DO COVID-19 PATIENTS WITH MULTIPLE SCLEROSIS ALWAYS DEVELOP SEVERE CONDITIONS? A SYSTEMATIC REVIEW

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ABSTRACT.

SARS-CoV-2, which causes COVID-19, infects hosts and promotes various manifestations, from asymptomatic to severe pneumonia. COVID-19 can develop into acute respiratory distress syndrome (ARDS) and induce cytokine storm which results on the need of intensive care and higher risk of mortality. This gives rise to a concern whether the patients who are treated with immunosuppressive therapy have a higher risk to suffer poor prognosis during SARS-CoV-2 infection, including patients with multiple sclerosis who are treated with disease-modifying therapy (DMT) which has immunomodulating and immunosuppressive effects. This systematic review aims to assemble the conditions of COVID-19 patients with multiple sclerosis comorbidity. **Methods:** This systematic review is conducted by compiling literatures about the conditions of COVID-19 patients with multiple sclerosis comorbidity through a database, "PubMed", using the PRISMA-P method. The literatures are then appraised using the JBI Critical Appraisal Checklist. **Results:** There are 12 literatures in the good category and 5 literatures in the medium category which demonstrate the conditions of COVID-19 patients with multiple sclerosis. **Conclusion:** The course of COVID-19 in patients with multiple sclerosis are diverse, according to their other comorbidities, race, age, gender, EDSS score, and the DMT they are given. Further cohort research with a broader range of samples are needed to assess the relationship of SARS-CoV-2 infection and the pantient's multiple sclerosis condition, along with the effects of DMT usage and lymphocyte status in multiple sclerosis patients to the severity of COVID-19 symptoms.

Keywords: COVID-19, disease-modifying therapy, multiple

1. Introduction

In December 2019, the world was shocked by the new type of Coronavirus, SARS-CoV-2, which originated in Wuhan, China. This virus can infect the respiratory tract and is known as COVID-19. This disease is spreading rapidly throughout the world, and as a result, on March 11, 2020, COVID-19 was declared a global pandemic by the World Health Organization with substantial mortality and morbidity(1–4).

To infect a host, SARS-CoV-2 uses the ACE2 and TMPRSS2 viral receptors. These receptors are membrane-related proteins expressed in many cells throughout the body, particularly the respiratory system. (5). Immunopathology of COVID-19 continues to grow, including understanding the heterogeneity of symptoms among the affected population. SARS-CoV-2 infection can be asymptomatic or symptomatic with varying degrees of severity, from mild flu to severe pneumonia. The prognosis for COVID-19 also varies from complete recovery to acute respiratory failure and death (6,7). Most of the cases were classified as mild. However, in several patients, the disease progresses to acute respiratory distress syndrome (ARDS) (8) or disorders of the immune system that cause cytokine storms and require intensive care lead to increased mortality (9).

Based on these observations, there is concern that patients treated with immunosuppressive drugs may be at higher risk of poor prognosis during SARS-CoV-2 infection, such as in patients with multiple sclerosis. Multiple sclerosis (MS) is an autoimmune disease in which inflammation of the central nervous system (CNS) causes demyelination and axonal damage. The etiology of MS is multi-faceted, with environmental factors interacting with a genetic predisposition (10).

MS patients are generally susceptible to infection with the additional factor of using disease-modifying therapy (DMT), namely immunomodulating and immunosuppressive drugs. DMT can cause lymphopenia and a reduction in the number of B lymphocytes, which may lead to a higher risk of SARS-CoV-2 infection, as well as a more severe one (11). On the one hand, immunocompromised patients may have more severe COVID-19 disease due to the absence of an adequate immune response to SARS-CoV-2. On the other hand, however, some therapies that act on the immune response can play a protective role by reducing cytokine release syndrome (12–14).

Based on these observations, researchers have great interest in observing the impact of COVID-19 on patients with autoimmune diseases such as MS, judging from the patient's clinical course. With a systematic review method, this publication was created to describe the condition of COVID-19 patients with MS based on the available literature to increase the awareness of health workers to determine the proper treatment.

2. Method

2.1. Research Design

Systematic Review (15), using the PRISMA-P 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) Checklist (16).

2.2. Search Strategy

Literatures searching was conducted in "PubMed" databases according to the PRISMA-P 2020 method. We included all studies published up to 3rd May 2021. The search string applied was "COVID-19 AND Multiple Sclerosis" (15)(16).

2.3. *Inclusion and Exclusion Criteria*

The inclusion criteria in this study included studies that described the clinical manifestations of COVID-19 patients with a history of multiple sclerosis. The search was limited to articles written in English and Bahasa Indonesia. The exclusion criteria were studies with inappropriate topics, using the review method, patients diagnosed with MS after being infected with SARS-CoV-2, and being completely inaccessible.

2.4. Quality Assessment and Data Extraction

Four reviewers (BOP, CDR, ASN, SAW) performed an independent assessment of included articles by using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist (17,18). Conflicts were resolved through consensus, and unresolved ones were decided by the fifth reviewer (RV). The literature was considered good if it fulfilled at least 80% of the requirements, moderate if it fulfilled 50– 80% of the requirements, and weak if it fulfilled less than 50% of the requirements. We only included articles with moderate and good categories for this study. Four reviewers (BOP, CDR, ASN, SAW) separately extracted data from the identified literatures regarding main characteristics such as author, year of publication, title, country, age, sex, type of MS, years at the diagnosis of MS, EDSS, DMT, and comorbid.

3. Results

3.1. Identification and Screening

We found 398 articles from the literature search. Seventeen studies (1 cohort and 16 case reports) met our eligibility criteria for further data extraction (**Figure 1**) **(Table 1).** Data synthesis was carried out by classifying the extracted data according to the points needed to conclude **(Table 2).** Based on our critical appraisal, we rank 12 studies as good category and 5 studies as medium category.

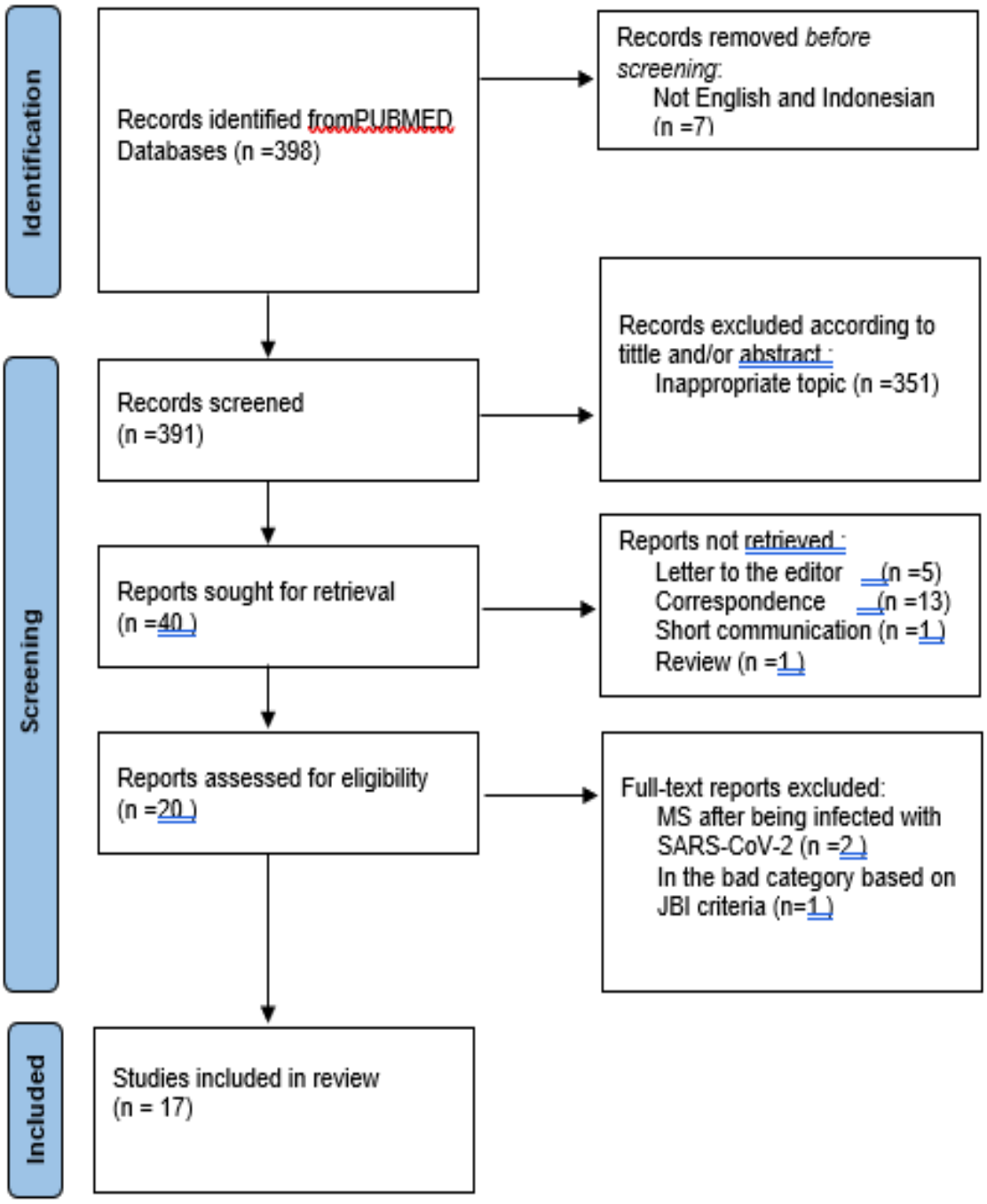

Figure 1. Literature Selection Flow Using PRISMA Diagram.

Table 1. Data Extraction

No	Source	Title	Country	Age	Sex	MS Type	Year diagnosed	EDSS	DMT used	Comorbidity (s)
						COHORT				
1.	Louapre et al, 2020	Clinical Characteristics and Outcomes in Patients With Coronavirus Disease 2019 and Multiple Sclerosis	France	347 patients Mean age =44.6	F:M = 249:98	Clinically Isolated : 6 RRMS : 276 Secondary progressive : 48 Primary progressive : 17	Mean : 13.5 years	0.0-9.5 (Median : 2)	IFN beta (20) Glatiramer (33) Teriflunomide (33) Dimethylfumarate (35) Natalizumab (57) Fingolimod (42) Ocrelizumab (38) Cladribine (3) Alemtuzumab (1) Other (5) None (63	CVD (23) Pulmonary disease (15) Diabetes (16) Obesity (24) Smoking (33)
						Case Reports				
2.	Capone *et al.*, 2021	COVID-19 in teriflunomide-treated patients with multiple sclerosis: A case report and literature review	Italy	57	Male	RRMS	2018 (3 years)	3	Teriflunomide	Hy D
3.	Gomez-Mayordomo *et al.*, 2021	Clinical exacerbation of SARS-CoV2 infection after fingolimod withdrawal.	Spain	57	Female	RRMS	1996	6.00	FNG	
4.	Barzegar *et al.*, 2020	COVID-19 infection in a patient with multiple sclerosis treated with fingolimod	Iran	42	Female	RRMS	2001 (19 years)	4	Fingolimod	Major depression, Hypotiroidism UTI, Pulmonary embolism, Myasthenia gravis
5.	Borriello dan Ianniello, 2020	COVID-19 Occurring During Natalizumab Treatment: A Case Report in a Patient with Extended Interval Dosing Approach	Italy	28	Male	MS	2000 (20 years)	1.5	Natalizumab	-

6.	Creed *et al.*, 2020	Mild COVID-19 infection despite chronic B cell depletion in a patient with aquaporin-4-positive neuromyelitis optica spectrum disorder	USA	59	Female	MS diagnosed as NMSOD	MS since 2006,NMSOD since 2014	-	Rituximab	-
7.	Dersch *et al.*, 2020	COVID-19 Pneumonia in a Multiple Sclerosis Patient with Severe Lymphopenia due to Recent Cladribine Treatment	Germany	60	Male	RRMS	2016 (4 years)	-	Cladbirine	-
8.	Devogelaere, et al, (2020)	Coronavirus disease 2019: favorable outcome in an immunosuppressed patient with multiple sclerosis	Italy	33	Female	RMS	2004	8.00	Rituximab Interferon beta 1a	-
9.	Foerch *et al.*, 2020	Severe COVID-19 infection in a patient with multiple sclerosis treated with fingolimod	Germany	57	Female	RRMS	2010	2.0	Fingolimod	-
10.	Gemcioglu et al, (2020)	Are type 1 interferons treatment in Multiple Sclerosis as a potential therapy against COVID-19	Turkiye	31	Male	MS	2018	-	Interferon beta	Allergic rhinitis
11.	Adamczyk-sowa *et al.*, 2020	SARS-CoV-2/COVID-19 in multiple sclerosis patients receiving disease-modifying therapy	Poland	30	Female	RRMS	2019	4.0	Dimethyl fumarate	Hypothyroidism, lower limb varicose veins, overweight
				38	Female	RRMS	2019	3.5	Dimethyl fumarate	-
				41	Female	RRMS	2006	4.5	Interferon β1b	Hashimoto's thyroiditis
				57	Female	RRMS	2014	4.5	Glatiramer acetate	Dyslipidaemia, migraine headaches
12.	Lallana-Mecca, et al, (2020)	COVID-19 in 7 Multiple Sclerosis patients in treatment with ANTI-CD20 therapies	Spain	60	Male	RMS	2010	8.0	Rituximab	-
				49	Male	RMS	2014	3.0	Ocrelizumab	-
				45	Male	RMS	2015	2.0	Ocrelizumab	-
				25	Female	RMS	2012	1.0	Ocrelizumab	-
				36	Female	RMS	2009	2.0	Ocrelizumab	-
				60	Female	PMS	2014	6.5-7.5	Ocrelizumab	
				52	Male	RMS	2009	-	Ocrelizumab	
13.	Moghadasi, (2020)	Encephalopathy associated with COVID-19 in a	Iran	34	Female	Active progressive MS	2005 (15 years)	-	Cyclophospamide	-

		patient with multiple sclerosis								
14.	Novi *et al.*, 2020	COVID-19 in a MS patient treated with ocrelizumab: does immunosuppression have a protective role?	Italy	58	Male	PPMS	2009 (11 years)	6	Ocrelizumab with lamivudine as profilaxis	Allergic rhinitis, Asthma Peptic ulcer
15.	Rimmer et al. (2020)	Fatal COVID-19 in an MS patient on natalizumab: A case report	USA	51	Female	RRMS	2006 (14 years)	6.5	Natalizumab	Obesity, hypertension, UTI
16.	Sanchez et al. (2020),	A fine balance: Immunosuppresion and immunotherapy in a patient with multiple sclerosis and COVID-19	USA	58	Female	RMS	2007	6.00	FNG	Migraine, Diabetes Mellitus, Hypertension, Hyperlipidemia, Obesity, Transient ischemic attack
17.	Wurm et al. (2020)	Recovery from COVID-19 in a B-cell-depleted multiple sclerosis patient	Germany / UK	59	Female	MS	2016 (4 years)	6	Rituximab	-

Table 2. Data Synthesis

No.	Literature	Case	COVID-19 Manifestations	Degree	Lymphocyte status	Radiology Examination	Outcome	DMT used during COVID-19
			Cohort					
1.	Louapre et al, 2020	347 patients • Mean age=44.6 F:M = 249:98	• Asthenia (290) • Fever (260) • Cough (266) • Anosmia (150) • Headache (180) • Dyspnea (162) • Digestove disorders (88) Dizziness(54)	-	• Normal (128/187) Lymphopenia (59/187) Lymphopenia, excluding patients receiving fingolimod (34/157)	Ground-glass opacity on thoracic CT (62/93)	• Do not support an increased risk of severe outcome associated with DMTs • High EDSS and older age are at highest risk of severe COVID-19	-
			Case Reports					
2.	Capone et al., 2021	Male, 57 year old	Fever (39.5) and cough	-	Normal	Chest CT indicate interstitial pneumonia	Clinical condition and laboratory values improved rapidly 3 days post-infection, patient is afebrile 10 days post-infection, CRP is normal. Patient is discharged in good condition after 2 PCR test came back negative.	Stopped
3.	Gomez-Mayordomo et al., 2021	Female, 57 year old	Intermittent fever, dyspnea	Mild with exacerbation	Lymphopenia	Abnormal chest x-ray	Improved progressively	Stopped
4.	Barzegar et al., 2020	Female, 42 year old	Dry cough, dyspnea, fever (38,7 celcius), low oxygen saturation	Severe	Lymphopenia	Head MRI showed a moderate lesion in the brain and two right-sided cervical spine lesions. Chest X-ray showed ground glass opacity suggestive of community-acquired pneumonia. CT-scan of the chest indicated ground glass opacity.	Cough, dyspnea, and neurological manifestations improved after 13 days	Stopped
5.	Borriello dan Ianniello, 2020	Male, 28 year old	Persistent high fever, dyspnea	Moderate	Normal	Chest CT-scan showed mild bilateral interstitial pneumonia with ground-glass opacity	RT-PCR came back negative after 21 days	Resuming natalizumab therapy at 7th week (EID period)

6.	Creed et al., 2020	Female, 59 year old	Fever, chills, cough, malaise, shortness of breath, dyspnea, myalgia, headache	Mild	Lymphopenia	Chest X-ray: prominent bronchovascular pattern	Recovered after 3 days	None
7.	Dersch et al., 2020	Male, 60 year old	Malaise, persistent fever (39.5°C), progressive respiratory symptoms with chest pain	Moderate	Lymphopenia	Ultrasound of the lungs shows a suspicious appearance of lung consolidation	Respiratory symptoms and fever subsided and inflammatory markers decreased after 16 days	Stopped
8.	Devogelaere, et al, (2020)	Female, 58 year old	Fever, myalgia, headache, cough, mild shortness of breath	Not mentioned	Lymphopenia	Not mentioned	Recovered in 7 days	No explaination
9.	Foerch et al., (2020)	Female, 57 year old	Fever, dry cough, dyspnea	Severe	Lymphopenia	Chest X-ray: regressive peripheral consolidation	Discharged from ICU after 5 days	Stopped
10.	Gemcioglu et al, (2020)	Male, 31 year old	Dry cough, dyspnea	Not mentioned	Not mentioned	CT-Scan: ground-glass opacities in the right lower subpleural area	Recovered in good clinical condition after 5 days	Continued
11.	Adamczyk-sowa et al., 2020	Female, 30 year old	Osteoarticular pain, fever, diarrhea, lethargy, headache, paraesthesia of left upper limb	Mild	Lymphopenia	Head MRI with contrast: similar to the previous examination, no active lesion	Recovered in 7 days	Continued
		Female, 38 year old	Headache and dizziness, rhinitis, fever, impaired smell and taste, attention deficit disorder	Mild	Normal	Head MRI with contrast: similar to the previous examination, no active lesion	Recovered in 10 days	Stopped
		Female, 41 year old	Osteoarticular pain, fever, headache, impaired smell and taste	Mild	Normal	Head MRI with contrast: similar to the previous examination, no active lesion	Recovered in 6 days	Continued
		Female, 57 year old	Osteoarticular pain, headache and dizziness, cough, fever	Mild	Normal	Head MRI with contrast: similar to the previous examination, no active lesion	Recovered in 12 days	Stopped
12.	Lallana-Mecca, et al, (2020)	Male, 60 year old	Fever, dry cough, dyspnea	Severe	Lymphopenia	Chest X-ray: infiltrate on left hemithorax (unilateral pneumonia)	Recovered without sequelae after 5 days	Not mentioned

		Male, 49 year old	Cough, Fever, dyspnea	Moderate	Lymphopenia	Chest X-ray : normal	Recovered without sequelae after 5 days	Not mentioned
		Male, 45 year old	Cough, dyspnea, myalgia, low-grade fever	Moderate	Normal	Chest X-ray: bilateral infiltrates	Recovered without sequelae after 5 days Dyspnea was monitored for a week	Not mentioned
		Female, 25 year old	Asymptomatic	Mild	Not mentioned	Chest X-ray : normal	Not explained. Patient is treated at home.	Stopped
		Female, 36 year old	Fever, headache	Mild	Not mentioned	Not mentioned	Recovered without sequelae after 7 days	Not explained
		Female, 60 year old	Fatigue, headache, cough, fever, hyposmia	Mild	Not mentioned	Not mentioned	Not explained	Not explained
		Male, 52 year old	Asymptomatic	Mild	Not mentioned	Not mentioned	Not explained. Patient is treated at home.	Not explained
13.	Moghadasi, (2020)	Female, 34 year old	Fever, cough, dyspnea, decreased consciousness	Severe	Normal	Chest CT scan: bilateral lung involvement, especially on the right lung	Improved after >10 days in hospital	Monthly therapy
14.	Novi et al., 2020	Male, 58 year old	Persistent high fever and cough	Mild	Normal	Chest X-ray is nonspecific	Fever subsided after 2 days, leukocyte and lymphocyte counts were normal and CRP levels decreased after 3 days	Not explained
15.	Rimmer et al. (2020)	Female, 51 year old	ARDS	Severe	Normal	Chest X-ray: decreased lung volume, diffuse air-space opacity	Died on the 12th day	Monthly therapy
16.	Sanchez et al. (2020),	Female, 33 year old	Fever, dry cough, dyspnea, ARDS	Severe	Lymphopenia	Chest X-ray: multifocal pneumonia CT-Scan: multiple ground-glass opacities in both lungs	Recovered after 14 days with sequelae (dysgeusia and hyposmia)	Not explained
17.	Wurm et al. (2020)	Female, 59 year old	Dry cough, dyspnea, fatigue, headache, nausea, fever, low oxygen saturation	Not mentioned	B cell 0%	Chest X-Ray interstitial pneumonia	Symptoms disappeared and swab test results were negative twice on 14th and 15th days.	Not explained

4. Discussion

4.1. The clinical conditions of COVID-19 patients with MS

The clinical conditions of SARS-COV-2 infection vary from mild, moderate, to severe, critical, and asymptomatic (10,19–21) (22). Risk factors were age, race, sex, comorbidities, EDSS score, DMT used, and time from exposure to onset of infection prolonged than the incubation period (19) (23). The risk of infection and pathogenesis of COVID-19 in MS patients is still unclear (13) (19) (24) (25). MS patients are more susceptible to infection (40) (30), and correlated with the degree of disability, comorbidities, and length of time diagnosed with MS (14). However, previous research has suggested that patients with MS and NMODS are not at risk to infected with COVID-19. (31) Critical conditions in patients by ARDS are caused by desquamation of pneumocytes, formation of hyaline membranes in lung tissue, and pulmonary edema by increased vascular permeability. (32). The recovery experienced in patients with severe critical symptoms can increase the risk of sequelae and be associated with sensory and taste neurological disorders, such as dyspnea, ageusia, anosmia (33). Several comorbidities reported by multiple sclerosis patients with severe COVID-19 conditions, such as major depressive disorder, hypothyroidism because viral infections can decrease in thyroid hormone synthesis T3 and T4, recurrent urinary tract infections, history of pulmonary embolism affecting hemodynamics and pulmonary obstruction, and myasthenia gravis due to immunosuppression and breath fatigue (34) (35) (36). Other comorbidities that affect severity conditions of COVID-19 with MS patients are hypertension and obesity. Hypertension tends to increase incidences of complications and a high mortality rate (37). Obesity can decrease expiratory reverse volume, reduce diaphragm movement, and suppress ventilation (38). Obesity can also decrease the immune system ability to fight chronic infections due to increasing anti-inflammatory cells (Th2 cells and T regulatory cells), accumulation of proinflammatory cells (macrophages, dendritic cells, cytotoxic T cells, and Th1 cells) (39), and cytokines secreted by Th1(IL-6, IFN-γ, and GM-CSF) can cause cytokine storms that can lead to ARDS, multi-organ failure, and death (37).

4.2. The association of DMT in the clinical course of COVID-19

Fingolimod (FNG) is one of the most used treatment options for multiple sclerosis (MS). FNG, which is an SIP-1 analogue, works by sequestrating active lymphocytes in the lymph nodes that can possibly cause severe lymphopenia (40). In several cases, FNG administration was discontinued because it was associated with the incidence of ARDS in MS patients with COVID-19 (41). Meta analysis conducted by Zhao et al. stated that FNG significantly increases the risk of serious infection and is associated with a higher risk of lower respiratory tract infections (42).

However, several other studies have hypothesized that FNG has protective effect that leads to milder course of COVID-19. Discontinuation of FNG can cause relapsing-rebound, in which the infected lymphocytes that have been exiled are re-released into the bloodstream. This may cause the circulating viral load to increase and activate the disease all over again. The potential beneficial effects of FNG are likely to increase the integrity of pulmonary endothelial cells and reduce cytokine storms (24). FNG has strong angiogenic factors, therefore it is able to stabilize the vascular wall which is required in the immune responses to SARS-COV-2 infection (40).

The increased risk of COVID-19 infection in MS patients was not found in patients treated with IFNs and glatiramer acetate (43), but the this therapeutic option was not very effective for MS (44). On the other hand, Interferons, which is the first-line tratment especially in RMS, can also reduce pro-inflammatory cytokines (45). The advantage of IFNs administration as MS therapy is that, when the patient is infected with COVID-19, this drug can still be given, as it also has an antiviral effect. The mechanism of IFNs' antiviral ability is based on the presence of antiviral gene expression through signal transduction as well as the activation of transcription pathways in bronchial and alveolar epithelial cells (46).

Some DMTs have the risk of affecting the adaptive immunity consisting of B cells and T cells, which is known to have an important role in the body's defense against COVID-19. Wurm et al. reported a case of COVID-19 in a MS patient on rituximab therapy who had B lymphocyte depletion (47). This type of immunotherapy can eliminate the ability to produce antibodies in the body's defense response.

Rituximab is one of the anti-CD20 monoclonal immunotherapy agents that need to be given attention to because of its effect on B lymphocytes, which have an important role in the antiviral response against SARS-CoV-2 and other viral infections. There have been several reports of severe and even fatal viral infections in patients taking rituximab, including encephalitis due to Coxsackie A169, Enterovirus (48,49), Powassan (50), Tick-Borne Encephalitis (51), West Nile (52), Neurologic diseases of JCV including PML (53,54) and granule cell neuronopathy (55).

Several other anti-CD20 classes such as Ocrelizumab have also been proven to have a medium-risk to increase the likelihood of SARS-CoV-2 infection in MS patients due to B lymphocyte depletion (29). However, Ocrelizumab and other anti-CD20 had little effect on T lymphocyte levels and had no association with the severity of viral infections. Anti-CD20 therapy is still able to provide a primary immune response to the early phase of infection. OCR and RTX only reduce circulating CD20 + levels and have no effect on lymphoid organs (44).

The pharmacodynamics of Rituximab are closely related to the pathogenesis process that occurs in COVID-19, which generally occurs in two stages. The first stage is the invasion of viruses and infection of human cells and the second stage relates to cytokine storms (56). Immunosuppression regimens, one of which is Rituximab, can increase the risk of severity in the first phase (57), because Rituximab can decrease the ability of immunoglobulin production to eliminate viruses due to B cell depletion (44) and inhibit the action of APCs to activate T cell action (43). However, Rituximab is able to suppress cytokine storm in phase 2, thereby preventing severe symptoms (57).

Investigators observed that in both patients who discontinued DMT and those whose DMT was ongoing, the course of SARS-CoV-2 infection remained similar (20). There is also evidence that there is no association between low levels of B lymphocytes and the severity of SARS-CoV-2 infection (58). This suggests that B cells and immunoglobulins may not be absolutely necessary for viral elimination (59).

Apart from the anti-CD20 activity or B lymphocyte suppression, several other DMT therapies are also of concern. Rimmer et al. reported a patient experiencing fatal MS with COVID-19 in the treatment of Natalizumab . Natalizumab which acts as a monoclonal antibody does not have suppressive activity against peripheral immunity like other DMT regimens, however, Natalizumab is able to increase T cell activity to produce cytokines, notably IL-6 (60). It is known that an increase in IL-6 and other cytokines such as IL-2R, IL-8, MCP, and TNF-alpha is the pathophysiological basis for the worsening of COVID-19 patients who are often characterized by complications of ARDS (61,62).

Natalizumab, which is a monoclonal antibody agent (humanized anti-VLA4), is also able to decrease the activity of immune cells, especially in the central nervous system, which may lead to progressive multifocal leukoencephalopathy (63). This is even more worrying because SARS-CoV-2 has been shown to be able to invade the central nervous system through the olfactory bulb epithelium, therefore the risk of neurological complications in COVID-19 patients on Natalizumab therapy is predicted to be higher.

In contrast to the reports of Rimmer et al, Borriello and Ianniello actually reported cases of COVID-19 patients with a history of MS on Natalizumab therapy who managed to recover without any short-term complications (11). This shows that the use of Natalizumab does not always cause worsening of the symptoms of COVID-19 and MS in patients, although the risk of central nervous system disorders remains. On the other hand, discontinuation of Natalizumab therapy in MS patients has actually been shown to cause recurrence of multiple sclerosis symptoms (64).

A strategy to prevent complications of therapy DMT is to extend interval time of DMT administration, except if it is proven to cause patient's deterioration. It is best if MS treatment is stopped

in patients with severe COVID-19 for at least 4 weeks (29). In addition, the use of DMT by injection or infusion that cannot be done independently can increase the risk of exposure to COVID-19 in MS patients who are required to come to the hospital regularly (65). Special attention is needed regarding the interval of drug administration in patients to minimize this risk.

4.3. Lymphopenia in COVID-19 Patients with Multiple Sclerosis

Lymphopenia occurs in the majority of multiple sclerosis patients who are infected with SARS-CoV-2. A latest research shows that sustainable lymphopenia, particularly CD8+ T cell, is an independent predictor of COVID-19 severity (66). The absolute neutrophil count (ANC) increases as the severity of the disease progresses, and later decreases because the absolute lymphocyte count is partly recovered. Aside from that, the reappearance of CD8+ T cells preceding the resolution of symptoms and consistent with immune response are effective toward SARS-CoV-2 in non-severe cases (67). Therefore, the ANC/ALC ratio has been proposed as the marker of the severity of COVID-19 infection (68).

Lymphopenia is an important aspect to assess the severity od COVID-19 patients' conditions, with the lymphocyte count level less than $1.5x10^9$/L, followed by poor clinical outcomes. Nevertheless, there are possibilities that lymphopenia might occur in a mild COVID-19 (69). Lymphopenia is caused by the SARS-CoV-2 pathogenic process, such as direct infection, lymphocyte destruction, the cytokines which mediate lymphocyte destruction, and the usage of SIP-1 analogue (FNG) (41,70)

There has been a concern about COVID-19 patients with multiple sclerosis who are treated with anti-CD20 therapy, suggesting that they could develop more severe course of COVID-19. On the other side, Wurm et al. report their patient with the same condition who showed clinical improvement (47). As well as B cells' role as a humoral immunity agent, CD4+ T cells, CD8+ cells, and NK cells aslo have dominant part as the cellular immunity agent toward SARS-CoV-2. Cellular immunity has been considered to have the strongest correlation to measure viral elimination than antibody level (71). This case report also implies that COVID-19 patients with multiple sclerosis who are treated with anti-CD20 could recover without any increased risk to develop poor complication and could eliminate the virus without either the role of B cells or the antiviral therapy.

Several other cases also show that lymphopenia arises in COVID-19 patients with multiple sclerosis (72,73). It might be related with the DMT the patient is given. Cladribine has a cytotoxic effect toward lymphocytes and fingolimod can prevent lymphocyte to escape secondary lymphoid organ. A research has showed that fingolimod has some side effects, such as the abnormality of routine laboratory result, which includes lymphopenia. Fingolimod therapy that has been going on for a year in multiple sclerosis patients is proved to decrease total lymphocyte count in peripheral blood in all patients, especially CD4+ Th cells ad B cells (89, 90).

Lymphopenia also might be caused by COVID-19 via lymphocyte exhaustion. Cytotoxic T cells which kill the infected cells will undergo a degradation of its function as the inflammation takes place (76). In addition, the stress mechanism in hypothalamus-pituitary-adrenal axis in COVID-19 will produce endogenous corticosteroid which can stimulate lymphocyte migration from peripheral blood, resulting in lymphopenia (77).

4.4. The Multiple Sclerosis Condition during SARS-COV-2 Infection

During the course of COVID-19, neurological symptoms from central and peripheral nervous system often occur and decline spontaneously (20)**.** There is rarely a report about increased multiple sclerosis relapse frequency during COVID-19 (10,19–21), regardless, SARS-CoV-2 is suspected to have a neurotropic activity.

SARS-CoV-2 receptors, ACE2 and TMPRSS2, are not abundantly expressed in the brain, although the initial evidence from cell RNA sequencing data shows that olfactory epithelium expresses these receptors. This might explain the anosmia that appears as one of COVID-19's symptoms. Nonetheless, there is an initial evidence which states that oligodendrocytes can express SARS-CoV-2 receptors, and

there is recently a case of encephalitis with SARS-CoV-2 seen in the CSF (78) needing a special attention. Apart from that, coronavirus' neurotropism might not depend on the expression of its receptors in brain cells (79). Other neurotropic coronavirus uses different receptors to induce diseases in immunosuppressed patients (21).

However, there is a report of an anxiety disorder in multiple sclerosis patients after being infected by SARS-CoV-2 and lasted only when the infection took place (20). The disorder might occur from the patient's awareness of the ongoing COVID-19 pandemic, for even without any infection of the virus, it can promote a negative impact toward one's stress and anxiety levels, as well as cognitive and neuropsychiatric functions in patients with multiple sclerosis, and might be related to the patient's knowledge about the therapy they are using and its effect on their immunity (80).

Barzegar et al. stated that in RRMS patient they reported, the initial presentation of COVID-19 was a worsening neurologic symptoms of multiple sclerosis. The worsening neurologic symptoms of multiple sclerosis also often seen in other infections, such as viral infection which precedes one-fourth to half relapse events (24,81). The decrease of sensation that occurs in the patient reported by Barzegar et al. might be caused by the blockage of conduction, resulted from axon demyelination. Furthermore, the mechanism of relapse might also associated with an acute demyelination episode ensued from inflammation (82). The decreased muscle strength usually occurred with other pyramidal symptoms, for example, the Babinski sign which was showed in this patient (83)

On the fifth day of hospitalization, the patient who was reported by Moghadasi et al. experienced an altered conciousness, localized response from a pain stimuli, and stiffness of the neck (84). Several researches demonstrated an increased white blood cell in the CSF of the patients which might suggest encephalopathy, despite the normal head CT-scan and MRI result (85,86). Nevertheless, there are possibilities about the occurrence of encephalopathy without increased white blood cell in the CSF. There is also a case of altered conciousness in COVID-19 patient with a normal CSF analysis who shows a periventricular lesion in their MRI result, suspecting that it is induced by multiple sclerosis (84).

However, more researches with cohort metode and larger sample are needed to be done, since the studies regarding this matter are still limited.

5. Conclusions and Suggestions

COVID -19 patients with co-morbid MS show a course of infection that varies from asymptomatic to severe. The use and termination of DMT still raise pros and cons in influencing the journey of COVID-19. In addition, lymphopenia predominantly occurs in the examination of MS patients after being infected with SARS-CoV-2 and is an essential part of assessing the severity of COVID-19 patients. COVID-19 patients with MS also frequently experience neurological symptoms. A further cohort study with a larger sample needs to be done to see the condition of COVID-19 in MS patients and the effects of using DMT in COVID-19 patients with MS.

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