Title: Effects of COVID-19 on Multiple Sclerosis Relapse: A Comprehensive Review

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1. Multiple Sclerosis patients constitute a vulnerable population to COVID-19.
2. Research has been lacking on SARS-CoV-2's impact on MS relapse and symptom exacerbation.
3. MS patients on DMTs have high risk of COVID-19 but not necessarily an increased risk of severe COVID-19.

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ABSTRACT.

Multiple Sclerosis is a chronic inflammatory disease. It is characterized by demyelinating lesions throughout the central nervous system. Patients suffering from multiple sclerosis constitute a vulnerable population to coronavirus disease-2019. This review focuses on the effects of coronavirus disease-2019 on relapse and symptom exacerbation in multiple sclerosis patients and their treatment. It highlights how the blood-brain barrier may be compromised by severe acute respiratory syndrome coronavirus 2, allowing inflammatory mediators and lymphocytes to infiltrate the central nervous system. This may increase the risk of relapse in multiple sclerosis patients. Also, in patients who did not have a prior history of multiple sclerosis, coronavirus disease-2019 has been found to impact multiple sclerosis onset and pathogenesis. However, more comprehensive research is required to fully understand the interplay between multiple sclerosis and coronavirus disease-2019.

Key Words: Blood-Brain Barrier, Coronavirus Disease-2019, Disease Exacerbation, Multiple Sclerosis, Neurologic Symptoms

INTRODUCTION.

The coronavirus disease 2019 (COVID-19) first emerged in Wuhan, China, in December 2019.[1] However, COVID-19 rapidly spread across the globe over the next six months and has affected every aspect of healthcare.[2] COVID-19 is the result of infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Although the infection has its main site of pathophysiologic significance at the pulmonary level, a number of multiple sequelae, signs and symptoms, and associated pathologies have been observable in multiple body systems, including the nervous system; there has been a growing number of neurologic problems associated with the SARS-CoV-2 infection, including complications with multiple sclerosis (MS).[3-5]

MS is a chronic inflammatory disease of the central nervous system (CNS) characterized by demyelinating lesions that can lead to various neurologic dysfunction, including cognitive dysfunction, dysesthesia, hyperreflexia, hypoesthesia, paresthesia, and visual deficits (diplopia, nystagmus, and optic neuritis), depending on the location and severity of inflammatory lesions.[6]

The most common disease course in MS is relapsing-remitting multiple sclerosis (RRMS); it is characterized by acute exacerbations of symptoms, followed by more extended periods of remission, these short exacerbations, also called relapses, consist of days to weeks of fully or partially reversible neurological disability. Principal manifestations of relapses are monocular visual loss, limb weakness and/or sensory loss, double vision, and ataxia.[6]

The exact causes of relapses remain unknown, but relapse rates have been correlated with times of increased stress.[7] Other disease courses of MS involve clinically isolated syndrome (CIS), primary progressive multiple sclerosis (PPMS), and secondary progressive multiple sclerosis (SPMS). The CIS is diagnosed after the first episode of a demyelinating attack. It presents as a neurologic deficit for more than 24 hours, PPMS is a progressive form in which neurologic deficits accumulate in the absence of relapse and do not regress to baseline despite treatment; whereas SPMS often occurs as a later stage of RRMS where neurologic deficits do not return to baseline after relapses, and deficits accumulate after each relapse.[8]

This review primarily focuses on the RRMS as this is the most common course characterized by relapses. MS relapse and even its onset have been known to be impacted by viral infections.[7, 9] The stress of a viral infection combined with the host immune response creates a proinflammatory environment and increases the risk of relapse in Persons with Multiple Sclerosis (PwMS). However, the literature is lacking regarding SARS-CoV-2 and its potential impact on the onset and relapse in PwMS. Therefore, this review highlights the neurological effects of COVID-19 on PwMS and its impact on their disease status and symptom exacerbation.

STRATEGIES FOR LITERATURE SEARCH AND STUDY SELECTION.

We conducted a literature search through the PubMed and EBSCO databases from March 2020 through July 2021 for studies measuring relapses in PwMS who had been infected by COVID-19. Inclusion criteria included: 1) studies being written in English; 2) any case report, retrospective cohort study, and prospective cohort study that included PwMS who were infected with SARS-CoV-2; 3) studies that measured neurologic symptom exacerbation or relapse. We used the following search terms: “Coronavirus Multiple Sclerosis,” “Coronavirus MS Relapse,” “Coronavirus MS Exacerbation,” “COVID-19 Multiple Sclerosis,” “COVID-19 MS Relapse,” “COVID-19 MS Exacerbation,” “SARS-CoV-2 Multiple Sclerosis,” “SARS-CoV-2 MS Relapse,” “SARS-CoV-2 MS Exacerbation.”

Our search resulted in 399 articles in total. Of those, one study was not written in English, 390 were not case reports, retrospective cohort studies, or prospective cohort studies that included PwMS who were infected with SARS-CoV-2, and one study did not measure neurologic symptom exacerbation or relapse. Of the seven studies meeting the inclusion criteria, two were retrospective studies, one was a prospective cohort study, one was an observational study, and three were case reports. The level of evidence for the included studies was determined based on the previous literature.[10] The methodology used in the review is illustrated in **Figure 1**, which is based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[11]

PATHOPHYSIOLOGY.

MS is an autoimmune disease characterized by plaque-like sclerosis found throughout the CNS, its most common disease course is RRMS that is identified by symptom exacerbations; during exacerbations, acute demyelinating attacks occur between more prolonged periods of quiescence.[8] Throughout these demyelinating episodes, myelin basic protein (MBP), a critical component of the myelin sheath, is adversely impacted.[12] These inflammatory lesions are more significantly found in the white matter but have also been seen in the gray matter; lesions are widely observed in the periventricular region, juxtacortical areas, infratentorial region, and spinal cord.[13]

The MS diagnosis relies on the dissemination of the disease in space and time as defined by the revised 2017 McDonald criteria.[14] Typical onset of the disease occurs between the ages of 20 and 40 years old; inflammatory lesions are thought to result from proinflammatory factors and demyelination that occurs in the CNS after the blood-brain barrier (BBB) has been compromised.[15]

Although the exact mechanism of the autoimmune action against CNS antigens in MS remains undetermined, the bulk of evidence attributes pathology to both the adaptive and innate immune responses in an attack against myelin and oligodendrocytes. Both cluster of differentiation (CD) 4+ and CD8+ T cells have been found in MS lesions, suggesting cell-mediated immunity in the inflammatory lesions.[16] T cells are the major driving factor of experimental autoimmune encephalitis, a murine MS model; the success of therapies that limit T cell access to the CNS also supports cell-mediated immunity.[17] Moreover, the recent success of B cell-depleting therapies in MS treatment has also suggested a more prominent role of the humoral response in MS pathology.[18] Furthermore, B cells have been shown to activate autoreactive T cells that target the brain.[19]

Macrophages of the innate immune system promote the inflammatory response of T and B cells and execute the tissue damage seen in MS.[6, 20] Microglial cells of the CNS also contribute to pathology through secretion of the inflammatory cytokines, chemokines, and free radicals.[21] The autoimmune mechanism of MS pathogenesis is illustrated in **Figure 2**.

EFFECT OF VIRAL INFECTIONS IN MULTIPLE SCLEROSIS.

Viral infections, mostly considered as the environmental factor, have been known to induce relapses in PwMS. Significantly, upper respiratory infections (URIs) have long been correlated with MS relapse risk.[22, 23] The extensive history of viral infection and MS outcomes has been seen in members of the Herpesviridae family, including Epstein-Barr virus, Varicella-Zoster virus, and human herpesvirus 6.[24-27] Also, parainfluenzas, adenoviruses, and coronaviruses have been correlated with the risk of MS relapse.[23, 28] Furthermore, multiple viral infections have been shown to increase the risk for relapse, suggesting a common mechanism across the viral immune response. This could be from increased permeability of the BBB due to antiviral cytokines or molecular mimicry of viral and host proteins.[29]

Coronaviruses have been previously reported to be involved and complicate MS pathophysiological processes. A postmortem study found human coronavirus (HCV) 229E ribonucleic acid (RNA) in CNS tissues of 4 out of 11 MS patients compared to control groups (6 neurological controls and 5 healthy controls). The specific specimens were scraped from white matter plaques, typical gray and white matter, and tissues from the cervical cord.[30] Four of the neurological controls had Alzheimer's disease, one had ischemic vascular disease, and one had subacute meningoencephalitis. Another research group has corroborated the presence of coronavirus RNA in CNS tissues of PwMS. During the autopsy, researchers found 11 out of 21 MS patients had HCV RNA in their CNS tissue obtained from the cerebral cortex, brainstem, and spinal cord compared to the control group.[31]

Based on these histopathological findings, it can be inferred that HCV compromised the structural integrity of the BBB and invaded the specific CNS areas containing MS lesions and caused pathophysiological complications in already vulnerable MS patients.[30, 31]

Interestingly, not only have coronaviruses been reported to have deleterious effects on MS pathophysiology, but also, they have been shown to indirectly promote demyelination through T cell activation in cell lines obtained from MS patients.[32] A study found 29% of T cell lines from MS patients showed MBP and HCV 229E cross-reactivity compared to only 1.3% of T cell lines from healthy controls. Furthermore, 4 out of 16 MS patients displayed reciprocal cross-reactivity profiles while none of the healthy controls did.[32] These findings further indicate the possible environmental trigger of coronaviruses on MS pathogenesis and pathophysiology.[30-32] Thus, the SARS-CoV-2 strains are most likely to have similar effects of previously studied coronaviruses and other viral infections on MS status.

COVID-19 AND ITS NEUROLOGICAL MANIFESTATIONS.

SARS-CoV-2 that causes COVID-19, has a well-described cell entry mechanism.[33] Antigen presentation by antigen-presenting cells (APCs) is crucial to antiviral cell-mediated immunity. A recent study suggests a defect in the MHC class II gene expression for the presentation of SARS-CoV-2 by APCs.[34]

The polymorphic nature of the MHC region of the human genome plays an essential role in individual susceptibility to diseases such as MS.[35] The innate and adaptive immune system response to coronaviruses is integral to the infection's clinical presentation; the innate immune response is triggered by pattern recognition receptors (PRRs), recognition by PRRs triggers a downstream signaling cascade that results in the secretion of inflammatory cytokines such as interferons (IFN), tumor necrosis factor-alpha (TNF-α), interleukin (IL) -1, and IL-6.[35] Humoral immunity to SARS-CoV-2 can be seen through the presence of antibodies directed to the viral surface glycoproteins S protein and N protein of the SARS-CoV-2. APCs trigger the cell-mediated immune response by presenting antigens to virus-specific CD4+ and CD8+ T cell antigen receptors.[36]

Upon activation of the innate and adaptive immune systems by SARS-CoV-2, another massive quantity of proinflammatory cytokines and chemokines are produced from immune effector cells; this immune-mediated cytokine storm has been attributed to the severe clinical presentation of acute respiratory distress syndrome in COVID-19 patients.[35, 36] Thus, this cytokine storm could lead to increased permeability through cytokine-mediated inflammation at the BBB. This could be detrimental to more susceptible patients with neurodegenerative conditions, for instance, MS patients.

Beyond the significant respiratory complaints of COVID-19, there has been an increasing number of reported neurological complications of the disease.[37-40] A nationwide retrospective observational study in Italy showed 72.1% of the 646 patients surveyed reported neurological symptoms during their COVID-19 infection. Headache was the most reported symptom (41.1%), followed by smell (37.9%) and taste (36.8%) impairment.[5] A significant number of people have been reported to develop psychiatric issues including depression, anxiety, and stress, particularly in those with pre-existing mental conditions.[41-43] Moreover, there have also been reports of more serious neurological complications of COVID-19, such as Guillain Barre syndrome and acute transverse myelitis.[44-46] In addition, as mentioned before, some studies have shown the correlation between coronaviruses and demyelination.[47-49]

There have been several proposed mechanisms of coronavirus infection of the nervous system. Viruses have been shown to migrate through retrograde or anterograde neuronal axonal transport.[37, 50] This has also been seen in the olfactory and trigeminal nerves, leading to CNS infection in mouse models.[51] The binding of SARS-CoV-2 to angiotensin-converting enzyme 2 receptors on vascular endothelium may damage the BBB, leading to its entry into the CNS,[52] thus allowing infiltration of the activated immune response into the CNS. The suggested breakdown of BBB by SARS-CoV-2 may shed light on the pathophysiologic mechanism of how MS patients are significantly impacted by COVID-19. Also, PwMS have been considered particularly vulnerable to SARS-CoV-2 infection due to high disability rates and increased susceptibility to infection.[53]

MS RELAPSE AND COVID-19.

In an observational study of MS patients with COVID-19 (72 MS patients), 21.1% reported neurologic symptoms suggestive of relapse.[54] A retrospective cohort study by Etemadifar et al. found 7.14% of the 56 PwMS experienced a relapse from the period of two weeks before and six months after recovering from COVID-19.[55]

Another retrospective study assessing 41 PwMS found an increased relapse rate of 0.017 attacks per "at-risk" week compared to 0.007 attacks per week during a not "at-risk" period of the two years prior. The "at-risk" period was defined as the two weeks before and five weeks after COVID-19 infection.[56] A more extensive study performed in the United Kingdom found 57% of PwMS (230/404) experienced MS exacerbation during the time of their COVID-19 infection.[57] The key findings of some studies about MS relapse in PwMS infected with SARS-CoV-2 are summarized in **Table 1.**

Although these studies present evidence of relapse in MS patients with COVID-19, there is a tremendous variation in the percentage of MS patients suffering from relapse between the studies. This might be attributed to the patient age group and MS status; older patients, in general, have a weaker immune system, and MS geriatric patients placed on disease-modifying therapies (DMTs) are at an even greater risk of contracting infection, let alone SARS-CoV-2.[58] Thus, had the clinical trials controlled for the age and MS status, there is a more likelihood for more extensive and enormous evidence of MS relapse in COVID-19 PwMS.

In addition to these studies, three case reports described recent or concurrent COVID-19 infection with an initial MS event and diagnosis. A 27-year-old female presented with MS symptoms, including dysesthesia, hyperreflexia, and hypoesthesia six months after developing COVID-19. The patient was diagnosed with MS that was confirmed by gadolinium-enhancing lesions on the magnetic resonance image (MRI) and the presence of oligoclonal bands in her cerebrospinal fluid (CSF).[59] The temporal relationship between MS and COVID-19 could be explained by SARS-CoV-2-induced processes.

In another case report, a 29-year-old female with a history of asthma presented with COVID-19 symptoms, including anosmia, dysgeusia, asthenia, and proximal myalgias in her limbs that disappeared within a week after developing COVID-19. She presented two weeks later with a ten-day history of right visual acuity deficits (typical MS symptom). SARS-CoV-2 Immunoglobulin (Ig) M/ IgG immunological testing was positive, confirming past infection of the virus. Oligoclonal bands were present in CSF. MRI displayed optic nerve lesions with contrast enhancement and sparse demyelinating lesions in the brain, confirming MS.[60] Before contracting SARS-CoV-2, the patient did not have a medical history of MS, and within two weeks of infection, she exhibited MS symptoms and received a confirmed MS diagnosis. Hence, there is a possibility, and unbeknownst to the investigators, the patient might have been genetically predisposed to developing MS. And exposure to SARS-CoV-2 would have triggered MS pathogenesis and resulted in her clinical manifestations.

Yet another case report of a 28-year-old male presented with a two-day history of binocular diplopia was found to have MS and COVID-19 infection concurrently. The patient's COVID-19 symptoms of sore throat, cough, anosmia, and headache had started two weeks before diplopia,[61] indicating a possible link between MS onset and SARS-CoV-2 infection. However, more research is required to investigate and understand the relationship between MS onset/pathogenesis and COVID-19.

The research findings evidence COVID-19's role in symptom exacerbation in PwMS. Infection with SARS-CoV-2 can lead to MS onset, pathogenesis, and trigger complex pathophysiological changes, resulting in a relapse in MS patients. However, there are several limitations to the interpretations of these studies' results **(Table 2)**. First, the definition of relapse or exacerbation varies between studies. A couple of research studies used a formal definition of relapse involving the new onset of symptoms lasting more than 24 hours, but one study defined relapse as any neurologic symptom that suggested a recurrence. Second, the period utilized to measure COVID-19-related exacerbations was not consistent. One research group used a period of two weeks before COVID-19 infection to six months after the illness. While another group only utilized the duration patients were infected with COVID-19 as the time frame for measuring relapse. Future studies enrolling larger cohorts with a clear definition of MS relapse and a consistent timeframe for measuring MS relapse will be required to draw further inferences.

TREATMENT OF MS PATIENTS WITH COVID-19.

Treating COVID-19 patients with MS safely and effectively is critical partly because MS patients are on DMTs, which can be a crucial risk factor of COVID-19. Patients on immunomodulating therapies have been shown to have an increased risk of developing COVID-19 but not necessarily the increased risk of severity of COVID-19.[62] Despite an increased risk of COVID-19, some studies have shown better prognoses for COVID-19 in MS patients treated with B cell-depleting therapies such as Ocrelizumab and Rituximab measured by the severity of symptoms.[63, 64] The results of these studies suggest that a suppressed immune system limits the body's harmful response to SARS-CoV-2 infection. Another study demonstrated a decreased risk of COVID-19 in patients being treated with IFN and glatiramer acetate.[65] While these findings are optimistic, other studies have found that treatment of MS with sphingosine-1-phosphate modulators (Fingolimod) has shown a more significant severe disease course of COVID-19.[66] The worst clinical outcomes of SARS-CoV-2 infection have been seen in PwMS who are not on any DMTs and PwMS with comorbidities associated with worsened outcomes such as male gender, obesity, and advanced age.[67]

Remdesivir

There have not been any studies regarding the treatment of COVID-19 in PwMS. Although the treatment of COVID-19 patients depends on the individual clinical presentation, there has been only one drug (up to the writing of this review) that has got the full United States Food and Drug Administration (FDA) approval for the treatment of COVID-19 patients—Remdesivir. It is a parenteral antiviral drug that acts as an adenosine analog to disrupt viral RNA production through host RNA-dependent RNA polymerase.[68] However, to our knowledge, there has not been any research reporting the use, benefits, and adverse effects of Remdesivir in COVID-19 patients with MS or other patients on DMTs.

Immunization

It is currently recommended by the National Multiple Sclerosis Society that most PwMS get vaccinated for COVID-19.[69] The consensus of previous inactivated vaccines in PwMS is that these vaccinations are safe and recommended for most PwMS.[70] Still, there is less known about live-attenuated vaccinations in PwMS. Vaccine safety and efficacy in PwMS can be primarily attributed to the DMTs of the patient. With many DMTs suppressing the immune system, a weakened vaccine response leads to decreased immunity. Furthermore, live-attenuated vaccines can be contraindicated in patients receiving immunosuppressive treatment due to the potential for vaccine-transmitted disease.[71, 72]

Treatment with IFN-beta, Glatiramer acetate, Teriflunomide, Natalizumab, and Fumarates have not been shown to decrease efficacy in other inactivated vaccines and are not expected to show reduced effectiveness in the COVID-19 vaccine.[73] The worst vaccine efficacies are seen in patients taking B cell-depleting therapies such as Ocrelizumab, Rituximab, and Alemtuzumab.[74-76] For patients on these therapies, the timing of vaccines and treatment is a crucial determining factor of vaccine efficacy.[71, 77]

The three vaccines approved by the FDA in the United States are the *BNT162b2 vaccine* developed by Pfizer-BioNTech, the *messenger RNA-1273 vaccine* developed by Moderna, and the *Ad.26.COV2.S vaccine* by Janssen Biotech, Inc., a Janssen Pharmaceutical company of Johnson & Johnson. Thus far, there have been a few studies regarding vaccine safety and efficacy in PwMS.

In a large observational study, 555 PwMS were vaccinated with at least one dose of the *BNT162b2 vaccine* (435 received both doses). No life-threatening reactions or anaphylaxis events were reported after

either dose. Common adverse effects were injection site pain, fatigue, headache, muscle/joint pain, and flu-like symptoms. Of the 388 RRMS patients who received the first dose, 2.1% experienced a relapse within 10-19 days after injection. Of the 306 RRMS patients who received the second dose, 1.6% experienced a relapse within 14-21 days of injection. These rates were compared to corresponding periods of previous years of RRMS patients who presented for acute relapses in 2017, 2018, 2019, and 2020. The number of acute relapses divided by the number of patients in these years was 2.7%, 2.9%, 2.6%, and 2.3%, respectively.[78] Thus, this study did not demonstrate any increased risk of relapse activity in those patients who received the Pfizer vaccine.

CONCLUSIONS.

SARS-CoV-2 can increase the relapse rates in MS patients, most likely through compromising the structural integrity of the BBB. Although based on these study findings, it is evident that SARS-CoV-2 can trigger MS onset and pathogenesis, more research will be needed to further understand the underlying pathophysiologic dynamics between COVID-19 and MS. Even though COVID-19 vaccines have been safer in MS patients and have not altered MS status, a further understanding of the relationship between COVID-19 and MS is crucial in managing MS patients with COVID-19 on immunomodulating therapies.

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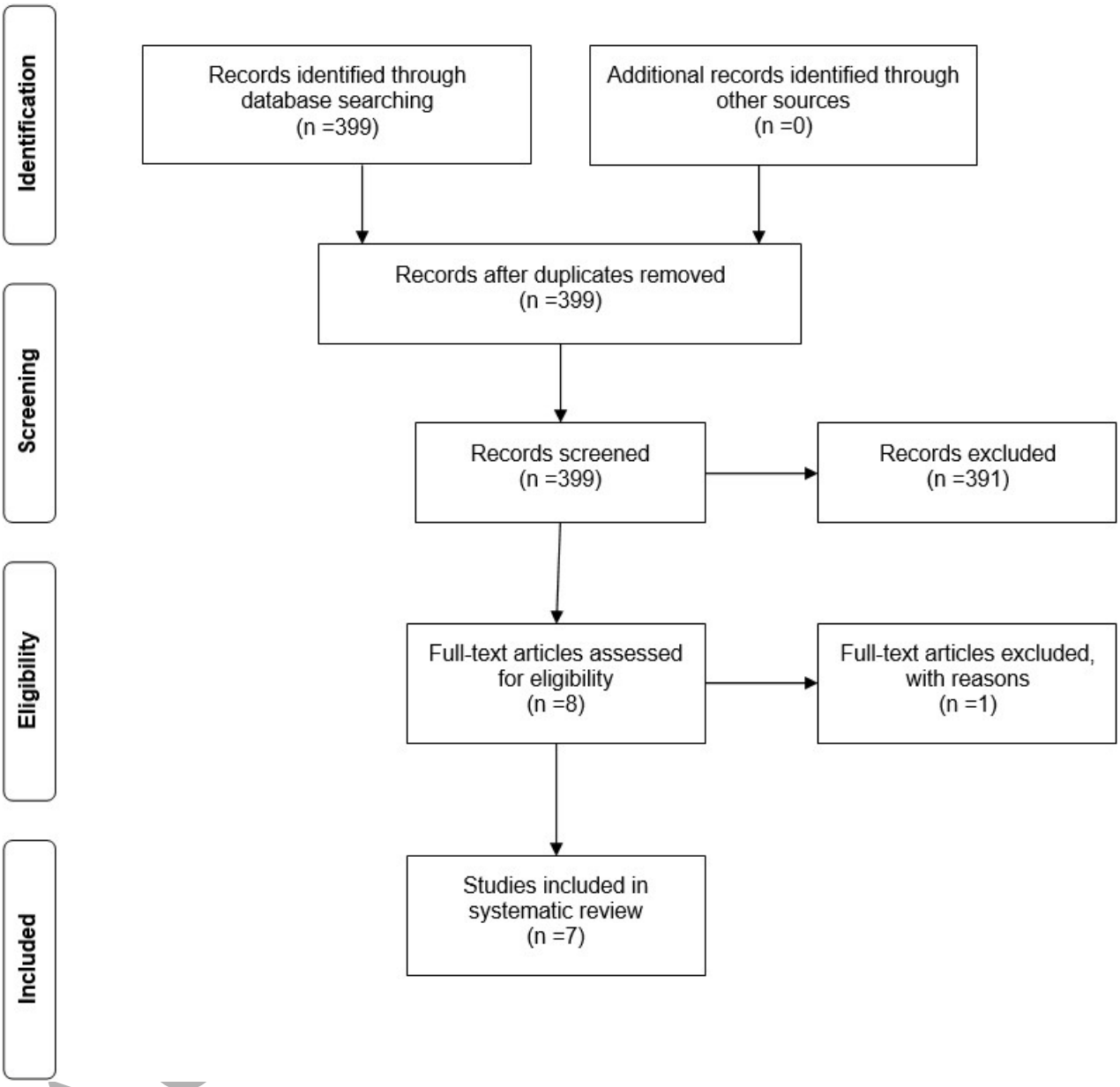
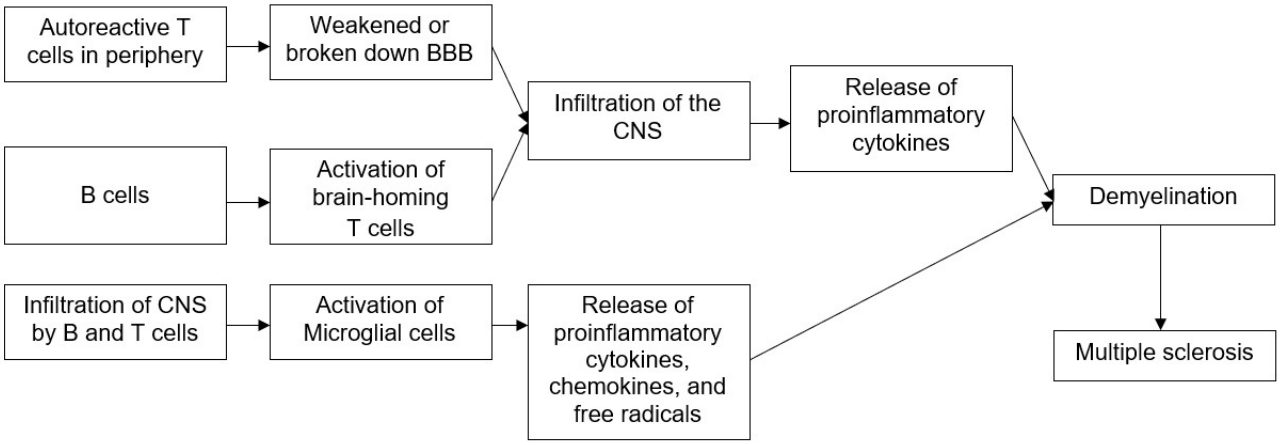
FIGURES AND TABLES.

Figure 1. Method Employed to Search Literature



We searched PubMed and EBSCO databases from March 2020 to July 2021. The search terms “Coronavirus Multiple Sclerosis,” “Coronavirus MS Relapse,” “Coronavirus MS Exacerbation,” “COVID-19 Multiple Sclerosis,” “COVID-19 MS Relapse,” “COVID-19 MS Exacerbation,” “SARS-CoV-2 Multiple Sclerosis,” “SARS-CoV-2 MS Relapse,” “SARS-CoV-2 MS Exacerbation” were utilized. This yielded 399 articles, out of which 7 studies meeting the inclusion criteria for this review paper were selected. COVID-19, coronavirus disease 2019; MS, multiple sclerosis; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Figure 2. Autoimmune Mechanism of Multiple Sclerosis



Autoreactive T cells in the periphery infiltrate the CNS through a weakened or broken down BBB, releasing inflammatory cytokines, attacking myelin and oligodendrocytes, and causing demyelination. B cells activate brain-homing T cells in the periphery, further breaking through the CNS and resulting in demyelination through a similar mechanism. Microglial cells are activated by the infiltration of T and B cells in the CNS, releasing more proinflammatory cytokines, chemokines, and free radicals, contributing to demyelination. BBB, blood-brain barrier; CNS, central nervous system.

Table 1. Multiple Sclerosis Relapse in COVID-19 Patients

Studies	Level of Evidence	Patients	Study Findings	Study Bias	p - value
Barzegar et al. (2021) – Retrospective cohort study	3	41 RRMS with COVID-19	• Five patients (12.2%) displayed neurological symptoms consistent with relapse during the at-risk period of SARS-CoV-2 infection. • The study demonstrated increased risk of relapse of these patients during their at-risk period compared to the previous 2 years during the not at-risk period.	• Study did not compare results of SARS-CoV-2-infected PwMS to non-infected PwMS. • Instead, this study compared the at-risk period (2 weeks before through 5 weeks after infection) to the not at-risk period (previous 2 years).	p = 0.034
Etemadifar et al. (2021) – Retrospective cohort study	3	125 RRMS patients (56 with COVID-19 and 69 without COVID-19)	• Study reported a lower incidence rate of neurological symptom exacerbation in the PwMS with COVID-19 (7.14%) in the six months following	• Participants were contacted biweekly through telephone surveys. This likely increased the likelihood of exaggerated reporting of symptoms.	p = 0.006

			confirmed infection with SARS-CoV-2 compared to PwMS without COVID-19 in the six months measured from Jun 1, 2020 – November 1, 2020 (26.09%).		
Fragoso et al. (2021) – Case report	4	1 PwMS	• Study of a healthy individual who was diagnosed with MS six months after having COVID-19. • The temporal relationship of the COVID-19 onset and MS diagnosis are thought to be related.	• Six months post SARS-CoV-2 infection is a substantial time to develop MS independent of any viral infection let alone SARS-CoV-2. • Many other factors could have played a role in disease onset in that time.	Not applicable
Garjani et al. (2021) – Prospective cohort	3	404 PwMS (277 RRMS, 65 SPMS, 39 PPMS, 23 Non-defined MS)	• Study showed 230/404 PwMS (56.9%) and COVID-19 reported symptom exacerbation during or soon after infection with SARS-CoV-2 from July 20, 2020, through January 25, 2021.	• Study did not have a control group of PwMS who were not infected with SARS-CoV-2. • Use of an online questionnaire to assess symptom exacerbation could have led to increased responses of symptom exacerbation.	No statistically significant difference between PwMS with COVID-19 who reported MS symptom exacerbation versus PwMS with COVID-19

				• The study's protocol did not require PwMS with confirmed SARS-CoV-2 diagnosis. Patients who had symptoms consistent with COVID-19 were included in the study. • Study included patients with SPMS, PPMS, and non-defined types of MS rather than just RRMS patients.	who did not report MS symptom exacerbation.
Moore et al. (2021) – Case report	4	1 PwMS	• Patient presented with concurrent MS onset and SARS-CoV-2 infection.	• Patient presented in case had glaucoma and underwent prior laser ablation treatment. This could have impacted the retinal ganglionic cells and triggering structural changes in the blood-brain barrier, most likely predisposing him to developing MS. This was not adequately addressed by the authors.	Not applicable.

Palao et al. (2020) – Case report	4	1 PwMS	• Patient presented with signs of MS onset (visual acuity deficits and periventricular lesions on the MRI). She had symptoms of COVID-19 (anosmia and ageusia) 2-3 weeks prior to presentation. Serological testing revealed immunoglobulin M and G antibodies to SARS-CoV-2. This suggests MS onset after recent infection with SARS-CoV-2.	• The authors assumed the MS pathogenic process started prior COVID-19 disease. • The SARS-CoV-2 PCR testing protocol in the cerebrospinal fluid was not properly validated.	Not applicable.
Parrota et al. (2020) – Observational study	3	76 patients: 72 PwMS [55 RRMS, 17 progressive MS (SPMS, PPMS)] and 4 with related disorders (chronic relapsing inflammatory optic neuropathy, myelin oligodendrocyte	• Study measured clinical outcomes in PwMS and related conditions after infection with SARS-CoV-2. • 21.1% of study participants reported neurological symptoms suggestive of a relapse.	• Patients were not randomly selected. • Study included four participants who were not diagnosed with MS. • Authors did not make any statistically significant comparisons between study groups.	Not reported.

		glycoprotein-immunoglobulin G–associated disorder spectrum disorder, neurosarcoidosis, and neuromyelitis optica)			

%, percentage; COVID-19, coronavirus disease 2019; MRI, magnetic resonance imaging; MS, multiple sclerosis; PwMS, persons with multiple sclerosis; RRMS, relapsing remitting multiple sclerosis; p – value, probability value; PPMS, primary progressive multiple sclerosis; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SPMS, secondary progressive multiple sclerosis

Table 2. Variations Between Research Studies on MS Patients with COVID-19

Studies	Period measured for PwMS with COVID-19	Definition of relapse
Parrota et al. (2020)	March 16, 2020 - April 30, 2020	Neurologic symptom recurrence suggestive of a relapse
Etemadifar et al. (2021)	Two weeks prior to and six months after COVID symptoms	Development of a new neurologic abnormality or worsening of a pre-existing symptom for more than 24 hours
Barzegar et al. (2021)	Two weeks before until five weeks after COVID-19 onset	Worsening of pre-existing symptoms or developing new symptoms, in the absence of fever, lasting at least 24 hours, after at least 30 days of improvement and stability, confirmed by presence of gadolinium enhancement on MRI
Garjani et al. (2021)	During or soon after COVID infection July 20, 2020 – January 25, 2021	Development of new MS symptoms, worsening of pre-existing MS symptoms, or experiencing both
Fragoso et al. (2021)	Six months	New diagnosis by McDonald criteria
Palao et al. (2020)	Two weeks	New diagnosis by McDonald criteria
Moore et al. (2021)	Two weeks	New diagnosis by McDonald criteria

PwMS, persons with multiple sclerosis; MRI, magnetic resonance image