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## The MuSC-19 study: The Egyptian cohort

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### ABSTRACT

**Objective:** : This study aimed to report the severity of COVID-19 in a cohort of Egyptian patients with multiple sclerosis (MS) with particular attention on the impact of disease modifying drugs (DMDs).

**Methods and study population:** : We included 119 MS patients recruited from two centers, Ain-Shams university and Cairo university with confirmed or suspected COVID-19 during the period from May to September 2020 as a part of the MuSC-19 project. Univariate logistic regression was fitted to assess risk factors for severe COVID-19 (at least one outcome among hospitalization, ICU admission and death).

**Results:** : Females were 77%, mean age was 34 years, mean duration of MS was 5.28 years, median EDSS was 3, most of the patients (83%) had RRMS, while 15% and 2% had respectively SPMS and PPMS. Only eleven patients (9% of study population) had a severe outcome and 3 patients (3%) died. Headache was the only symptom significantly associated with the severity of COVID-19 (OR=10.85,  $P = 0.001$ ). There was no association between any of the DMDs and severe COVID-19 outcome.

**Conclusion:** : This study showed an acceptable safety profile of DMDs in Egyptian MS patients who developed COVID-19, as 91% of the cohort had a favorable outcome. Headache as a symptom associated with severe outcome in Egyptian patients' needs further validation.

## 1. Introduction

The Covid-19 global pandemic caught the world by surprise, fear and confusion. Patients with multiple sclerosis (MS) may be at increased risk of infection or severity of disease as they are treated with disease modifying drugs (DMDs) that have an impact on the immune response (Winkelmann et al., 2016). Therefore, it is important to assess the risk factors for the severity of Covid-19 among MS patients including a probable effect of DMDs. Large cohort studies, such as the MuSC-19 study (Sormani et al., 2021), attempted to solve this problem that was particularly relevant at the beginning of the pandemic due to the lack of

data. (Sormani et al., 2021; Salter et al., 2021).

We here report the data of the Egyptian cohort which was included in the MuSC-19 study.

## 2. Methods and study population

The Neurological Society (SIN) and the Italian Multiple Sclerosis Foundation (FISM) set up the MuSC-19 project, an international program coordinated by the University of Genoa with the aim of collecting data on MS patients affected by confirmed or suspected COVID-19 infection through a dedicated electronic case report form (eCRF). Two

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Egyptian centers took part of that project, Ain-Shams university and Cairo university. Patients were recruited during the period from May to September 2020. Patients with confirmed or suspected COVID-19, who contacted the neurologists at the two Egyptian MS units were offered to participate in this study.

The confirmed patients were those with a positive real-time polymerase chain reaction (RT-PCR) test on nasal and/or pharyngeal swabs for SARS-CoV-2 or a positive serological test obtained at any point during the observation period, while the suspected patients were those who had radiological computed tomography (CT) chest findings, typical for Covid-19, or symptoms highly suggestive of SARS-CoV-2 infection without a positive swab, serology, or CT chest, in the absence of an alternative more probable diagnosis: fever, cough, fatigue, shortness of breath, sore throat, sputum production, nasal congestion, headache, bone aches, chills, loss of taste or smell and had a close contact with a confirmed COVID-19 case in the 14 days prior to the onset of symptoms. Severe COVID-19 outcome was characterized by death or the need for hospitalization.

Data were collected retrospectively from the date of first contact and during the follow up period until recovery or death. The first contact was a hospital visit, a phone call or a web-based visit, upon patients' or neurologists' request. The records of patients included demographic data, medical history, Expanded Disability Status Scale (EDSS) scores at their last visits, investigations including PCR, serology, chest CT, details of Covid-19 symptoms and course of illness, received DMDs, were obtained according to the data collection sheets of the MuSC-19 study (Sormani et al., 2021) after agreement to participate in the study. All the study participants were assured that all data would be de-identified and handled anonymously.

## 2.1. Statistical methods

Data entry, processing and statistical analysis was carried out using Stata version 15.1 (Stata Corporation, College Station, TX, USA). Categorical variables were presented as N (%) while continuous variables as Mean  $\pm$  (SD) or Median (IQR). Univariate logistic regression models were fitted to search for risk factors associated with severe COVID-19 course (at least one outcome among hospitalization, ICU admission and death). We also studied a possible interaction between the EDSS and the outcome, irrespective of the DMD used.

## 3. Results

The study population included 119 patients, 33 patients (28% of study population) were confirmed cases of COVID-19 and 86 patients (72%) were suspected cases of COVID-19.

Table 1 shows demographics, clinical characteristics and COVID-19 symptoms of the study population. The cohort included females (77%) females, (23%) males and the age ranged between 17 and 58, with mean $\pm$ SD of  $33.9 \pm 9.0$  years. Concerning MS phenotype, (83%) of the cohort had Relapsing Remitting MS (RRMS), (15%) had Secondary Progressive MS (SPMS) and only (2%) had Primary Progressive MS (PPMS). 12 patients (10%) had other comorbidities. We observed a median EDSS score (done at the latest visit) of 3 (IQR=2–4.5) and total duration of disease was  $5.28 \pm 4.2$  years. Most of the patients were treated with interferon-beta (32%) or fingolimod (31%) (Table 1).

Out of 119 patients, 60 patients (50%) showed typical Covid-19 CT chest radiological abnormalities (61% of confirmed cases and 47% of suspected) (Table 2).

Among the study population, 11 patients (9%) were hospitalized, 5 patients (4%) were admitted to an intensive care unit, and 3 patients (3%) died. All patients who died, tested positive to COVID-19 by RT-

**Table 1**  
Demographics, clinical characteristics and COVID-19 symptoms of study population.

		Overall study population (N = 119)	Confirmed COVID-19 (N = 33)	Suspected COVID-19 (N = 86)
Age (years)	Mean $\pm$ SD	33.9 $\pm$ 9.01	34.4 $\pm$ 9.67	33.8 $\pm$ 8.81
Body mass index	Mean $\pm$ SD	22.4 $\pm$ 3.98	23.3 $\pm$ 3.77	22.0 $\pm$ 4.02
Gender	Male	27(23%)	10(30%)	17(20%)
	Female	92(77%)	23(70%)	69(80%)
Type of MS	RRMS	98(83%)	24(73%)	74(87%)
	SPMS	18(15%)	8(24%)	10(12%)
	PPMS	2(2%)	1(3%)	1(1%)
Total disease duration (years)	Mean $\pm$ SD	5.28 $\pm$ 4.18	5.48 $\pm$ 3.91	5.20 $\pm$ 4.30
EDSS score	Median (IQR)	3 (2–4.5)	3.5(2.5–4.5)	3(2–4.5)
DMDs	Interferon-Beta	38(32%)	6(18%)	32(37%)
	Dimethyl fumarate	2(2%)	1(3%)	1(1%)
	Teriflunomide	11(9%)	2(6%)	9(10%)
	Fingolimod	37(31%)	12(36%)	25(29%)
	Rituximab	16(13%)	6(18%)	10(12%)
	Ocrelizumab	4(3%)	0(0%)	4(5%)
	Natalizumab	2(2%)	1(3%)	1(1%)
	Cyclophosphamide	1(1%)	0(0%)	1(1%)
	Methotrexate	2(2%)	2(6%)	0(0%)
	No therapy	6(5%)	3(9%)	3(3%)
Received methyl prednisolone during the last month	7(6%)	1(3%)	6(7%)	
COVID-19 symptoms	Fever, N (%)	75(66%)	22(76%)	53(63%)
	Cough, N (%)	69(58%)	27(82%)	42(49%)
	Fatigue, N (%)	82(69%)	20(61%)	62(72%)
	Sputum Production, N (%)	5(4%)	3(9%)	2(2%)
	Sore Throat, N (%)	62(52%)	19(58%)	43(50%)
	Headache, N (%)	22(18%)	14(42%)	8(9%)
	Bone Aches, N (%)	18(15%)	10(30%)	8(9%)
	Shortness of Breath, N (%)	46(39%)	11(33%)	35(41%)
	Nasal Congestion, N (%)	3(3%)	0(0%)	3(3%)
	Chills, N (%)	3(3%)	2(6%)	1(1%)
	Taste Loss, N (%)	54(45%)	12(36%)	42(49%)
	Smell Loss, N (%)	63(53%)	14(42%)	49(57%)

**Table 2**  
Radiological CT chest abnormalities in the cohort.

	Confirmed COVID-19 (N = 33)	Suspected COVID-19 (N = 86)
Radiological abnormalities N = 60	20(61%)	40(47%)
No Radiological abnormalities N = 59	13(39%)	46(53%)

PCR, showed radiological CT chest abnormalities and were hospitalized, one of them, a female 20 years old, was not admitted to the ICU (Table 3).

Eleven patients (9%) had a severe COVID-19 course and the only symptom significantly associated with the severity of COVID-19 was having headache (OR=10.85, P = 0.001). In particular, 32% (7/22) of the patients with headache showed a severe COVID-19 course compared to only 4% (4/97) for those without headache. Patients with bone aches had a higher odd of developing a severe outcome (OR=3.84, P = 0.051) while, on the other hand, individuals reporting smell loss had a lower odd of severe COVID-19 course (OR=0.300, P = 0.087) (Table 4). Interactions between the EDSS and severity of Covid-19 was not statistically significant (Table 4).

**4. Discussion**

In this study we present the results of the Egyptian Cohort of the MuSC-19 study, which is an international platform for data collection (Sormani et al., 2021). Although most cases in this registry are from Italy, yet other countries including Turkey, Kuwait and Egypt have participated with a substantial number of cases.

The Egyptian cohort included 119 cases, 33 (28%) with positive PCR confirmed cases and 86 (72%) suspected. However, 40 of the suspected cases, representing 33.6% of the total cohort, had typical Covid-19 chest CT abnormalities. Consequently, 73 cases (61.3%) of the cohort had a test (PCR or chest CT) indicating the presence of Covid-19, while 38.7% were selected on clinical grounds only. The reason for including patients on clinical grounds only was related to the timing of recruitment (May-September 2020) where PCR was not available as today.

Studying the risk factors for severe COVID-19 in MS patients and the impact of DMDs on outcome helps providing effective monitoring for these patients.

In this study, only 9% of the cases had a severe outcome (hospitalization, ICU admission or death) and 4% were admitted to the ICU. The percentage of ICU admissions was similar to the Italian cohort of the MuSC-19 (5.2%) (Sormani et al., 2021) and the COViMS registry (6.4%) (Salter et al., 2021). The observed death rate (2.5%) was higher than the Italian cohort (1.5%) and slightly lower than the COViMS (3.3%).

The sample size and the number of severe cases limited the possibility of detecting significant associations with risk factors.

Although headache is a nonspecific symptom, it was the only symptom significantly associated with the severity of COVID-19 (OR=10.85, P = 0.001). Headache is the most common COVID-19-related neurological symptom; according to a recent meta-analysis, the prevalence of headache was 10.9% with a high level of heterogeneity (Pinzon et al., 2020). Moreover, headache can be an isolated feature of the illness (Toptan et al., 2020).

A possible explanation of headache related to COVID-19 is direct invasion of trigeminal nerve endings in the nasal or oral cavity according

**Table 3**  
Characteristics of deceased patients.

Gender	Age	MS Type	Disease Duration[years]	EDSS score	DMD	RT-PCR for COVID-19	CT chest abnormalities
Male	43	SPMS	5	6.5	Rituximab	Positive	Positive
Female	36	SPMS	9	5	Methotrexate	Positive	Positive
Female	20	RRMS	1	2	No Therapy	Positive	Positive

**Table 4**  
Univariate logistic regression models evaluating risk factors for severe Covid-19 course (hospitalization, or ICU admission or death).

		Univariate OR [95% CI]	Univariate P- value
Age	< 50 years	—	—
	≥ 50 years	1.41 [0.16–12.69]	0.757
Body mass index	1.02 [0.88–1.19]	0.779	
Gender	Male	2.112 [0.57–7.84]	0.264
	Female	—	—
Type of MS	RRMS	—	—
	SPMS or PPMS	1.985 [0.48–8.25]	0.345
		0.976 [0.84–1.14]	0.759
Total disease duration (years)	0.976 [0.84–1.14]	0.759	
EDSS score	< 5	—	—
	≥ 5	1.88[0.45–7.76]	0.386
DMDs	Anti-CD 20 agents versus All	0.47[0.06–3.88]	0.482
	Interferon-B versus All	0.44 [0.09–2.17]	0.316
	Fingolimod versus All	1.30[0.36–4.74]	0.692
	Received methyl prednisolone during the last month	1.7 [0.19–15.56]	0.639
COVID-19 symptoms	Fever	4.42 [0.53–36.71]	0.169
	Cough	2.05[0.52–8.17]	0.307
	Fatigue	1.23[0.31–4.91]	0.774
	Sputum	2.60	0.413
	Production	[0.26–25.56]	
	Sore Throat	2.67 [0.67–10.59]	0.163
	Headache	10.85 [2.83–41.61]	0.001
	Bone Aches	3.84 [0.99–14.81]	0.051
	Shortness of Breath	1.36[0.39–4.75]	0.628
	Taste Loss	0.42[0.11–1.67]	0.217
	Smell Loss	0.30[0.08–1.19]	0.087

to one study that showed a close relation between headache and anosmia/ageusia (Uygun et al., 2020). Some coronaviruses were shown to be neurotropic and former SARS-CoV has been observed in brain tissue (Ding et al., 2004; Gu et al., 2005). SARS-CoV-2 uses the trans-membrane ACE 2 receptor to enter the host cells, and this receptor was detected in the neuronal cells in the trigeminal ganglia, olfactory bulb, and other cortical and subcortical areas (Bolay et al., 2020; Hoffmann et al., 2020). One study reported hyperintensity in the gyrus rectus and olfactory bulb in patients with COVID-19 suggesting brain involvement (Politi et al., 2020).

The association between headache and severe outcome in COVID-19 in this study was not validated in two large cohorts (Salter et al., 2021; Louapre et al., 2020), indicating that this symptom may be specific for Egyptian MS patients, or was a statistical finding driven by our small sample but with no prognostic value. Further Egyptian studies are required.

Ninety one percent of our cases showed a favorable outcome. There was no association between any of the DMDs and the severity of COVID-19 in this study, due to the lack of power. Treatment with interferon-

beta, the most used DMD in this study (32%) does not appear to affect the course of COVID-19 in patients with MS (Sormani et al., 2021; Sahraian et al., 2020; Sharifian-Dorche et al., 2021), and can be even associated with a favorable outcome (Pinschewer et al., 2011). Fingolimod, the second most used DMD in this study (31%) blocks only central memory T cells in lymphoid tissue, without compromising the circulation of effector memory T cells, thus preserving the response to infections (Wang et al., 2020). One study demonstrated that dimethyl fumarate induces a distinct antiviral program that is broadly effective in limiting virus replication and in suppressing the pro-inflammatory responses of human pathogenic viruses, including SARS-CoV2 (Olagnier et al., 2020). However, our sample size included only 2 patients (2%) on DMF.

Anti CD20 monoclonal antibodies cause depletion of B-lymphocytes with inadequate humoral immune response, especially close to the time of drug infusion (Meca-Lallana et al., 2020), and therefore expected to be associated with increased risk of COVID-19 infection (Reder et al., 2021). In our cohort, anti CD20 treatment represented 16% of DMD used, one Rituximab patient died, but had SPMS with 6.5 EDSS score. The Italian cohort of the MuSC-19 (Sormani et al., 2021) reported increased frequency of severe COVID-19 outcome in patients treated with ocrelizumab and rituximab. In another cohort, COVID-19 patients treated with rituximab were found to have an increased risk of hospitalization compared to those treated with ocrelizumab, and it was attributed to the longer duration of exposure to rituximab (Salter et al., 2021).

Although it was reported that neurological disability and older age were risk factors for severe forms of COVID-19 (Sormani et al., 2021; Salter et al., 2021), this was not shown in our study, possibly because of the low rate of severe outcomes (9%) and a smaller sample size.

One of the limitations of this study was the inclusion of suspected cases of COVID-19; this was done for better sample size, because at the time of data collection, serology and PCR testing were not widely used. Yet, 60 cases [50.4%] had typical chest radiological abnormalities characteristic of Covid-19. Overall, this study shows an acceptable safety profile of DMDs in patients with MS who developed COVID-19. The emergence of a new virus means that our understanding of the clinical features and severity of infection is still limited. Encouraging such clinical trials allows us to understand the impact of COVID-19 in Egyptian patients with MS and facilitate international comparisons.

## 5. Conclusion

This study showed an acceptable safety profile of DMDs in Egyptian MS patients who developed COVID-19 as 91% of the cohort had a favorable outcome. Headache as a symptom associated with severe outcome in Egyptian patients' needs further validation.

## Credit author statement

I have participated sufficiently in the conception and design of this work or the analysis and interpretation of the data, as well as the writing of the manuscript, to take public responsibility for it. I believe the manuscript represents valid work.

## Declaration of Competing Interest

The authors declare that they have no conflict of interest in relation

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