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COVID-19 in multiple sclerosis patients and risk factors for severe infection

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ABSTRACT

Multiple sclerosis (MS) patients have been considered a higher-risk population for COVID-19 due to the high prevalence of disability and disease-modifying therapy use; however, there is little data identifying clinical characteristics of MS associated with worse COVID-19 outcomes. Therefore, we conducted a multicenter prospective cohort study looking at the outcomes of 40 MS patients with confirmed COVID-19. Severity of COVID-19 infection was based on hospital course, where a mild course was defined as the patient not requiring hospital admission, moderate severity was defined as the patient requiring hospital admission to the general floor, and most severe was defined as requiring intensive care unit admission and/or death. 19/40(47.5%) had mild courses, 15/40(37.5%) had moderate courses, and 6/40(15%) had severe courses. Patients with moderate and severe courses were significantly older than those with a mild course (57[50–63] years old and 66[58.8–69.5] years old vs 48[40–51.5] years old, $P = 0.0121$, $P = 0.0373$). There was differing prevalence of progressive MS phenotype in those with more severe courses (severe:2/6[33.3%]primary-progressing and 0/6[0%]secondary-progressing, moderate:1/14[7.14%] and 5/14[35.7%] vs mild:0/19[0%] and 1/19[5.26%], $P = 0.0075$, 1 unknown). Significant disability was found in 1/19(5.26%) mild course-patients, but was in 9/15(60%, $P = 0.00435$) of moderate course-patients and 2/6(33.3%, $P = 0.200$) of severe course-patients. Disease-modifying therapy prevalence did not differ among courses (mild:17/19[89.5%], moderate:12/15[80%] and severe:3/6[50%], $P = 0.123$). MS patients with more severe COVID-19 courses tended to be older, were more likely to suffer from progressive phenotype, and had a higher degree of disability. However, disease-modifying therapy use was not different among courses.

1. Introduction

Patients with multiple sclerosis (MS) are four times more likely to succumb to serious infection when compared to the general population, thus making them potentially at higher-risk from the ongoing novel coronavirus disease (COVID-19) [1]. This may be because a significant number of MS patients have a high level of disability and are on immunosuppressive disease-modifying therapies (DMTs). Most information regarding the association of MS characteristics and DMT-usage with COVID-19 comes from case-reports and case-series surveys [2–4]. In this prospective cohort study we assessed the MS disease characteristics with differing COVID-19 infection severity.

2. Methods

2.1. Study design

We enrolled 40 consecutive MS patients with confirmed COVID-19 via nasopharyngeal/oropharyngeal-PCR from 3 different hospital systems in the U.S, Henry Ford Health Systems (HFHS) in Detroit, MI, Detroit Medical Center (DMC) in Detroit MI, and University of Chicago (UOC) in Chicago, IL (28 at HFHS, 4 at DMC and 8 at UOC) between

Abbreviations: MS, Multiple Sclerosis; DMT, Disease Modifying Therapies; COVID-19, Novel Coronavirus 2019; PPMS, Primary Progressive MS; RRMS, Relapsing-Remitting MS; SPMS, Secondary Progressive MS; EDSS, Extended disability status scale

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Table 1
Patient characteristics.

	All	Mild	Moderate	Severe	*P*-value
n	40	19	15	6	
a) Demographics and MS characteristics					
Age in years (IQR)	52 (45.5–61)	48 (40–51.5)	57 (50–63)*	66 (58.8–69.5)*	0.0013
African American	21/40 (52.5%)	7/19 (36.8%)	9/15 (60%)	5/6 (83.3%)	0.102
Male	16/40 (40%)	5/19 (26.3%)	8/15 (53.3%)	3/6 (50%)	0.258
BMI (IQR)	30.6 (25.5–35.9)	30.7 (27–36.4)	28.4 (23.1–33.8)	36.1(34.2–38.8)	0.142
Smoker	6/39 (15.4%) 1 not specified	0/19 (0%)	5/14 (35.7%)*	1/6 (16.7%)	0.0145
Phenotype of MS					
PPMS	3/39 (7.69%), 1 not specified	0/19 (0%)	1/14 (7.1%)*	2/6 (33.3%)	0.0075
RRMS	30/39 (76.9%)	18/19 (94.7%)	8/14 (57.1%)*	4/6 (66.7%)	
SPMS	6/39 (15.4%)	1/19 (5.26%)	5/14 (35.7%)*	0/6 (0%)	
Years with MS(IQR)	12 (6.5–19)	11 (6–14.5)	16 (11.5–27)*	5 (3−10)^	0.0166
EDSS ≥6.0	11/37 (29.7%), 3 not specified	1/18 (5.6%)	8/14 (57/1%)*	2/5 (40%)	0.0045
On DMT	32/40 (80%)	17/19 (89.5%)	12/15 (80%)	3/6(50%)	0.123
Nursing Home	8/40 (20%)	0/19 (0%)	7/15 (46.7%)*	1/6 (16.7%)	0.0015
Healthcare Worker	6/40 (15%)	5/19 (26.3%)	1/15 (6.67%)	0/6 (0%)	0.132
Baseline Absolute Lymphocyte Count(IQR)	1.6 (0.9–1.8), 19 labs not obtained	1.7 (1.35–1.72), *n* = 4	1.4(0.925–1.85), *n* = 14	1.6(1.2–2.8),*n* = 3	0.908
b) Comorbidities					
Hypertension	16/40 (40%)	3/19 (15.8%)	10/15 (66.7%)*	3/6 (50%)	0.0085
Hyperlipidemia	7/40 (17.5%)	1/19 (5.26%)	4/15 (26.7%)	2/6 (33.3%)	0.172
Diabetes	9/40(22.5%)	1/19 (5.26%)	4/15 (26.7%)	4/6 (66.7%)*	0.005
Asthma/COPD	2/40 (5%)	0/19 (0%)	1/15 (6.67%)	1/6 (16.7%)	0.277
c) Presentation					
Fever	26/40 (65%)	10/19 (52.6%)	11/15 (73.3%)	5/6 (83.3%)	0.331
Cough	26/40 (65%)	16/19 (84.2%)	6/15 (40%)*	4/6 (66.7%)	0.0275
Myalgia	14/40 (35%)	9/19 (47.4%)	3/15 (20%)	2/6 (33.3%)	0.302
Shortness of Breath	20/40 (50%)	7/19 (36.8%)	8/15 (53.3%)	5/6 (83.3%)	0.148
Diarrhea	4/40 (10%)	1/19 (5.26%)	3/15 (20%)	0/6 (0%)	0.275
Sore Throat	4/40 (10%)	3/19 (15.8%)	0/15 (0%)	1/6 (16.7%)	0.366
Headache	7/40 (17.5%)	3/19 (15.8%)	4/15 (26.7%)	0/6 (0%)	0.42
Altered Mental Status	4/40 (10%)	0/19 (0%)	4/15 (26.7%)	0/6 (0%)	0.0185
Require Chest X-Ray	23/40(57.5%)	2/19(10.5%)	15/15(100%)*	6/6(100%)*	0.0005
Chest X-Ray Abnormality	17/23 (73.9%)	2/2 (100%)	9/15 (60%)	6/6 (100%)	0.132
Elevated Troponin	3/17 (17.7%), 23 labs not obtained	0/1 (0%)	2/12 (16.7%)	¼ (25%)	0.371
Elevated LDH; median(IQR) IU/L	15/16 (93.8%), 24 labs not obtained; 357(254–433)	0/0	11/12 (91.7%); 312(245–394)	4/4 (100%); 598 (402–807)	0.0452
Elevated Procalcitonin; median (IQR) ng/mL	9/13 (69.2%), 27 labs not obtained; 0.31 (0.02–0.57)	0/0	7/10 (70%); 0.295 (0.08–0.507)	2/3 (66.7%);1.07 (0.535–6.07)	0.307
Elevated Ferritin; median(IQR) ng/mL	11/16 (75%), 24 labs not obtained;703.5(288–1107)	0/0	8/12 (66.7%); 494 (195–1030)	3/4 (75%); 980 (675–1218)	0.332
Elevated D-Dimer; median (IQR) ug/mL	14/16 (87.5%), 24 labs not obtained; 2.14 (0.988–3.32)	0/0	9/11 (81.8%); 2.15 (0.985–2.84)	5/5 (100%); 2.13 (1.91–5.5)	0.461
Elevated CRP; median (IQR) mg/dL	16/16 (100%) 24 labs not obtained: 9 (5–13)	0/0	12/12 (100%); 9 (4–13)	4/4 (100%); 9.5 (7.25–12)	0.734
Elevated CPK; median (IQR) IU/L	8/15 (53.3%), 25 labs not obtained; 290 (85–442.5)	0/0	5/11 (45.5%); 94 (79.5–442)	3/4 (75%); 308 (238–3296)	0.514
Elevated LFT; median (IQR) IU/L	10/20 (50%), 20 labs not obtained; 24.5 (19.5–40.8) ALT, 30 (22.75–49.3) AST	0/1 (100%);21ALT, 17AST	8/14 (57.1%); 24 (18.5–37) ALT, 34 (24.5–48) AST	2/5 (40%); 32 (25–70) ALT,28 (22−121) AST	0.638
White Blood Cell Count (IQR) K/uL	6.5 (5.20–8.3), 19 labs not obtained	4.3, *n* = 1	5.6 (5.2–9.35), *n* = 15	7.8 (7.1–8.2), *n* = 5	0.352
Neutrophil%(IQR)	79 (65–86), 19 labs not obtained	52, *n* = 1	79 (64.5–85.5), *n* = 15	83 (80–88), *n* = 5	0.163
Lymphocyte%(IQR)	12 (9–15), 19 labs not obtained	38, *n* = 1	12 (9–18), *n* = 15	13 (7–14), *n* = 5	0.313
d) Treatment specifically for COVID-19					
Given Treatment	21/40 (52.5%)	4/19 (21.1%)	12/15 (80%)*	5/6 (83.3%)*	0.001
Hydroxychloroquine	14/40 (35%)	1/19 (5.26%)	8/15 (53.3%)*	5/6 (83.3%)*	0.001
Antibiotic	13/40 (32.5%)	3/19 (15.8%)	6/15 (40%)	4/6 (66.7%)	0.048
Methylprednisone	10/40 (25%%)	0/19 (0%)	6/15 (40%)*	4/6 (66.7%)*	0.002
e) Outcome					
Days Admitted(IQR)	8 (4–14)	NA	4 (4–9.5)	15.5 (14.2–16.8)	0.006
Days with COVID-19 Symptoms (IQR)	16 (13–20.3)	16 (14–21)	14 (4–18.5)	16.5 (14.2–21.8)	0.304
Require Ventilator	4/40 (10%)	NA	NA	4/6 (66.7%)	
Death	4/40 (10%)	NA	NA	4/6 (66.7%)	

Characteristics of all patients. a) Patient demographic data, b) Comorbidities, c) Initial presentation, d) Treatment, e) Outcomes. DMT = Disease Modifying Therapies (Details on MS drugs shown in Table 2), PPMS = Primary progressive MS, RRMS = Relapse-remitting MS, SPMS = Secondary progressive MS. EDSS = Expanded Disability Status Scale. BMI = Body Mass Index. All continuous variables are expressed with median and interquartile range as median (IQR). All frequencies are presented as fraction of counts over number of available counts (Percentage). Lab data is expressed as frequency of elevated labs (%); median (IQR).(Reference values shown in Supplementary Table 1) Lactate Dehydrogenase(LDH), C-reactive protein (CRP), Creatine Phosphokinase (CPK), Liver Function Test (LFT).

* Statistically significant difference compared with mild course.

^ Statistically significant difference compared with moderate course.

March 1st and May 18th. Study was approved by each institution review board (IRB).

2.2. Data collection

We obtained information regarding age, race, sex, smoking status, MS phenotype (Primary Progressive MS, PPMS; Relapsing-Remitting MS, RRMS; Secondary Progressive MS, SPMS), duration of MS, DMT, and comorbidities. Expanded disability status scale (EDSS) from last clinic visit was used for disability assessment with ≥6.0 indicating severe disability [5,6]. Symptoms of infection and laboratory data at presentation were also included in the analysis. Days of COVID-19 symptoms was a patient-reported metric.

2.3. Outcome measured

Clinical severity of COVID-19 was based on hospital course: mild course was defined as not requiring hospital admission, moderate course was defined as requiring admission to general floor only, and severe course was defined as requiring intensive care unit (ICU) admission and/or death [7].

2.4. Statistical analysis

R-version 3.6.3 was used for statistical analysis. Continuous variables were reported as median with interquartile ranges (median [IQR]). Categorical variables were reported as counts (percentages). Lab data was expressed as frequency of elevated labs using cut off values (Supplement Table 1) and median [IQR]. Continuous variables were compared using Kruskal-Wallis-H test with post hoc Dunn's test for pairwise-comparisons. Due to small sample size, proportions of categorical variables were compared using Chi-squared test with Monte-Carlo simulation with 2000 replicates [8]. Then Fisher multiple-pairwise tests were used for post hoc comparisons with Benjamini-Hochberg adjustments [9]. Differences among COVID-19 courses and pairwise comparisons were considered statistically significant if *P*-value or adjusted *P*-value were less than 0.05.

3. Results

3.1. Overall outcomes

20/40 (50%) patients were admitted, of which 5/20 (25%) patients required ICU admission. Of the 20 patients admitted, 4/20 (20%) were ventilated and 3/20 (15%) died. One patient died on arrival at the emergency department. Therefore, a total of 4/40 (10%) patients died, while all other patients recovered (36/40 [90%]).

3.2. Demographics

19/40 (47.5%) had mild courses, 15/40 (37.5%) had moderate courses, and 6 (15%) had severe courses. Moderate (57 [50–63 years old) and severe (66 [58.8–69.5] course-patients were significantly older than mild (48 [40–51.5]) course-patients ($P = 0.0121$, $P = 0.0373$ respectively). Moderate course-patients were more likely to be smokers compared to mild course-patients (5/14 [35.7%] vs 0/19 [0%], $P = 0.0253$).

3.3. MS characteristics

There was differing prevalence of progressive phenotypes of MS among courses of COVID-19. Out of severe course 2/6 [33.3%] had PPMS and 0/6 [0%] had SPMS and out of the moderate course 1/14 [7.14%] had PPMS and 5/14 [35.7%] had SPMS (1 patient had unknown MS history). This is in comparison to out of mild course where 0/19 [0%] had PPMS and only 1/19 [5.26%] had SPMS ($P = 0.0075$). Moderate course-patients had a significantly longer duration of MS than patients with mild, but not compared to those with severe courses(16 [11.5–27] years vs 11 [6–14.5] years and 5 [3–10] years, $P = 0.0480$, $P = 0.283$).(Table 1a).

EDSS was ≥6.0 in 1/19 (5.26%) with the mild course, significantly less than patients with moderate courses (9/15 [60%], $P = 0.00435$). This was also less than patients with severe course-patients, though not statistically significant (2/6 [33.3%], $P = 0.200$). More patients with moderate courses were residents of nursing homes compared to those with mild courses (7/15[46.7%] vs 0/19 [0%], $P = 0.0036$).

3.4. DMT usage

There was a relatively higher prevalence of DMT use in patients with mild and moderate courses compared to those with severe courses, although not found to be statistically significant across groups (mild:17/19[89.5%] and moderate:12/15[80%] vs. severe:3/6[50%], $P = 0.123$). Frequencies of different types of DMT appeared to be similar across courses. (Table 2)

3.5. Comorbidities

There were more patients with moderate courses who had hypertension compared to those with mild courses (10/15 [66.7%] vs 3/19 [15.8%], $P = 0.0127$). There were more patients with severe courses who had diabetes compared to those with mild courses (4/6 [66.7%] vs 1/19 [5.26%], $P = 0.005$).(Table 1b).

3.6. Clinical course of infection

Overall, initial presenting symptoms were similar among each course of COVID-19. All moderate and severe courses, as expected, had chest X-ray obtained compared to only 2/19 (10.5%) patients with mild courses ($P = 0.0005$). Patients with severe courses had quantifiably higher levels of lactate dehydrogenase (LDH, 598 [402–807] IU/L vs 312 [245–394] IU/L, $P = 0.0452$).(Table 1c) Patients with moderate and severe courses were more likely to be treated for COVID-19 compared to those with mild courses (12/15 [80%] and 5/6 [83.3%] vs4/19 [21.1%], $P = 0.00429$, $P = 0.0178$).(Table 1d).

All admitted patients were not given DMTs during admission (20/20, 100%). Duration of COVID-19 symptoms was similar among all courses ($P = 0.304$). Patients with severe courses were more likely to be admitted longer compared to those with moderate courses (15.5 [14.2–16.8] days vs 4 [4–9.5] days, $P = 0.006$). (Table 1e).

Table 2
Different types of DMTs frequency.

DMT	All	Mild	Moderate	Severe
None	8	2	3	3
Alemtuzumab	1	1	0	0
Dimethyl Fumarate	6	3	2	1
Fingolimod	2	2	0	0
Glatiramer acetate	3	1	2	0
Interferon-beta	2	1	1	0
IV Steroids	1	0	1	0
Natalizumab	2	2	0	0
Ocrelizumab	12	6	4	2
Teriflunomide	3	1	2	0

Table showing the frequency of different DMTs for each COVID 19 disease course.

4. Discussion

4.1. MS characteristics and comorbidities associated with worse COVID-19 course

MS is a heterogeneous disease as PPMS and SPMS are associated with a later age of onset. Also since SPMS evolves from RRMS, these patients tend to be older with more disablities [10–12]. Older age, certain comorbidities and living in nursing homes are significant risk factors for COVID-19 [13]. Therefore, as expected, MS patients with moderate-severe courses were more likely to have PPMS and SPMS phenotypes, comorbidities (smoking, hypertension, and diabetes), and EDSS scores $\geq$6.0. These patients also tended to be older and frequently resided in nursing homes.

4.2. DMT usage and infection risk

It is known that certain DMTs have higher infectious risk compared to others; therefore, it has been a concern that cell depleting DMTs would be associated with higher COVID-19 risk [14]. Our cohort was not powered to detect differences in infectious outcomes based on type of DMT, however, it doesn't appear to be bias regarding certain DMTs in moderate-severe courses. In fact, it appears that more patients with moderate and severe courses were not on any DMT compared to those with mild courses. DMTs have been hypothesized to attenuate the cytokine-storm response in COVID-19, though this is still purely speculative [14]. In fact, Louapre et al. found that there were higher proportions of severe COVID-19 cases in MS patients that were not receiving DMTs [15]. Nonetheless, usage of DMTs do not necessarily appear to be associated with more severe COVID-19-courses. These findings correspond to those in ongoing North American COVID-19 MS survey database (covims.org) and Italian cohort surveyed by Sormani el al. where patients who died tended to be older, have PPMS or SPMS, and have significant disability and comorbidities, but were less likely to be on DMT [3,16].

4.3. Overall mortality of COVID-19 in MS

As of 5/25/2020, the Detroit Health Department has reported a 12.3% citywide COVID-19 mortality rate among laboratory confirmed cases [17]. Even though we had a small sample size, our MS cohort reported a similar mortality rate (10%) and was like that reported by Sormani et al. in confirmed-COVID-19 positive MS patients (5/57 [8.78%]) [3]. Therefore, our mortality rate could possibly be consistent with a larger sample size and similar to that of the general population.

What is unique to our cohort compared to the Italian cohort is that both Detroit and Chicago have large populations of African Americans who are believed to suffer from worse COVID-19 outcomes when compared to that seen in white Americans [18]. Our cohort did not show any statistically significant difference in terms of MS characteristics and outcomes based on race, however it appears that patients with more severe courses tended to be African American. This may be due to significant socioeconomic disadvantages and higher prevalence of comorbidities (i.e hypertension, diabetes) among African Americans, however our cohort was small and more studies are required to investigate this racial disparity [19].

5. Limitations and conclusions

A significant limitation to our study is the relatively small sample size collected; therefore risk-stratification adjusting for confounders was not possible. Larger studies are therefore required in order to correct for potential confounding variables. Also, there was a significant discrepancy in sample-size for each course, as there were only 6 patients with severe disease course. Therefore, significant differences may not have been detected in post hoc comparisons and only very strong factors were found to be associated with disease outcomes. Regardless, we showed that certain MS-characteristics were more frequent in those with more severe COVID-19 courses.

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Declaration of competing interest

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