Outcome of COVID-19 Infection in Multiple Sclerosis (MS) Patients

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Received date: 03-October-2022, Manuscript No: jmso-22- 76453; **Editor assigned:** 06-October-2022, PreQC No. jmso-22-76453(PQ); **Reviewed:** 18-October-2022, QC No. jmso-22-76453(Q); **Revised date**: 21-October-2022, Manuscript No: jmso-22-76453(R); **Published date:** 31-October-2022, DOI: 10.35248/2376-0389.22.9.10.466

Abstract

Objective: To measure the relation between COVID-19 infection and relapse rate in comparison with average Annual Relapse Rate(ARR) in MS patients assessment of infection severity according to line of Disease Modifying Treatment (DMT) in different patients determining the effect of COVID-19 infection on Expanded Disability Status Scale(EDSS). Methods: A prospective multi-center Cohort study was conducted at Menoufia university hospital and Elsheikh Zayed Al Nahyan Hospital on a sample of 200 patient with COVID-19 infection and Multiple Sclerosis(MS) disease during the period from June 2020 to June 2022, it started at the time of visit and for follow up till six-month clinical study after covid-19 infection. Results: There is no significant increase in number of relapses in the 6 months follows up after COVID yet with less number of clinical relapses,There is no significant relation between COVID severity and line of MS treatmentand There is high significant increase in the EDSS of the studied MS patients after 6 months post COVID infection (P-value<0.002). However the mean rate of EDSS change is 0.17±0.06 which is considered not clinically significant on any of the major EDSS domains Conclusion: There is no significant increase in number of relapses in the 6 months follows up after COVID infection There is no significant relation between COVID severity and line of DMT patients with higher EDSS and higher relapse rate before infection have more severe COVID symptoms.

Keywords: COVID-19 • Multiple sclerosis • Disease modifying treatment

Introduction

Multiple Sclerosis (MS) is a chronic, inflammatory, neurodegenerative, demyelinating, potentially progressive, neurological disorder of the central nervous system (CNS) in which the insulating covers of nerve cells in the brain and spinal cord are damaged [1]. Since the onset of the COVID-19 outbreak, MS patients receiving Disease-modifying Therapies (DMTs) were considered at a higher risk for experiencing severe disease courses. MS patients, especially those with more severe forms of the disease, are on the whole more prone to infections. In addition, many MS patients take DMTs, which are drugs that have immunomodulatory and also immunosuppressive effects. Several studies suggest that viral respiratory tract infections increase the risk of MS exacerbations and relapses [2-4]. Potential mechanisms for the suggested increased risk of relapse, following infection with viral agents, include the detection of viral epitopes, activation of host's T cells, and secretion of proinflammatory cytokines, including IL-1β, IL-6, and Tumor Necrosis Factor (TNF)-α. This proinflammatory profile increases the expression of endothelial adhesion molecules and increases BBB permeability, allowing for transmigration of previously activated, autoreactive T-cells across the BBB. Moreover, these proinflammatory cytokines contribute to the activation of CNS glial cells and macrophages, as well as expression of major histocompatibility complexes I/II and co-stimulatory molecules, promoting T cells reactivation and localized inflammation [5]. IL-1β and TNF-α may further maintain the migration and recruitment of autoreactive T cells into the sites of inflammation by increasing chemokine (e.g., CCL2 and CCL20) production by astrocytes and microglia cells [5,6].

It is these effects of DMTs that are the main reason for fears that these drugs may be responsible for a potential more severe course of COVID-19, as well as a higher mortality rate. Of particular concern are those DMTs that lead to lymphopenia and also a reduction in the B lymphocyte count, for example cladribine, alemtuzumab, ocrelizumab, and rituximab [7].

The prevalence of COVID-19 in MS patients based on current data appears to be similar to that in the total population. Current evidence shows that simply patients having MS does not make them more likely to develop COVID-19 or to become severely ill or die from the infection than the general population. However, certain factors have been shown to increase the risk for a severe case of COVID-19 e.g., progressive MS, older age, male sex, black race, using a mobility device or a wheelchair, having health conditions like obesity (body mass index of 30 or higher), diabetes or heart disease, and taking certain disease modifying therapies (see MS Treatment Guidelines During Coronavirus) [8]. This study aims to measure the relation between COVID-19 infection and relapse rate in comparison with average annual relapse rate (ARR) in MS patients assessment of infection severity according to line of Disease Modifying Treatment (DMT) in different Patients determining the effect of COVID-19 infection on EDSS.

Materials and methods

A prospective multi-center Cohort study was conducted at two "tertiarty health care hospitals" Menofya university hospital and El sheikh Zayed Al Nahyan Hospital on a sample of 200 patient both gender with COVID-19 infection and MS disease selected according to inclusion and exclusion criteria,sample size was divided between 2 health care hospitals during the period from June 2020 to June 2022, it will start at the time of visit and for follow up till six-month clinical study after Covid-19 infection.All participants signed an informed consent after explaining them the objective of the study. Patients were enrolled in the study according to the following criteria: Patients from both genders have been included, above 18 and below 50, whom confirmed diagnosis of MS, whom confirmed Covid-19 diagnosis and who agreed to participate in the study after obtaining a written informed consent. While Patients younger than 18 and older than 50, those who have other chest comorbidities before covid-19 infection, aggressive relapsing remitting course of disease and MS variants (NMO, ADEM, transverse myelitis. etc) were excluded from the study

Demographic and clinical data were obtained from patients and medical records including date of onset and the nature of the first MS related presenting symptoms, date of diagnosis of MS, date of advice to start a (DMT), current DMT, total number of relapses during the course of disease, number of relapses annually, the EDSS scores were obtained from the patients records throughout their illness namely the EDSS scores before and after six month, the MRI scans of the patients were reviewed before and after six month from starting the current disease for the number of T2 lesions, T1 hypo intensity, and the CT chest of the patient during covid 19 infection.

Statistical analysis

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations and ranges when parametric and median, Inter-quartile Range (IQR) when data found non-parametric. Also qualitative variables were presented as number and percentages. The comparison between groups with qualitative data was done by using Chi-square test.The comparison between two groups with quantitative data and parametric distribution were done by using Independent t-test. While the comparison between two groups with quantitative data and non-parametric distribution was done by using Mann-Whitney test. The confidence interval was set to 95% and the margin of error accepted was set to 5%. Result

Table 1. Descriptive for age, gender, MS type, line of treatment, duration of treatment, relapse rate and EDSS before and after Covid of the studied patients.

			No.= 150
Center	ZAN		121 (80.7%)
	MUH		29 (19.3%)
Age	Mean±SD		33.20 ± 8.87
	Range		17 – 58
Gender	Female		119 (79.3%)
	Male		31 (20.7%)
MS type	RRMS		143 (95.3%)
	SPMS		7 (4.7%)
Line of treatment	NA		1 (0.7%)
	Interferon		54 (36.0%)
	Teriflunamide		13 (8.7%)
	Fingolimod		66 (44.0%)
	Natlizumab		4 (2.7%)
	Dimethilfumerate		8 (5.3%)
	Ocreluzumab		4 (2.7%)
Duration (Month)	Median (IQR)		24 (12 – 36)
	Range		1 – 156
RR before COVID		0	82 (54.7%)
		1	68 (45.3%)
RR after COVID		0	107 (71.3%)
		1	43 (28.7%)
Current EDSS	Mean±SD		2.90 ± 1.29
	Range		1 – 6.5
EDSS after COVID	Mean±SD		3.07 ± 1.23
	Range		1 – 6.5

Table 1 showed that the majority of the patients were collected from Zayed Al Nahyan hospital. 79.3% of the selected patients are female. The most of the patients were weather on fingolimod or interferons.

Table 2. Descriptive for risk factors of the studied patients

Risk factors		No.= 150
	Range	2.3 – 13.3
Pregnancy	No	148 (98.7%)
	Yes	2 (1.3%)
Smoking	No	136 (90.7%)
	Yes	14 (9.3%)
Obesity	No	131 (87.3%)
	Yes	19 (12.7%)
HTN	No	138 (92.0%)
	Yes	12 (8.0%)
DM	No	139 (92.7%)
	Yes	11 (7.3%)
BA	No	143 (95.3%)
	Yes	7 (4.7%)
Epilepsy	No	148 (98.7%)
	Yes	2 (1.3%)
Hypothyroid	No	142 (94.7%)
	Yes	8 (5.3%)

Most of the patients were not smokers nor pregnant, and there were very low percentage of patients with other risk factors (Table 2).

Table 3. Descriptive of imaging and lab results done for patients during Covid.

Imaging and labs results		No.= 150
TLC (x 103/uL)	Mean±SD	5.37 ± 2.77
	Range	2 – 18.9
Lymph. (x 103/uL)	Mean±SD	1.40 ± 0.88
	Range	0.2 – 4.9
CRP	Negative	29 (29.6%)
	Positive	69 (70.4%)
D dimmer (mg/L)	Median (IQR)	0.4 (0.22 – 0.6)
	Range	0.1 – 2.19
S. Ferritin (ng/mL)	Median (IQR)	64.05 (34 – 223)
	Range	3.4 – 1118
Chest imaging	CORADS II	105 (70.0%)
	CORADS III	40 (26.7%)
	CORADS IV-V	5 (3.3%)

Most of the selected patients in the study were lymphopenia, D-dimer values were high normal for most of the patients, and serum ferritin values were normal in most of the patients. Regarding chest imaging most of the patients were CORADS II (Table 3).

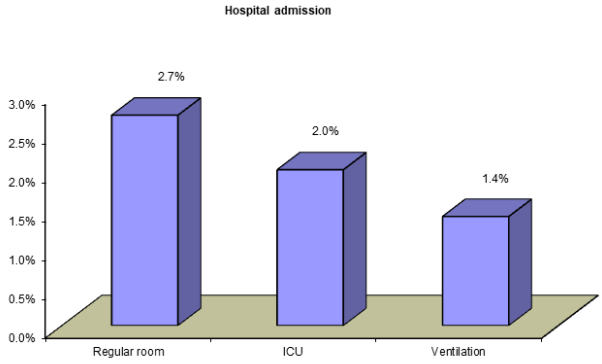

Figure 1. Descriptive of percentage of different types of hospitalization for selected patients.

Only 2% of the patients in the study were admitted to ICU,and only 1.4% of them were mechanically ventilated (Figure 1).

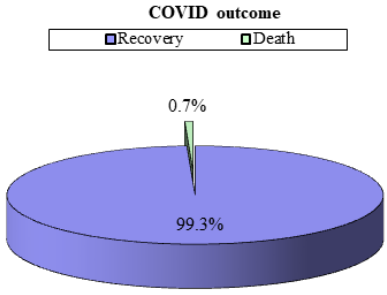

Figure 2. Descriptive for COVID outcome in studied MS patients

The figure Shows that survival rate of COVID in studied patients is 99.3% (Figure 2).

Table 4. Duration (by days) for recovery from Covid in studied patients.

Recovery duration		No.= 150
Duration of recovery (days)	Mean±SD	10.85 ± 5.40
	Range	5 – 28

The mean of duration of recovery from COVID was around 10 days (Table 4)

Table 5. Comparison between number of relapses before and after Covid.

Patients	Before	After
No. of patients with relapses	68 (45.3%)	43 (28.7%)

Table 5 shows that there was no significant increase in number of relapses in the 6 months follow up after Covid yet the number of patients experiencing relapses is decreasing.

Table 6. Comparison between different types of DMTS and their relation to severity of Covid.

		Line of treatment								
		Interferon	Teriflunamide	Fingolimod	Natlizumab	Dimethilfumerate	Ocreluzumab	Test value*	P-value	Sig.
		No.= 54	No.= 13	No.= 66	No.= 4	No.= 8	No.= 4			
Severity	Mild	38 (70.4%)	8 (61.5%)	47 (71.2%)	4 (100.0%)	6 (75.0%)	2 (50.0%)	10.732	0.379	NS
	Moderate	16 (29.6%)	5 (38.5%)	14 (21.2%)	0 (0.0%)	2 (25.0%)	2 (50.0%)			
	Severe	0 (0.0%)	0 (0.0%)	5 (7.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)			

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant *: Chi-square test

Table 6 shows that there is no significant relation between line of treatment and Covid severity.

Table 7. Comparison between ages, gender, relapse rate and EDSS; and their relation with Covid severity

			Severity					
			Mild	Moderate	Severe	Test value	P- value	Sig.
			No.= 105	No.= 40	No.= 5			
Age	Mean±SD		32.52 ± 8.40	34.83 ± 10.07	34.40 ± 8.50	1.021•	0.363	NS
	Range		18 – 58	17 – 56	26 – 43			
Gender	Female		85 (81.0%)	33 (82.5%)	1 (20.0%)	11.148*	**0.004**	HS
	Male		20 (19.0%)	7 (17.5%)	4 (80.0%)			
RR before COVID		0	60 (57.1%)	22 (55.0%)	0 (0.0%)	6.291*	0.043	S
		1	45 (42.9%)	18 (45.0%)	5 (100.0%)			
EDSS	Mean±SD		2.82 ± 1.34	2.94 ± 0.93	4.30 ± 2.05	3.271•	0.041	S
	Range		1 – 6.5	1 – 4.5	2.5 – 6.5			

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
*: Chi-square test; •: Independent t-test; ≠: Mann-Whitney test

The previous table shows that there is no significant relation between the age of MS patient and Covid severity. And that male MS patient has higher possibility of having more severe Covid than female MS patients. Also shows that the higher the EDSS of the patients the more severe his COVID infection is; and that patients with relapses in the last six months before Covid shows more severe Covid infection than patients with no relapses.

Previous table shows that there is high significant increase in number of studied MS patients that had increase in their EDSS in the 6 months follow up; yet this is only marginal increase.

Discussion

The clinical features and outcomes of COVID-19 among MS patients on DMTs among Egyptian population is not yet studied and described. Our study is to Measure the relation between COVID-19 infection and relapse rate in comparison with average Annual Relapse Rate (ARR) in MS patients assessment of infection severity according to line of Disease Modifying Treatment (DMT) in different Patients determining the effect of Covid-19 infection on EDSS.

In our study most of the patients were on fingolimod (44%) and interferons (36%) Most of the patients were not smokers (90.7%) nor pregnant (97.8%), and there were very low percentage of patients with other risk factors, as regarding the clinical symptoms of COVID-19 infection in the studied MS patients most of the patients were presented with fever (72.7%), fatigue (72%) , anosmia (60%) sore throat (49.3%) and loss of taste (48%) while with more severe symptoms were less as dyspnea (40%) and Frank Pneumonia (18.7%) indicating overall milder presentation of Covid; in comparison to(Barzegar, Mahdi, et al. 2021)The most common symptoms were fever (68.8%), followed by cough (63.9%), fatigue/asthenia (51.2%), and shortness of breath (39.5%)

Most of the selected patients in the study are lymphopenic (Mean: 1.4 +/- 0.88), D-dimer values are high normal (Median: 0.4) and serum ferritin values are normal (Median: 64.05). Regarding chest imaging most of the patients are CORADS II (70%) with 26.7% as CORAD III and only 3.3% as CORAD IV and V, Only 2% of the patients in the study are admitted to

ICU,and only 1.4% of them are mechanically ventilated. Survival rate of COVID in studied patients is 99.3% with mean duration of recovery around 10.85 ± 5.40 days. This goes with the same finding as Etemadifar who showed good outcome among 45 patients with Covid and MS with 5 only patients with unfavorable outcome [9].

Such findings come with the same line as Alroughani.who demonstrated good prognosis of COVID infection in MS patients that can be explained by the younger age, lack of risk factors and possible role of immune-modulators on the Covid related immune response and cytokine storm [10].

Our study also shows that there is no significant increase in number of relapses in the 6 months follows up after Covid yet with less number of clinical relapses that came along the same line with Etemadifar who stated lower incidence of RRMS exacerbation among patients who were symptomatic for Covid infection (P=0.026) [9-10]. explaining such finding by the Covid related lymphopenia hindering the auto-reactive memory cells from reaction and activation causing clinical relapses, it also may have been caused by the good control of patients' visits to clinics and MS units to prevent infection spread, so most of the patients didn't visit the clinic except if having a relapse of disease activity.

In addition to that we also suggest that receiving steroids whether oral or intravenous decreases the disease activity and prevents further relapses among the 6 months following the Covid infection.

Moreover there is no significant relation between Covid severity and line of MS treatment (P= 0.379) neither the age of the patient (P=0.36) in comparison toSormani [11]. The number of deaths and ICU admissions according to DMT use in the lower- and in the higher-risk groups is reported. In the higher-risk group, the excess of death risk was mainly in the no therapy group and in the anti- CD20 group, even if the low number of events does not allow to conclude for an heterogeneity of mortality risk according to the DMT group and regarding Portaccio, knowing that none of the studied patients in this study were on no medication and the only death were of a patient on ocrilozomab [12].

On the other hand, More severe COVID infection among the studied MS patients is associated with male gender (P= 0.004), in comparison to Barzegar male sex seem to be risk factors for worse disease outcome [13].

From addition to higher number of relapses 6 months before Covid infection (P=0.043) and higher EDSS (P=0.041) that finding is similar to Sormani et al. [11], Louapre, et al. [14]; Loonstra, et al. [15]; Parrotta, et al. [16]; Zabalza, et al. [17] and also regarding Zabalza et al. [18], older patients with longer disease duration, a higher disability, and previous comorbidities, and regarding Sormani, et al. [11], the EDSS score cutoff was chosen based also on the EDSS distribution of cohort to have 2 balanced groups. Therefore, the lower-risk group included patients with EDSS score ≤ 3 and no comorbidities, whereas the higher-risk group included patients with EDSS score > 3 or at least 1 comorbidity.

A higher risk of a severe Covid-19 disease confirmed the significant relation between higher EDSS and more severe Covid infection. That can be explained by the more aggressive immune-suppressants, more physical disability, possible chest expansion limitations and aspiration.

At last, our study demonstrates that there is high significant increase in the EDSS of the studied MS patients after 6 months post Covid infection (P-value Less than 0.002). However the mean rate of EDSS change is 0.17 +/- 0.06 which is considered not clinically significant on any of the major EDSS domains, our explanation is the effect of Covid on reported fatigability as fatigue is one of the common symptoms of Covid infection and also fatigue is a common and disabling symptom in Multiple Sclerosis (MS). In this study we evaluated if fatigue is associated with different demographic and clinical features of MS [18-19]. In most of the patients in addition to the COVID related cognitive fog which is described in literature [20]. While, regarding Kataria et al. [21], the patients with Multiple Sclerosis can experience worsening of their symptoms due to Covid-19 infection and they can present possibly as pseudo exacerbation. It is paramount for the physicians to determine if the patient has an underlying acute exacerbation of the disease or a pseudo-relapse.

Conclusion

Our study showed that Regarding the common symptoms of Covid 19 infection in MS patients were fever, fatigue, anosmia sore throat and loss of taste and that there is no significant increase in number of relapses in the 6 months follows up after Covid infection also no significant relation between Covid severity and line of MS treatment neither the age of the patient; also that male patients and patients with higher EDSS and higher relapse rate before infection have more severe Covid symptoms. Most of the patient had increase in their EDSS in the 6 months follow up but this increase was subtle and not clinically significant.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Zaniuk, M., et al. "Ocrelizumab as a breakthrogh in multiple sclerosis treatment." *J Educ Health Sport* 11.5 (2021): 50-56.
2. Buljevac, D., et al. "Prospective study on the relationship between infections and multiple sclerosis exacerbations." Brain 125.5 (2002): 952-960.
3. Correale, J., et al. "The risk of relapses in multiple sclerosis during systemic infections." Neurology 67.4 (2006): 652-659.
4. Tremlett, H., et al. "Monthly ambient sunlight, infections and relapse rates in multiple sclerosis." Neuroepidemiology 31.4 (2008): 271-279.
5. Marrodan, M., et al. "The role of infections in multiple sclerosis." Mult Scler J 25.7 (2019): 891-901.
6. Steelman, A.J. "Infection as an environmental trigger of multiple sclerosis disease exacerbation." Front Immunol 6 (2015): 520.
7. Adamczyk-Sowa, M., et al. "SARS-CoV-2/COVID-19 in multiple sclerosis patients receiving disease-modifying therapy." Clin Neurol Neurosurg 201 (2021): 106451.
8. Mado, H., and Adamczyk-Sowa, M. "Multiple sclerosis patients and COVID-19." Egypt J Neurol Psychiatry Neurosurg 57.1 (2021): 1-2.
9. Etemadifar, M., et al. "COVID-19 and the risk of relapse in multiple sclerosis patients: a fight with no bystander effect?." Mult Scler Relat Disord 51 (2021): 102915.
10. Alroughani, R., et al. "Prevalence, severity, outcomes, and risk factors of COVID-19 in multiple sclerosis: An observational study in the Middle East." J Clin Neurosci 99 (2022): 311-316.
11. Sormani, M.P, et al. "COVID-19 severity in multiple sclerosis: putting data into context." Neurol Neuroimmunol Neuroinflammation 9.1 (2022).
12. Portaccio, E., et al. "Impact of COVID-19 on multiple sclerosis care and management: Results from the European Committee for Treatment and Research in Multiple Sclerosis survey." Mult Scler J 28.1 (2022): 132-138.
13. Barzegar, Mahdi, et al. "Characteristics of COVID-19 disease in multiple sclerosis patients." Mult Scler Relat Disord 45 (2020).
14. Louapre, C., et al. "Clinical characteristics and outcomes in patients with coronavirus disease 2019 and multiple sclerosis." JAMA Neurol 77.9 (2020): 1079-1088.
15. Loonstra, F.C., et al. "COVID-19 in multiple sclerosis: the Dutch experience." Mult Scler J 26.10 (2020): 1256-1260.
16. Parrotta, E., et al. "COVID-19 outcomes in MS: Observational study of early experience from NYU Multiple Sclerosis Comprehensive Care Center." Neurol Neuroimmunol Neuroinflammation 7.5 (2020).
17. Zabalza, A., et al. "COVID-19 in MS patients: susceptibility and severity risk factors." Mult Scler J (2020): 61.
18. Zabalza, Ana, et al. "COVID‐19 in multiple sclerosis patients: susceptibility, severity risk factors and serological response." Eur J Neurol 28.10 (2021): 3384-3395.
19. Colosimo, C., et al. "Fatigue in MS is associated with specific clinical features." Acta Neurol Scand 92.5 (1995): 353-355.
20. Garjani, A., et al. "Recovery from COVID-19 in Multiple Sclerosis: A prospective and longitudinal cohort study of the United Kingdom Multiple Sclerosis Register." Neurol Neuroimmunol Neuroinflammation 9.1 (2022).
21. Kataria, S., et al. "A case series and literature review of multiple sclerosis and COVID-19: Clinical characteristics, outcomes and a brief review of immunotherapies." Eneurologicalsci 21 (2020): 100287.

Cite this article: Mohamed R.T. et al. Outcome of COVID-19 Infection in Multiple Sclerosis (MS) Patients. J Mult Scler. 2022, 09(10), 466.