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Review Article

Incidence of multiple sclerosis (MS) relapse after COVID-19 infection: A systematic review and meta-analysis

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Abstract

Background: COVID-19 could exacerbate the symptoms of autoimmune diseases such as multiple sclerosis (MS). Literature shows an increase in the incidence of relapse in patients with MS after COVID-19. We designed this systematic review and meta-analysis to estimate the pooled incidence of MS-relapse after COVID-19.

Methods: We performed a systematic search in PubMed, Scopus, EMBASE, Web of Science, and Google scholar. Gray literature including references of the references and conference abstracts were also searched to find relevant articles. We extracted data regarding the total number of participants, the name of the first author, publication year, country of origin, mean age, mean disease duration, mean Expanded Disability Status Scale (EDSS), and the number of patients with relapse after COVID.

Results: A literature search revealed 5160 articles, after deleting duplicates, 2270 remained. After careful evaluation of the full texts, twelve studies were included for meta-analysis. Totally, 1595 patients with MS who had a history of COVID-19 were evaluated. Most studies were done in Iran. The mean age of included patients ranged between 35 and 49 years, and mean durations of the disease were between 7and 15.4 years. The incidence of relapse ranged between 2% and 20% in included studies.
The pooled incidence of relapse after COVID-19 was 7% (95%CI:5-10%) (I2=64%, p<0.001).

Conclusions: The results of this systematic review and meta-analysis show that the pooled incidence of MS-related relapse after COVID-19 is 7%.

Keywords: Multiple sclerosis, Relapse, Incidence, COVID-19.

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In December 2019, a new coronavirus was introduced which causes severe acute respiratory syndrome (1). Now, it is in the pandemic stage while the first and the most symptoms were cough, fever, dyspnea, hyposmia/ anosmia, and hypogeusia/ageusia (2). During the time, neurological manifestations such as headache, dizziness, impaired consciousness, and muscle pain were considered as COVID-19 related symptoms (3). On the other hand, there were concerns regarding the risk of infection in patients who were under treatment with immunosuppressive or immunomodulatory agents such as patients with multiple sclerosis (MS) (4). Relapses which are characterized as exacerbations of neurological disability could impair quality of life of affected cases, and physicians and patients pay attention to them (5). In general, the annualized relapse rates of MS ranges from 0.27 to 1.66 relapses per year (6). A recent systematic review and meta-analysis have showed that the pooled prevalence of COVID-19 in patients with MS was 4% and the pooled prevalence of hospitalization was 10% (7). Considering the effects of infection on disease course in patients with MS is crucial as it promotes proinflammatory immune profile and leads to the exacerbation of the disease in patients with MS (8).

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Literature shows increase in the incidence of relapse in patients with MS after COVID-19. So, we designed this systematic review and meta-analysis to estimate the pooled incidence of relapse after COVID-19 in patients with MS.

Methods

We performed a systematically search in PubMed, Scopus, EMBASE, Web of Science, and Google Scholar. Gray literature including references of the references and conference abstracts were also searched to find relevant articles. After deleting duplicates, two independent researchers screened the titles and abstracts of the potential studies and in the case of discrepancy they asked the third one to solve the disagreement.

Then the full texts of the remained studies were assessed and the data were extracted. The extracted data were entered by each researcher in a datasheet and the third one checked the data of two sources. Data extraxtion was performed based on a predefine table including: the total number of participants, first author, publication year, the country of origin, mean age, mean disease duration, mean Expanded Disability Status Scale (EDSS), number of patients with relapse after COVID. The search was done on October 1st, 2022. The keywords which were used for searching were as follows:

((Multiple Sclerosis) OR (Sclerosis, Multiple) OR (Sclerosis, Disseminated) OR (Disseminated Sclerosis) OR (Multiple Sclerosis, Acute Fulminating)) AND ((COVID-19) OR (COVID 19) OR (SARS-CoV-2 Infection*) OR (Infection, SARS-CoV-2) OR (SARS CoV 2 Infection*) OR (2019 Novel Coronavirus Disease) OR (2019 Novel Coronavirus Infection) OR (2019-nCoV Disease*) OR (2019 nCoV Disease*) OR (Disease, 2019-nCoV) OR (COVID-19 Virus Infection*) OR (COVID 19 Virus Infection*) OR (Infection, COVID-19 Virus) OR (Virus Infection, COVID-19) OR (Coronavirus Disease 2019) OR (Disease 2019, Coronavirus) OR (Coronavirus Disease-19) OR (Coronavirus Disease 19) OR (Severe Acute Respiratory Syndrome Coronavirus 2 Infection) OR (SARS Coronavirus 2 Infection) OR (COVID-19 Virus Disease*) OR (COVID 19 Virus Disease*) OR (Disease, COVID-19 Virus) OR (Virus Disease, COVID-19) OR (2019-nCoV Infection*) OR (2019 nCoV Infection*) OR (Infection, 2019-nCoV) OR (COVID19) OR (COVID-19 Pandemic*) OR (COVID 19 Pandemic*) OR (Pandemic, COVID-19) OR (SARS-CoV-2) OR (SARS Coronavirus 2) OR (Coronavirus 2, SARS) OR (Coronavirus Disease 2019 Virus) OR (2019 Novel Coronavirus*) OR (Coronavirus, 2019 Novel) OR (Novel Coronavirus, 2019) OR (Wuhan Seafood Market Pneumonia Virus) OR (SARS-CoV-2 Virus*) OR (SARS CoV 2 Virus*) OR (Virus, SARS-CoV-2) OR (2019-nCoV) OR (COVID-19 Virus*) OR (COVID 19 Virus*) OR (Virus, COVID-19) OR (Wuhan Coronavirus) OR (Coronavirus, Wuhan) OR (COVID19 Virus*) OR (Virus, COVID19) OR (Viruses, COVID19) OR (Severe Acute Respiratory Syndrome Coronavirus 2)). Inclusion criteria were defined as follows: Retrospective/prospective cohort studies, articles published in English. Exclusion criteria were: Letters to the Editor, case-control, case reports, and cross-sectional studies which had no clear data.

Risk of bias assessment: Risk of bias assessment was performed using adapted version of NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE(NOS) for cohort studies (9).

Statistical analysis: All statistical analyses were performed using STATA (Version 14.0; Stata Corp LP, College Station, TX, USA). To determine heterogeneity, inconsistency (I2) was calculated. We used random-effects model for meta-analysis as the heterogeneity between study results (I2) was more than 50%.

Results

Literature search revealed 5160 articles by literature search, after deleting duplicates 2270 had remained. After careful evaluation of the full texts, twelve studies were included for meta-analysis (figure 1). Twelve articles were included. Totally, 1595 patients with MS who had COVID-19 were evaluated. Most studies were done in Iran. The mean age of included patients ranged from 35-49 years, and mean durations of the disease were between 7-15.4 years. The NOS score of the original studies were 6 and 8. The basic characteristics of the included studies (table 1). The incidence of relapses ranged between 2-20% in included studies. The pooled incidence of relpases after SARS-CO-19 infection was 7% (95%CI:5-10%)(I^2=64.8%, P<0.001) (figure 2).

Discussion

The results of this systematic review and meta-analysis show that the pooled incidence of MS-related relapse after COVID-19 is 7% which ranges between 2and 20% in included studies. The difference between the results of included studies could be due to different inclusion and exclusion criteria, the differences in relapse definition, and various follow-up time. Barzegar et al. enrolled 41 RRMS patients with definite COVID-19 diagnosis (11).

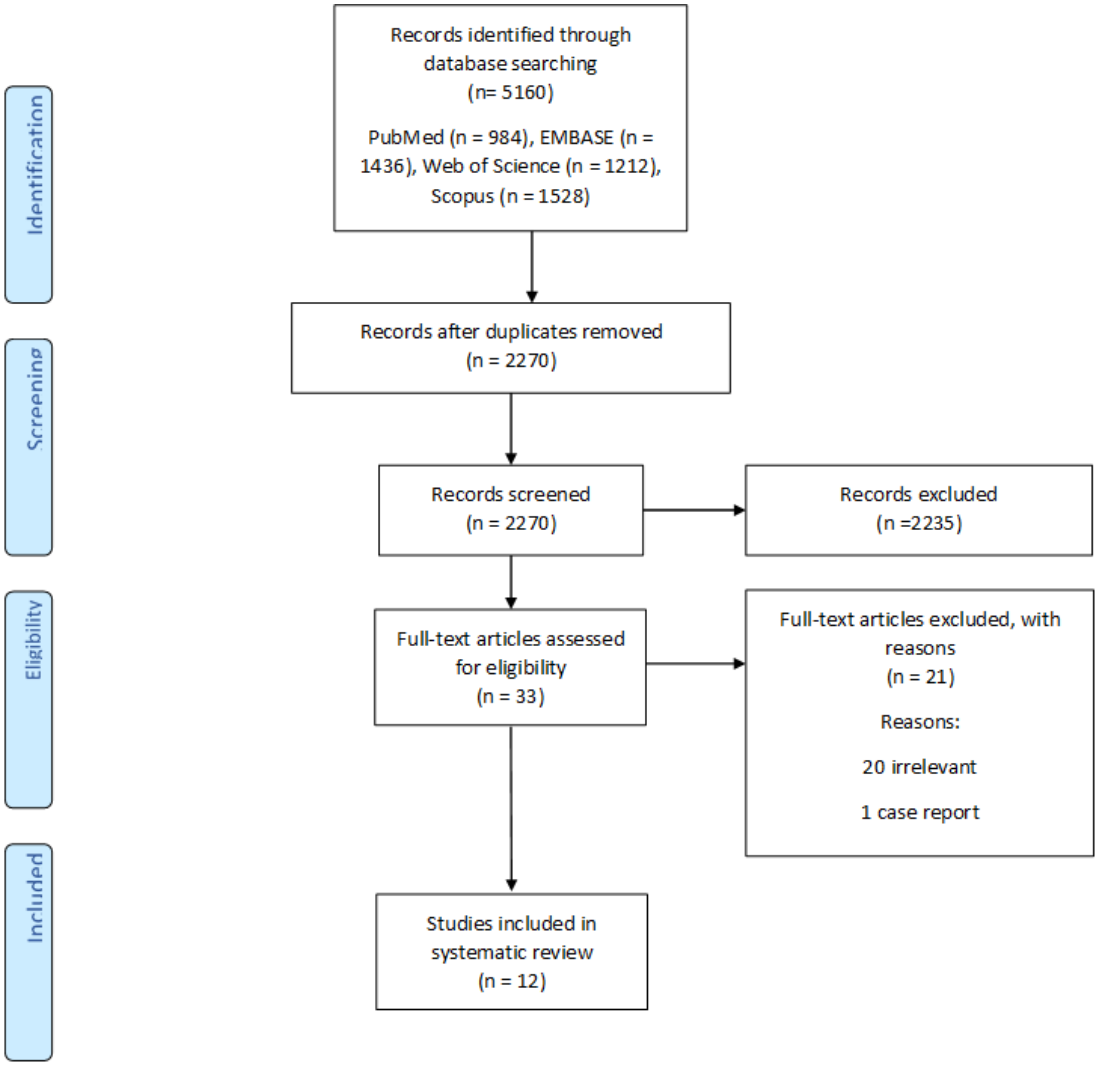

Figure 1. The flow chart of studies inclusion

Table 1. Basic characteristics of included studies

Author	Country/ year	MS population	MS type	Female/Male	Mean age of participants	Mean Disease duration	Median EDSS	Number of relapse	NOS score
G. Michelena (10)	Argentina/ 2021	41	RRMS:37/ SPMS:2/ PPMS:1/ CIS:1	24/17	42.9 (11.3)	9.6 (6.6)	2.4 (2.1) (mean)	3	6/9
M. Barzegar (11)	Iran/ 2021	41	RRMS:41	31/10	35.10 (9.2)	7.0 (5.0-10.7)	0.0 (0.0-1.5)	5	7/9
M. Etemadifar(8)	Iran/ 2021	56	RRMS:56	40/16	36.89 (9.06)	7.76 (5.07)	1.5	4	7/9
D. Khurana (12)	India/ 2021	5	RRMS:5	2/3	35.60 (13.94)	6.52 (3.42)	4 (1-5.5)	1	-
S. Conway (13)	USA/ 2021	111	RRMS:72/ SPMS:21/ PPMS:8/ CIS:2/ Other:8	85/26	49 (12.2)	NR	3.4 (2.7) (mean)	2	-

Author	Country/ year	MS population	MS type	Female/Male	Mean age of participants	Mean Disease duration	Median EDSS	Number of relapse	NOS score
S. Paybast (14)	Iran / 2022	76	CIS: 4 / RRMS: 55 / SPMS: 17	63/13	36.7 (8.5)	11.25 (7.22)	NR	13	7/9
M. Rahmani (15)	Iran / 2022	52	NR	39/13	37.6 (9.23)	NR	NR	6	7/9
G. Bsteh (16)	Austria / 2022	211	RRMS: 170 / SPMS: 30 / PPMS: 11	146 / 65	42.6 (12.2)	12.1 (9.3)	1.5 (0-7.5)	25	6/9
A. Czarnowska (17)	Poland / 2021	426	RRMS: 397 / PPMS: 17 / SPMS: 12	254 / 142	40.27 (10.12)	8.42 (5.75)	2.61 (1.40) mean	27	8/9
D. Stastna (18)	Czech / 2022	495	NR	365 / 130	45.84 (11.00)	15.44 (9.46)	NR	36	7/9
M. Palao Rico (19)	Spain / 2021	51	RRMS: 71% / SPMS: 13.7% / PPMS: 15.7%	66.7% / 33.3%	Median 44 range (18-71)	NR	1.5 IQR (0.75-6)	2	-
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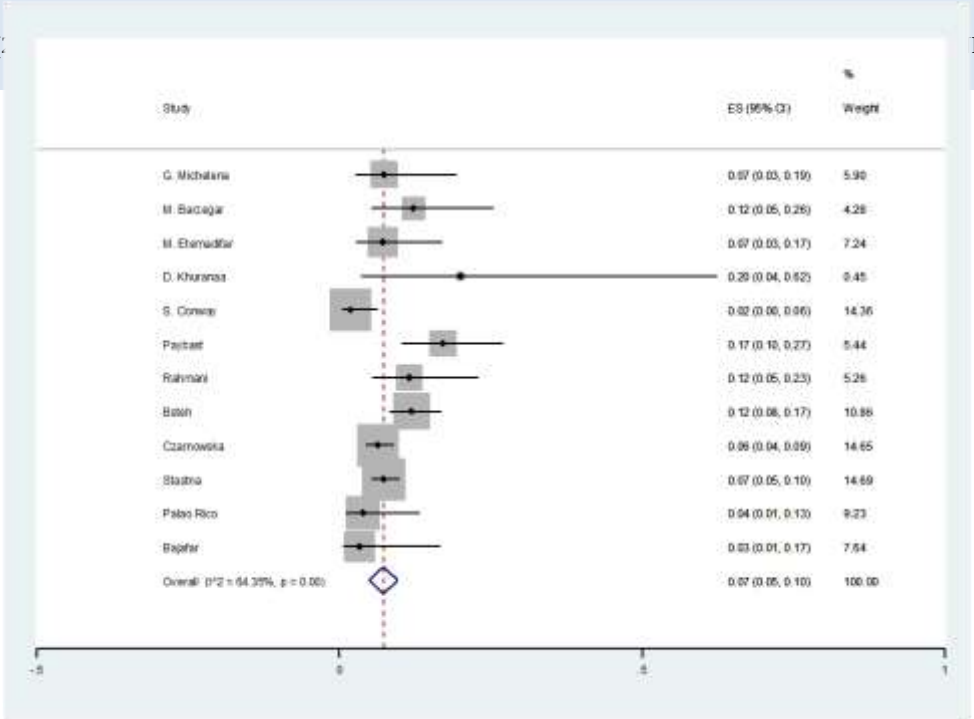

Figure 2. The pooled incidence of relapse after SARS-CO infection in subjects with MS

They investigated 32 attacks during two years in 22 patients while 5 relapses in 5 patients were at the time of the COVID-19 pandemic (11). They reported an annual average relapse rate of 0.32 during the previous two years (before COVID-19 introduction) (32 relapses in 22 patients) and 5 during the COVID-19 pandemic. Their results show that there was an increased risk of attack during COVID-19 in patients with MS. In a study which was conducted in Argentina by Michelena et al., they enrolled 41 patients with MS who had SARS-CO-19 infection. They reported that 25

patients had exacerbation of the symptoms while only three cases met the relapse criteria that needed corticosteroid treatment (21). They also found that among independent variables such as age, gender, EDSS, years of evolution of MS and previous vaccination against COVID-19, only EDSS was an independent predictor of MS-exacerbation. Khurana et al. collected data of 5 patients with MS without any comorbidities who had COVID-19. They were treated with various DMTs with mean age and disease duration of 35 and 6.5 years, respectively. Only one met relapse criteria and there were no associations between COVID-19 severity score and age, EDSS, and disease duration (12).

The increased risk of relapse in patients with MS who had COVID-19 diagnosis could be due to increased levels of peripheral pro-inflammatory mediators such as interleukins (IL)-6, IL-7, IL-10, IL- 17, granulocyte-colony stimulating factor, interferon (IFN)-γ, tumor necrosis factor (TNF)-α after SARS-CO-19 infection (22). Increased levels of these cytokines will laed to blood brain barrier dysfunction, and migration of monocytes, macrophages, and T cells which leads to exacerbation of MS related symptoms, and relapse incidence (11). On the other hand, SARS-CO- 19 virus may directly stimulate demyelination by activating toll-like receptors (TLRs) (23). It should be noted that picornavirus, influenza, respiratory syncytial virus, adenovirus and cytomegalovirus could lead to MS-related relapse and exacerbation of the symptoms (24-27). Maybe, peripheral infections exacerbate CNS damage by activating the microglia in slowly expanding lesions (28, 29) that include microglia peripherally and small amount of cells in the center (28, 30). Peripheral inflammation could activate the microglia that result in damage to surrounding tissue (29, 31) and presentation of clinical symptoms based on the location of the plaques. So, considering the disease exacerbation after peripheral infection is crucial. Review and meta-analysis had some limitations. First, relapse is a patient reported outcome and it is difficult to differentiate between relapse and pseudo-relapse. Second, the duration of follow-up varied between studies. So, adequate follow-up time is recommended. The results of this systematic review and meta-analysis show that the pooled incidence of MS-related relapse after COVID-19 is 7%.

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Data availability: Not applicable.

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