease awareness to guide clinical practice in MS.

## Conflict of Interests

The authors declare no conflict of interest in this study.

## Acknowledgments

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