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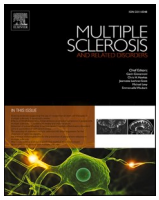

Original article

COVID-19 infection and vaccination against COVID-19: Impact on managing demyelinating CNS disorders in Southern India- experience from a demyelinating disease registry.

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ABSTRACT

Background and objective: The impact of COVID-19 infection and the effect of COVID-19 vaccinations on patients with demyelinating central nervous system disease in low middle income countries (LMIC's) have not been reported in detail earlier. We sought to identify risk factors associated with COVID-19 infection and the role of vaccination in order to develop management guidelines relevant to our patients.

Methods: A total of 621 patients from our registry that included 297 MS and 324 non MS disorders (Aquaporin- 4 antibody positive [50], Myelin oligodendrocyte glycoprotein antibody positive [81], seronegative [162] and clinically isolated syndrome [31]) were contacted. COVID-19 infection and vaccination status were queried. Patients who self reported COVID-19 infection based on a positive RT PCR report were compared with non infected patients to identify factors associated with susceptibility for COVID-19 infection. Univariate and multivariate analysis of potential risk factors included demographic and clinical features, body mass index (BMI), presence of comorbidities, absolute lymphocyte count, treatment types and vaccination status.

Results: Sixty seven patients with MS and 27 with non MS disorders developed COVID-19 infection. Among them 81 patients had mild infection and remained quarantined at home. All 13 patients who needed hospitalization recovered. Vaccination status was known in 582 patients among whom 69.8% had completed or taken one dose of vaccine at the time of inquiry. Majority of treated patients (61.3%) were on nonspecific immunosuppressants. In univariate analysis, presence of $\geq$1 comorbidity was significantly associated with COVID-19 infection in both MS (*p* value 0.01, OR-2.28, 95%CI- 1.18–4.4) and non MS patients (*p*- 0.001, OR-4.4, 95% CI-1.88–10.24). In the latter, BMI $\geq$ 30 (*p*-0.04, OR-3.27, 95% CI- 0.98–10.87) and EDSS score $\geq$ 3 (*p*-0.02, OR- 2.59,95% CI-1.08–6.23) were other significant associations. History of prior COVID-19 vaccination was associated with reduced frequency of COVID-19 infection among MS (*p*- 0.001,OR- 0.24,95% CI- 0.13–0.43) and non MS patients (*p*- 0.0001,OR-0.14, 95% CI- 0.058–0.35). In multivariate analysis presence of comorbidities significantly increased and prior vaccination significantly reduced frequency of COVID-19 infection for both MS and related disorders. Concurrent disease modifying treatments showed a trend for association with infection. In the unvaccinated group, patients on disease modifying treatment were significantly at risk of infection, 81.5% unvaccinated and treated versus 18.5% who were unvaccinated and untreated (*p*- 0.0001, OR-10.1, 95% CI-0.56–2.11).

Conclusion: Frequency and severity of COVID-19 infection was low among our patient cohort. Higher rate of infection in the treated group was significantly seen among unvaccinated patients. Our preliminary results suggests that in LMIC's, where "off label therapies" with inexpensive immunosuppressives are the main disease modifying drugs, mRNA vaccinations appear safe and effective against severe COVID-19 infection.

Abbreviations: RRMS, relapsing remitting MS; SPMS, secondary progressive MS; PPMS, primary progressive MS; AQP4-IgG $^{+}$, Aquaporin4 IgG positive; MOGAD, myelin oligodendrocyte glycoprotein associated disorder; CIS, clinically isolated syndrome; DMT, disease modifying therapy; IS, immunosuppressant; EDSS, expanded disability status scale. BMI-body mass index; RTX, rituximab; IS, immunosuppressant, AZA-azathioprine; MMF, mycophenolate mofetil.

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1. Introduction

Several studies from high income countries (HICs) have evaluated the impact of COVID-19 on patients with MS (Berger et al., 2020; Louapre et al., 2020; Parrotta et al., 2020; Loonstra et al., 2020; Barzegar et al., 2021). While the overall susceptibility to COVID-19 infection was not found to be higher in patients with MS than the general population (Berger et al., 2020), some studies showed that patients who were not on treatment with disease modifying therapy (DMT) for MS were at greater risk for COVID-19 infection (Louapre et al., 2020). Several risk factors were identified that were associated with hospital admissions and intensive care (Louapre et al., 2020; Parrotta et al., 2020; Loonstra et al., 2020). Overall ~20% of MS patients diagnosed with COVID-19 infection in HICs were hospitalized among whom ~3% died (Barzegar et al., 2021). There were fewer studies that looked at the impact on "non MS" disorders including AQP4-IgG positive neuromyelitis optica spectrum disorders (AQP4-IgG+ NMOSD), MOG-IgG associated disorders (MOGAD) and other monophasic and recurrent demyelinating disorders. Data from limited patient series suggested a high risk for severe COVID-19 (Stastna et al., 2021; Alonso et al., 2021) and higher mortality among NMOSD patients. All deaths occurred in patients on rituximab, were older and had higher expanded disability status scale (EDSS)scores and longer duration of disease (Alonso et al., 2021).Impact of COVID-19 vaccinations in patients with MS and related disorders has not been studied in detail. Recommendations were based on available data on the immunology of these disorders, mechanism of actions of disease modifying drugs and COVID-19 vaccines (Nojszewska et al., 2021; Coyle et al., 2021). Limited studies on safety (Achiron et al., 2021) and immune response (Dreyer-Alster et al., 2022) after COVID-19 mRNA vaccine in patients with MS have been published.

2. Prevailing conditions in lower middle income countries (LMICs) differ vastly from advanced nations

Limited health capacities, human densities, crowded housing and lack of government resources have challenged community compliance with shelter at home campaign during the ongoing COVID-19 pandemic. Due to financial constraints patients rely on generic versions of DMT and biosimilars. In India, country wide pandemic mitigation strategies included intermittent lockdowns, mandatory social distancing and masking in public. COVID-19 vaccinations (Covishield^{TM}/ Vaxzerviria, AstraZeneca and Covaxin / Bharat Biotech which are mRNA vaccines), were started in January 2021 prioritizing frontline workers, older populations and those with comorbidities initially.As per the ministry of health and family welfare (www.cowin.gov.in), currently 80% of eligible population ($\geq$ 15 years of age) are fully vaccinated and another 15% have received at least one dose of the vaccine. In this background we assessed the impact of COVID-19 infection and the effect of vaccination among our patients, in order to develop guidelines which would be informative for patient management in LMIC's.

2.1. Methodology

Six hundred and twenty one patients (51.6%) from our demyelinating disease registry in Southern India(Mangalore demyelinating disease registry [MANDDIR] (Malli et al., 2021) who are under regular follow up were contacted. These patients were reviewed telephonically between August 2020 and December 2021. Patient demographics, diagnosis, clinical details, medication history, the last recorded EDSS, comorbidities (smoking, obesity, hypertension, coronary artery disease, diabetes, other autoimmune disorders) and treatment details were obtained from our data base. Responders were queried about confirmed COVID-19 infection (at least one positive molecular test -RT- PCR on nasal and pharyngeal swabs), potential source of exposure, whether medications were discontinued or modified, specific treatments if any including hospitalization and outcome. Vaccination status was determined. Absolute lymphocyte counted reported within the previous 3 months to our registry and or at the time of COVID-19 infection was reviewed. Our registry patients had been advised to continue first line DMT (generic dimethyl fumerate [DMF], teriflunomide or beta interferon [IFN-β]) and nonspecific immunosuppressants (IS) namely generic versions of mycophenolate mofetil [MMF],Azathioprine [AZA] or rituximab[RTX] biosimilar (Pandit, 2021). We encouraged all patients to get vaccinated while on DMT, MMF&AZA. For patients on RTX, vaccinations were advised towards the end of the infusion cycle and treatment resumed4 weeks after vaccinations (Kelly et al., 2021).In addition, during COVID-19 infection peaks RTX infusions were postponed or dosing modified. Since ~ 70% of patients in our registry are dependent on subsidized medications regularly couriered to their homes or visit our hospital for infusions, we were able to monitor treatment compliance.

2.2. Statistics

Demographic and clinical features of demyelinating disorders were recorded from chart reviews. Categorical variables were expressed in percentages and continuous variables as mean and standard deviations. Data was compared between patients with and without COVID-19 infection. Univariate logistic regression models were performed on relevant variables to determine factors associated with susceptibility to COVID-19 infection. These included current age (<50 versus > 50 years), primary disease duration, gender, body mass index (BMI), EDSS, associated comorbidities including obesity, tobacco use, hypertension, diabetes, cardiovascular disease and chronic lung disease and absolute lymphocyte count. Concurrent disease modifying therapy and vaccination status was recorded. Therapy was categorized into 3 groups–i: first line DMT (DMF, teriflunomide and IFN β); ii:RTX and iii:oral IS (MMF&AZA). Based on these results, multivariate analysis was performed in MS and non MS disorders separately to determine which variable(s) was independently associated with risk of COVID-19 infection. Independent variables that showed a p value of < 0.20 were included in the multivariate analysis (Fragoso et al., 2021). A p value ≤ 0.05 was taken to be significant. Strength of association was expressed as adjusted odds ratios (OR) and 95%confidence intervals (CI). Analysis was performed on SPSS statistical software program (IBM, USA).

2.3. Standard protocol approvals, registrations and patient consents

This study was approved by the central ethics committee of Nitte University and written informed consent was obtained from all participants in accordance with our registry research protocols.

3. Results

There were 237 patients with relapsing remitting, 49 with secondary progressive and 11 with primary progressive multiple sclerosis. The non MS cohort comprised of 50 AQP4-IgG+ NMOSD (Wingerchuk et al., 2015), 81 MOGAD, 162 double seronegative (supplementary Table1) and 31 patients with clinically isolated syndrome (CIS). Live cell based assay (CBA) (Pandit et al., 2021) and a commercial fixed CBA (Euroimmun, Germany) were used to test forAQP4-IgG and MOG-IgG, respectively.

3.1. COVID-19 infection and outcome

Sixty seven patients with MS (22%) and 27 patients with non MS disorders (8.3%) had confirmed COVID-19 infection. They were mostly woman (61.7%) and31.8% of patients had $\geq$ 1 comorbidity. Eight patients with MS (2.7%) had asymptomatic infection. In both groups ~70% were on treatment either with first line DMT for MS or immunosuppressants for both MS and non MS group (Table 2). Majority of patients had a known family member with COVID-19 infection (60%), others had contracted it at the work place (22%), attending social

gatherings (10%) and in the remaining 8% the source was unknown. Symptoms were mild in the majority (82/94) and included fever, cough, sore throat, anosmia and or ageusia. They were home quarantined and took symptomatic treatment. Eleven patients had moderate COVID-19 infection and were hospitalized (supplementary Table 2) with high fever and or dyspnea.Two patients developed severe COVID-19 infection and remained in intensive care for COVID-19 associated pneumonia. Only 2/13(15%) admitted patients had been vaccinated. Median period of hospital stay was 5 days (3–21 days) and all made a good recovery.

Among patients who remained free of COVID-19 infection, 6 patients with MS and 5 patients with non MS disorders relapsed. While one MS patient had postpartum relapse, all others were noncompliant with medications due to pandemic related constraints. They were admitted in local hospitals for intravenous steroids and reported improvement to base line.

3.2. MS patients with COVID-19 infection

Demographic and clinical features are listed in Table 1. While comparing MS patients who had COVID-19 infection with those who were non infected, in univariate analysis (Table 2) presence of ≥ 1 comorbidity was significantly associated (27.7% versus 14.3%,*p* value 0.01, OR-2.28, 95%CI- 1.18–4.4) with COVID-19 infection.

3.3. Non MS Patients

Among non-MS patients, BMI ≥ 30 (*p*-0.04, OR-3.27, 95% CI-0.98–10.87), associated comorbidities(*p*- 0.001, OR-4.4, 95% CI-1.88–10.24)and an EDSS score ≥ 3 (*p*-0.02, OR- 2.59,95% CI- 1.08–6.23) were significantly associated with COVID-19 infection (Table 2). In multivariate analysis, presence of ≥ 1 comorbidities (*p*-0.01, OR 7.55, 95% CI-1.44–39.48) retained significance (Table 3).

3.5. Treatment and effect on frequency of COVID-19 infection

Majority of MS patients (62.2%) were on treatment as follows - oral IS (47.6%) followed by first line DMT (28%) and rituximab (24.40%). In multivariate analysis concurrent treatment showed a trend for association with infection (*p*-0.06, OR-2.4, 95%CI- 0.96–6.01). Treatment types (first line DMT /IS) were evenly distributed between groups. In the non MS cohort 36.1% were on treatment with either oral IS (91.1%) or RTX (9.9%). Among the latter, univariate analysis showed a significant number of infected patients were on concurrent IS therapy (70.4%) as compared to the non infected group (33.1%) [*p*- 0.0001,OR 4.79, 95% CI 2.02–11.34]. In multivariate analysis, after adjusting for other parameters, those on treatment showed a trend for association (*p*-0.059, OR 2.8, 95% CI- 0.96–8.58) with COVID-19 infection. There was no association noted between any specific immunosuppressant and frequency of COVID-19 infection.

3.6. Vaccination and effect on frequency of COVID-19 infection among patients on treatment with immunomodulatory therapy

Vaccination status was known in 582 patients among whom 69.8% (406) had completed or taken at least one dose of vaccine prior to inquiry. Among vaccinated patients, 9.9% (40/406) developed COVID-19 infection which was mostly mild or asymptomatic. Prior history of vaccination with Covaxin/Covishield vaccine was associated with significant reduction in frequency of COVID-19 infection among MS (*p*-0.001,OR- 0.24,95% CI- 0.13–0.43). In multivariate analysis vaccinated status was the most significant factor that influenced susceptibility for COVID-19 infection among MS (*p*-0.0001, OR- 0.17, CI -0.08–0.37). Among non MS patients a similar effect was seen in both univariate (*p*-0.0001,OR-0.14, 95% CI- 0.058–0.35) and multivariate analysis (*p*-0.0001, OR 0.04, 95%CI- 0.01–0.15). In the unvaccinated group (supplementary Table 3), patients on disease modifying treatment were significantly at risk of COVID-19 infection, 81.5% unvaccinated and treated versus 18.5% who were unvaccinated and untreated (*p*- 0.0001, OR-10.1, 95% CI-0.56–2.11).

4. Discussion

We evaluated a homogenous cohort of MS and non MS patients from southern India to determine risk factors associated with contraction of COVID-19 infection and the effect of vaccination among them. Our study had several distinctive features. There was real world data obtained from a demyelinating disease registry in a LMIC and included MS and non MS disorders such as AQP4+ NMOSD, MOGAD and other related diseases.Patients received subsidized medications which were mostly generic form of nonspecific immunosuppressants rather than specific DMT. Remote monitoring of blood counts and treatment compliance was possible. Besides, vaccination status was known. Additionally, patient outcome was relatively good.

All 94 patients who contracted COVID-19 survived. Similar to previous reports, a higher BMI and coexistence of comorbidities were risk associations in our patients (Louapre et al., 2020; Parrotta et al., 2020; Loonstra et al., 2020). Younger age (38.8 ± 13.2), a stable disease with low EDSS (< 3.0) in the majority (63.6%) and low frequency of comorbidities (4.7%) may have possibly contributed to this good outcome. In previous publications from HICs most patients were on MS specific DMT and among them untreated patients had more severe COVID-19 infection and death (Barzegar et al., 2021). With the exception of B cell depleting agents (Louapre et al., 2020; Stastna et al., 2021; Zabalza et al., 2021), treatments were not associated with increased susceptibility to COVID-19. Most notably vaccination status was not known in these patients. In our patient cohort, rituximab was prescribed

Table 1
Clinical and demographic features.

	MS (297)			Non MS disorders (324)			
	RRMS (237)	SPMS (49)	PPMS(11)	AQP4-IgG+(50)	MOGAD(81)	Seronegative(162)	CIS(31)
Gender (Female)	169	24	10	46	40	84	19
Age (Mean & SD)	37.0 ± 12.13	47.75 ± 11.39	41.18 ± 10.34	39.22 ± 11.66	30.41 ± 13.28	37.98 ± 14.63	40.1 ± 14.7
Disease Duration (Mean & SD)	9.9 ± 6.28	16.12 ± 7.23	11.8 ± 4.82	10.38 ± 7.55	7.11 ± 7.29	7.18 ± 5.24	9.58 ± 4.85
EDSS (Mean & SD)	1.85 ± 1.44	5.59 ± 1.72	5.58 ± 1.2	2.75 ± 1.86	1.23 ± 1.15	2.02 ± 2.33	0.89 ± 1.04
Treated with DMT/IS (no:)	157	26	2	43	34	40	0
COVID-19 infection (no:)	58	8	1	9	6	9	3
Vaccinated (no:)	167	26	11	37	45	103	17

In all, 621 patients were contacted including 297 MS (Thompson et al., 2018) and 324 non MS disorders (Table 1).
Abbreviations: RRMS- relapsing remitting MS, SPMS- secondary progressive MS, PPMS- primary progressive MS, AQP4-IgG $^{+}$ - Aquaporin4 IgG positive, MOGAD-myelin oligodendrocyte glycoprotein associated disorder, CIS- clinically isolated syndrome, DMT- disease modifying therapy, IS – immunosuppressant, EDSS-expanded disability status scale. SD- standard deviation.

Table 2
Risk factors associated with COVID-19 infection- Univariate analysis.

Disease	COVID+ MS	COVID-MS	*p* value	Odds ratio	95%CI	COVID +NON MS	COVID -NON MS	*p* value	Odds ratio	95%CI
Number	**67**	**230**				**27**	**297**			
Male	24(35.8%)	68(29.5%)	0.33	0.75	0.42–1.33	12(44.4%)	123(41.4%)	0.73	0.87	0.39–1.92
BMI <30	59(91%)	204 (91.5%)	0.85	1.09	0.41–2.85	20(74%)	229(94.2%)	**0.04**	**3.27**	**0.98–10.87**
BMI ≥30	6(9%)	19(8.5%)				4(26%)	14(5.8%)			
Age(Mean± SD)	39.7 ± 12.8	38.7 ± 12.5	0.6	0.99	0.97–1.01	40.5 ± 15.6	36.2 ± 14.1	0.26	0.97	0.95–1.006
Age <50	48(71.6%)	180 (78.3%)	0.26	1.4	0.76–2.6	19(70.4%)	242(82.3%)	0.12	1.96	0.81–4.71
Age≥ 50	19(21.4%)	50(21.7%)				8(29.6%)	52(17.7%)			
Disease Duration (Mean±sSD)	11.23 ± 7.28	10.97 ± 6.63	0.94	0.99	0.95–1.03	8.56 ± 6.82	7.6 ± 5.5	0.43	0.97	0.91–1.03
Comorbidity ≥ 1	18(27.7%)	33(14.3%)	**0.01**	**2.28**	**1.18–4.4**	11(42.3%)	41(14.3%)	**0.001**	**4.4**	**1.88–10.24**
EDSS <3	36(75%)	126 (61.4%)	0.07	0.53	0.26–1.08	16(64%)	217(82.2%)	**0.02**	**2.59**	**1.08–6.23**
EDSS ≥3	12(25%)	79(38.6%)				9(36%)	47(17.8%)			
Treated (All)	47(70.1%)	138 (60.3%)	0.14	1.55	0.86–2.78	19(70.4%)	98(33.1%)	**0.0001**	**4.79**	**2.02–11.34**
Untreated (All)	20(29.9%)	91(39.7%)				8(29.6%)	198(66.9%)			
RTX	9(19.1%)	37(26.6%)	0.3	0.65	0.28–1.48	1(5.3%)	7(7.1%)	0.76	0.72	0.08–6.23
Oral IS(AZA,MMF)	21(44.7%)	67(48.2%)	0.67	0.86	0.44–1.68	17(89.4%)	91(92.8%)	0.61	0.65	0.12–3.42
First line DMT	17(36.2%)	35(14.8%)	0.14	1.68	0.83–3.42	-	-	-	–	-
Vaccinated	33(49.3%)	171 (80.2%)	**0.0001**	**0.24**	**0.13–0.43**	7(25.9%)	195(70.9%)	**0.0001**	**0.14**	**0.058–0.35**
Unvaccinated	34(50.7%)	42(19.8%)				20(74.1%)	80(29.1%)			
Lymphocyte count X1000/ul (Mean±stdv)	1.98 ± 0.96	2.32 ± 0.91	0.1	1	1.00–1.001	1.71 ± 0.64	2.07 ± 0.88	0.39	1.001	0.99–1.002

Abbreviation: BMI-body mass index, EDSS- expanded disability status scale, RTX- rituximab, IS- immunosuppressant, AZA-azathioprine, MMF- mycophenolate mofetil, DMT- disease modifying therapy.

Table 3
Risk factors associated with COVID-19 infection- Multivariate analysis.

Disease	MS			Non MS		
Variables	***p* value**	**Odds ratio**	**95%CI**	***p* value**	**Odds ratio**	**95%CI**
Age (<50/ ≥50	0.53	1.36	0.51–3.59	0.56	1.57	0.33–7.32
Vaccination	**0.0001**	**0.17**	**0.08–0.37**	**0.0001**	**0.04**	**0.01–0.15**
Treatment	0.06	2.4	0.96–6.01	0.059	2.8	0.96–8.58
Comorbidity	0.23	1.87	0.66–5.26	**0.01**	**7.55**	**1.44–39.48**
EDSS<3 /≥ 3	0.19	0.54	0.21–1.34	0.46	1.63	0.44–6.08

Abbreviations: BMI- body mass index, EDSS – expanded disability status scale.

in 54/302 treated patients (17.9%), among whom only one unvaccinated patient developed severe COVID-19infection. Frequency of COVID-19 infection was significantly more among treated patients, 61.3% (196/302) of the latter were on nonspecific immunosuppressants (MMF&AZA) .To our knowledge, they were not on other concurrent or past medications with potential immune modulatory effect. Both MMF and AZA are purine synthesis inhibitors which causes immunosuppression of both T and B cells and known to increases risk of common viral, bacterial and fungal infections (Sormani et al., 2021; Kimbrough et al., 2012; Abboud et al., 2020; Mealy et al., 2014). *In vivo* studies of MERS-CoV animal models suggest that MMF could be associated with severe disease especially in those with associated leukopenia (Russell et al., 2020). Treated patients had no lymphopenia and similar to previous studies (Zabalza et al., 2021) lymphocyte count did not correlate with COVID-19 infection.

Real life data on effect of COVID-19 vaccines in patients with demyelinating disorders and concomitant disease modifying medications is limited (Achiron et al., 2021). Our study evaluated the clinical efficacy of COVID-19 vaccination in our patients, majority of whom had been fully vaccinated . No serious adverse effects were reported after vaccinations. Frequency of COVID-19 infection was significantly low in vaccinated patients with both MS and related disorders in this study. Among vaccinated patients~10% developed mild infection. Despite taking precautions, most patients contracted COVID-19 from an infected family member which in part reflects on the limitations for social distancing within their homes. Further our analysis showed that patient who were unvaccinated and on treatment were significantly at risk of COVID-19 infection when compared to vaccinated and treated patients. Underscoring this point is the fact that among the 13 hospitalized patients, 11 were unvaccinated. A similar result was reported in a recent study from China. Among 535 vaccinated patients with NMOSD concomitant treatment with general immunosuppressants or B cell depleting therapy did not predispose them to COVID-19 infection (Yin et al., 2021). Treatment interruption was associated with relapse in a small number of patients similar to our cohort.

There were several limitations in this study. The number of patients enrolled was small. Quantification of COVID-19 antibody titres at baseline and following vaccination was not done to monitor vaccine efficacy. Some bias may have been introduced inadvertently in correlating recent vaccinations with reduced frequency of COVID-19 infection. In addition, though our patient database maintains details of medications concurrently taken or in the recent past, the effect of other

medications with potential immunomodulatory effect cannot be completely excluded among those that showed greater vulnerability/protection from COVID-19 infection. Though our patient number was modest, in the absence of a national data base for demyelinating disorders in India, studies such as ours may provide a representation of patient management in LMIC settings during the COVID-19 pandemic.

5. Conclusions

The results of this study suggest that patients on disease modifying treatment with off label therapies, particularly nonspecific immunosuppressants may have increased vulnerability for COVID-19 infection. Our analysis suggests that COVID-19 vaccinations are safe and significantly mitigates the risk of severe infection especially when patients are on concurrent medications. In the background of the ongoing COVID-19 pandemic we would not only recommend the continuation of these drugs in patients with stable disease but encourage vaccination against COVID-19 infection especially for those on disease modifying off label therapies.

CRediT authorship contribution statement

L. Pandit: Conceptualization, Methodology, Formal analysis, Data curation, Writing – original draft, Writing – review & editing. **A. Sudhir:** Funding acquisition, Formal analysis, Visualization. **C. Malli:** Funding acquisition, Formal analysis, Visualization, Data curation. **A. D'Cunha:** Funding acquisition, Formal analysis, Data curation.

Declaration of Competing Interest

No disclosures to report

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2022.104033.

References

Abboud, H., Zheng, C., Kar, I., Chen, C.K., Sau, C., Serra, A., 2020. Current and emerging therapeutics for neuromyelitis optica spectrum disorder: relevance to the COVID-19 pandemic. Mult. Scler. Relat. Disord. 44, 102249 https://doi.org/10.1016/j.msard.2020.102249.

Achiron, A., Dolev, M., Menascu, S., Zohar, D.N., Dreyer-Alster, S., Miron, S., Shirbint, E., Magalashvili, D., Flechter, S., Givon, U., Guber, D., Stern, Y., Polliack, M., Falb, R., Gurevich, M., 2021. COVID-19 vaccination in patients with multiple sclerosis: what we have learnt by February 2021. Mult. Scler. 27 (6), 864–870. https://doi.org/10.1177/13524585211003476.

Alonso, R., Silva, B., Garcea, O., Diaz, P.E.C., Dos Passos, G.R., Navarro, D.A.R., Valle, L. A.G., Salinas, L.C.R., Negrotto, L., Luetic, G., Tkachuk, V.A., Míguez, J., de Bedoya, F.H.D., Goiry, L.G., Sánchez, N.E.R., Burgos, M., Steinberg, J., Balbuena, M. E., Alvarez, P.M., López, P.A., Ysrraelit, M.C., León, R.A., Cohen, A.B., Gracia, F., Molina, O., Casas, M., Deri, N.H., Pappolla, A., Patrucco, L., Cristiano, E., Tavolini, D., Nadu, R.D., Granda, A.M.T., Weise, R.R., Cassará, F.P., Sinay, V., Rodríguez, C.C., Lazaro, L.G., Menichini, M.L., Piedrabuena, R., Escobar, G.O., Carrá, A., Chertcoff, A., Pujols, B.S., Vrech, C., Tarulla, A., Carvajal, R., Mainella, C., Becker, J., Peeters, L.M., Walton, C., Serena, M.A., Nuñez, S., Rojas, J.I., 2021. COVID-19 in multiple sclerosis and neuromyelitis optica spectrum disorder patients in Latin America: COVID-19 in MS and NMOSD patients in LATAM. Mult. Scler. Relat. Disord. 51, 102886 https://doi.org/10.1016/j.msard.2021.102886.

Berger, J.R., Brandstadter, R., Bar-Or, A., 2020. COVID-19 and MS disease-modifying therapies. Neurol. Neuroimmunol. Neuroinflamm. 7 (4), e761. https://doi.org/10.1212/NXI.0000000000000761.

Barzegar, M., Mirmosayyeb, O., Gajarzadeh, M., Afshari-Safavi, A., Nehzat, N., Vaheb, S., Shaygannejad, V., Maghzi, A.H., 2021. COVID-19 among patients with multiple sclerosis: a systematic review. Neurol. Neuroimmunol. Neuroinflamm. 8 (4), e1001. https://doi.org/10.1212/NXI.0000000000001001.

Coyle, P.K., Gocke, A., Vignos, M., Newsome, S.D., 2021. Vaccine considerations for multiple sclerosis in the COVID-19 Era. Adv. Ther. 39, 822–830. https://doi.org/10.1007/s12325-021-01967-5.

Dreyer-Alster, S., Menascu, S., Mandel, M., Shirbint, E., Magalashvili, D., Dolev, M., Flechter, S., Givon, U., Guber, D., Stern, Y., Miron, S., Polliack, M., Falb, R., Sonis, P., Gurevich, M., Achiron, A., 2022. COVID-19 vaccination in patients with multiple sclerosis: safety and humoral efficacy of the third booster dose. J. Neurol. Sci. 434, 120155 https://doi.org/10.1016/j.jns.2022.120155.

Fragoso, Y.D., Schiavetti, I., Carmisciano, L., Ponzano, M., Steinberg, J., Treviño-Frenk, I., Ciampi, E., Vecino, M.C.A., Correa, E.P., Carcamo, C., Gomes, S., Pimentel, M.L.V., Santos, G.A.C., Vrech, C., Winckler, T.C.A., Sormani, M.P., 2021. Coronavirus disease 2019 in Latin American patients with multiple sclerosis. Mult. Scler. Relat. Disord. 55, 103173 https://doi.org/10.1016/j.msard.2021.103173.

Kelly, H., Sokola, B., Abboud, H., 2021. Safety and efficacy of COVID-19 vaccines in multiple sclerosis patients. J. Neuroimmunol. 356, 577599 https://doi.org/10.1016/j.jneuroim.2021.577599.

Kimbrough, D.J., Fujihara, K., Jacob, A., Lana-Peixoto, M.A., Leite, M.I., Levy, M., Marignier, R., Nakashima, I., Palace, J., de Seze, J., Stuve, O., Tenembaum, S.N., Traboulsee, A., Waubant, E., Weinshenker, B.G., Wingerchuk, D.M., GJCF-CC&BR, 2012. Treatment of neuromyelitis optica: review and recommendations. Mult. Scler. Relat. Disord. 1 (4), 180–187. https://doi.org/10.1016/j.msard.2012.06.002.

Loonstra, F.C., Hoitsma, E., van Kempen, Z.L., Killestein, J., Mostert, J.P., 2020. COVID-19 in multiple sclerosis: the Dutch experience. Mult. Scler. J. 26 (10), 1256–1260. https://doi.org/10.1177/1352458520942198.

Louapre, C., Collongues, N., Stankoff, B., Giannesini, C., Papeix, C., Bensa, C., Deschamps, R., Créange, A., Wahab, A., Pelletier, J., Heinzlef, O., Labauge, P., Guilloton, L., Ahle, G., Goudot, M., Bigaut, K., Laplaud, D.A., Vukusic, S., Lubetzki, C., De Sèze, J., for the Covisep investigators, 2020. Clinical characteristics and outcomes in patients with coronavirus disease 2019 and multiple sclerosis. JAMA Neurol. 77 (9), 1079–1088. https://doi.org/10.1001/jamaneurol.2020.2581.

Malli, C., Pandit, L., D'Cunha, A., Sudhir, A., 2021. Coexistence of autoantibodies and other autoimmune diseases with multiple sclerosis and related disorders – experience from the mangalore demyelinating disease registry (MANDDIR). Ann. Indian Acad. Neurol. 24 (5), 740–744. https://doi.org/10.4103/aian.AIAN_170_21.

Mealy, M.A., Wingerchuk, D.M., Palace, J., Greenberg, B.M., Levy, M., 2014. Comparison of relapse and treatment failure rates among patients with neuromyelitis optica: multicenter study of treatment efficacy. JAMA Neurol. 71 (3), 324–330. https://doi.org/10.1001/jamaneurol.2013.5699.

Nojszewska, M., Kalinowska, A., Adamczyk-Sowa, M., Kułakowska, A., Bartosik-Psujek, H., 2021. COVID-19 mRNA vaccines (Pfizer-BioNTech and Moderna) in patients with multiple sclerosis: a statement by a working group convened by the section of multiple sclerosis and neuroimmunology of the polish neurological society. Neurol. Neurochir. Pol. 55 (1), 8–11. https://doi.org/10.5603/PJNNS.a2021.0016.

Pandit, L., 2021. Fair and equitable treatment for multiple sclerosis in resource-poor regions: the need for off-label therapies and regional treatment guidelines. Mult. Scler. 27 (9), 1320–1322. https://doi.org/10.1177/13524585211028806.

Pandit, L., Malli, C., D'Cunha, A., Sudhir, A., 2021. Overcoming the challenges in diagnosis of AQP4-IgG positive neuromyelitis optica spectrum disorders in resource poor settings using an indigenized and cost effective cell based assay. J. Neuroimmunol. 360, 577706 https://doi.org/10.1016/j.jneuroim.2021.577706.

Parrotta, E., Kister, I., Charvet, L., Sammarco, C., Saha, V., Charlson, R.E., Howard, J., Gutman, J.M., Gottesman, M., Abou-Fayssal, N., Wolintz, R., Keilson, M., Fernandez-Carbonell, C., Krupp, L.B., Zhovtis Ryerson, L., 2020. COVID-19 outcomes in MS: observational study of early experience from NYU multiple sclerosis comprehensive care center. Neurol. Neuroimmunol. Neuroinflamm. 7 (5), e835. https://doi.org/10.1212/NXI.0000000000000835.

Russell, B., Moss, C., George, G., Santaolalla, A., Cope, A., Papa, S., Van Hemelrijck, M., 2020. Associations between immune-suppressive and stimulating drugs and novel COVID-19-a systematic review of current evidence. ecancermedicalscience 14, 1022. https://doi.org/10.3332/ecancer.2020.1022.

Stastna, D., Menkyova, I., Drahota, J., Mazouchova, A., Adamkova, J., Ampapa, R., Grunermelova, M., Peterka, M., Recmanova, E., Rockova, P., Rous, M., Stetkarova, I., Valis, M., Vachova, M., Woznicova, I., Horakova, D., 2021. Multiple sclerosis, neuromyelitis optica spectrum disorder and COVID-19: a pandemic year in Czechia. Mult. Scler. Relat. Disord. 54, 103104 https://doi.org/10.1016/j.msard.2021.103104.

Sormani, M.P., De Rossi, N., Schiavetti, I., Carmisciano, L., Cordioli, C., Moiola, L., Radaelli, M., Immovilli, P., Capobianco, M., Trojano, M., Zaratin, P., Tedeschi, G., Comi, G., Battaglia, M.A., Patti, F., Salvetti, M., Musc-19 Study Group, 2021. Disease-modifying therapies and coronavirus disease 2019 severity in multiple sclerosis. Ann. Neurol. 89 (4), 780–789. https://doi.org/10.1002/ana.26028.

Thompson, A.J., Banwell, B.L., Barkhof, F., Carroll, W.M., Coetzee, T., Comi, G., Correale, J., Fazekas, F., Filippi, M., Freedman, M.S., Fujihara, K., Galetta, S.L., Hartung, H.P., Kappos, L., Lublin, F.D., Marrie, R.A., Miller, A.E., Miller, D.H., Montalban, X., Mowry, E.M., Sorensen, P.S., Tintoré, M., Traboulsee, A.L., Trojano, M., Uitdehaag, B.M.J., Vukusic, S., Waubant, E., Weinshenker, B.G., Reingold, S.C., Cohen, J.A., 2018. Diagnosis of multiple sclerosis: 2017 revisions of

the McDonald criteria. Lancet Neurol. 17 (2), 162–173. https://doi.org/10.1016/S1474-4422(17)30470-2.

Wingerchuk, D.M., Banwell, B., Bennett, J.L., Cabre, P., Carroll, W., Chitnis, T., de Seze, J., Fujihara, K., Greenberg, B., Jacob, A., Jarius, S., Lana-Peixoto, M., Levy, M., Simon, J.H., Tenembaum, S., Traboulsee, A.L., Waters, P., Wellik, K.E., Weinshenker, B.G., International Panel for NMO Diagnosis, 2015. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 85 (2), 177–189. https://doi.org/10.1212/WNL.0000000000001729.

Yin, H., Zhang, Y., Xu, Y., Peng, B., Cui, L., Zhang, S., 2021. The impact of COVID-19 on patients with neuromyelitis optica spectrum disorder beyond infection risk. Front. Neurol. 12, 657037 https://doi.org/10.3389/fneur.2021.657037.

Zabalza, A., Cárdenas-Robledo, S., Tagliani, P., Arrambide, G., Otero-Romero, S., Carbonell-Mirabent, P., Rodriguez-Barranco, M., Rodríguez-Acevedo, B., Restrepo Vera, J.L., Resina-Salles, M., Midaglia, L., Vidal-Jordana, A., Río, J., Galan, I., Castillo, J., Cobo-Calvo, Á., Comabella, M., Nos, C., Sastre-Garriga, J., Tintore, M., Montalban, X., 2021. COVID-19 in multiple sclerosis patients: susceptibility, severity risk factors and serological response. Eur. J. Neurol. 28 (10), 3384–3395. https://doi.org/10.1111/ene.14690.