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Original Scientific Paper

INCREASED SEVERE COVID-19-RELATED FATALITY IN HOSPITALIZED MULTIPLE SCLEROSIS PATIENTS

Maja Budimkić Stefanović[1,2], Jovana Ivanović[1], Olivera Tamaš[1,2], Nikola Veselinović[1,2], Nikola Momčilović[1], Mirjana Ždraljević[1], Šarlota Mesaroš[1,2], Tatjana Pekmezović[3] and Jelena Drulović[1,2]

[1]Department of Neurology, University Clinical Center of Serbia, Belgrade, Serbia;
[2]Faculty of Medicine, University of Belgrade, Belgrade, Serbia;
[3]Institute of Epidemiology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia

SUMMARY – The aim of this study was to assess the case fatality ratio (CFR) in persons with multiple sclerosis (PwMS) hospitalized due to severe COVID-19, and to investigate the role of risk factors for fatal outcome in this well-defined cohort. This case series study included all PwMS (N=32) with severe COVID-19, who were hospitalized in the COVID-19 referral center in Belgrade from January 2021 to January 2022. Eight out of these 32 patients died from COVID-19 (CFR 25%). The cause of death was sepsis in 7 patients and pulmonary embolism in one patient. Results of univariate logistic regression analyses demonstrated that older age, EDSS higher than 6.0, progressive multiple sclerosis (MS) forms, cardiovascular comorbidities, and longer duration of hospital stay statistically significantly increased the risk of COVID-19-related death in MS patients. Treatment with ocrelizumab was associated with more than 2-fold increased death risk (p=0.408). Multivariate logistic regression analysis showed that progressive forms of MS (p=0.044) and longer hospitalization (p=0.006) significantly increased the risk of death in our MS cohort. In our study, older age, presence of comorbidities, and progressive disease course were independent predictors of increased lethality of COVID-19 in PwMS. More intense monitoring may be warranted in PwMS treated with anti-CD20 agents.

Key words: *Multiple sclerosis; Severe COVID-19; Fatality; Risk factors*

Introduction

The question of the severity of COVID-19 infection in persons with various neuroimmune disorders was raised during the COVID-19 pandemic[1]. Recently, it has already been suggested by Italian authors that there is an increased risk of death from COVID-19 in patients with multiple sclerosis (PwMS) in comparison with the general population[2]. However, more recently, it has been implicated that the risk of death from COVID-19 still remains unclear, and therefore the pooled analysis of observational studies was performed[3]. It demonstrated that there was a 24% increased risk of death from COVID-19 in PwMS by an indirect standardization method (using as reference the age-specific case-fatality ratio (CFR) of COVID-19 in the general population, set by the World Health Organization)[3]. In the North American registry-based cross-sectional study, increased disability was independently associated with worse clinical severity including death from COVID-19[4]. Other risk factors for worse outcomes in this cohort included older age, cardiovascular comorbidities, and

Correspondence to: *Prof. Jelena Drulović, MD, PhD,*
Department of Neurology, University Clinical Center of Serbia,
Dr Subotića 6, Belgrade 11000, Serbia
E-mail: drulovicjelena@gmail.com

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recent treatment with corticosteroids. The information about symptoms and other clinical characteristics of PwMS with severe COVID-19 who were admitted to the hospital is lacking. It is very difficult to define risk factors for in-hospital mortality in different categories of COVID-19 patients, and one of the most comprehensive contemporary approaches is artificial intelligence[5].

The aim of this study was to assess the CFR in PwMS hospitalized due to severe COVID-19 in the COVID-19 referral Batajnica Hospital, in Belgrade. Furthermore, we investigated the role of risk factors, especially those MS-specific, for death outcome in this well-defined cohort, in order to implement appropriate risk mitigation plans.

Patients and Methods

We conducted a case series study, which included all MS patients (N=32) who developed severe COVID-19 and were therefore hospitalized at one of the COVID-19 referral centers in Serbia, Batajnica Hospital, as part of the University Clinical Center of Serbia in Belgrade, from January 2021 to January 2022. Clinician-reported demographic and clinical data of patients with MS with confirmed COVID-19 were collected using a common electronic Case Report Form.

Regarding COVID-19, diagnosis was established based on a positive result of the SARS-CoV-2 polymerase chain reaction test (PCR) or positive antigen test. Patients were hospitalized based on the decision of the physician from the COVID-19 outpatient triage centers because of the estimated increased risk of complications, according to the National Protocol for the Treatment of COVID-19 Patients of the Ministry of Health, Republic of Serbia in 2021. In this referral center, admissions to the Intensive Care Unit (ICU) and all types of mechanical ventilation were available, if needed.

Multiple sclerosis phenotype was divided in two groups, i.e., relapsing remitting MS (RRMS) and progressive MS (secondary and primary progressive MS). Disability was assessed by the Expanded Disability Status Scale (EDSS)[6]. Information about comorbid conditions was collected, including cardiovascular diseases, hypertension, diabetes, other chronic neurologic disorders, or malignant diseases. Body mass index was calculated on admission. Current disease modifying therapies (DMTs) usage was considered in our analysis, including interferons, glatiramer acetate, teriflunomide, dimethyl fumarate, fingolimod, cladribine tablets, natalizumab, alemtuzumab, ocrelizumab, and ublituximab. Patients were considered fully vaccinated against COVID-19 if they received 2 doses of vaccines that had been approved in Serbia (mRNA-vaccine encoding protein S, Pfizer-BioNTech vaccine; two adenoviral vector-based vaccines, AstraZeneca and Gam-COVID-Vac-Sputnik V; and finally, inactivated vaccine developed from 2 SARS-CoV-2 strains, WIV04 and HB02, Beijing/Sinopharm BBIBP-CorV).

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the institutional Review Board of the Department of Neurology, University Clinical Center of Serbia (protocol code: 15/2020; date of approval December 5, 2020).

In statistical analysis, frequency distribution was presented as percentages and proportions. Average values were presented as mean ± standard deviation (SD) and median with interquartile range (IQR). Comparisons of values between two groups (dead and alive subjects) were assessed using χ^2-test and ANOVA. The predictive value of investigated variables was estimated by logistic regression analysis since the dependent variable was dichotomous (death: yes/no). All variables with significance levels of 0.05 by univariate analysis were included in the multivariate model. Two-tailed p-values less than 0.05 were considered significant. Data were analyzed using SPSS software (version 17.0, Chicago, IL, USA).

Results

This study comprised all 32 patients with MS consecutively admitted at the regional specialized hospital for COVID-19 during a one-year period, from January 2021 to January 2022. Eight out of these 32 patients died from COVID-19 (CFR 25%). The cause of death was sepsis in 7 patients and pulmonary embolism in one patient. Demographic and clinical characteristics of MS patients are shown in Table 1. Patients who died in comparison with those who survived were statistically significantly older (p=0.034), had higher median EDSS (p=0.045) and more frequently EDSS score ≥6.0 (p=0.036), progressive forms of MS (p=0.039), and cardiovascular comorbidities (p=0.026). More MS patients who survived were currently on DMTs in comparison

Table 1. Demographic and clinical characteristics of MS patients

	Overall (N=32)	Patients who survived (n=24)	Patients who died (n=8)	p
Female, n (%)	23 (71.9)	17 (73.9)	6 (75.0)	0.820
Age, mean (years)	54.0±12.7	51.3±11.9	62.1±12.2	**0.034**
MS duration, mean (years)	20.2±13.6	12.6±13.4	18.9±15.1	0.759
Progressive MS, n (%)	20 (87.5)	13 (54.2)	7 (77.8)	**0.039**
EDSS score, median (IQR)	6.5 (4.0)	4.5 (4.0)	6.5 (2.0)	**0.045**
EDSS score ≥6.5, n (%)	17 (53.1)	10 (41.7)	7 (87.5)	**0.036**
DMT naïve, n (%)	17 (53.1)	11 (64.7)	6 (35.3)	0.152
Treatment with DMTs, n (%)	15 (46.9)	13 (86.7)	2 (13.3)	
Interferon, n	3	3	0	
Glatimer acetate, n	1	1	0	
Teriflunomide, n	1	1	0	
Cladribine tablets, n	1	1	0	
Alemtuzumab, n	1	1	0	
Ocrelizumab, n	5	3	2	
Ublituximab, n	2	2	0	
Comorbidites (yes/no), n, %	24 (75.0)	17 (70.8)	7 (87.5)	0.346
Cardiovascular comorbidities, n	7	3	4	**0.026**
Hypertension, n	8	4	4	0.112
Chronic neurological diseases, n	8	5	3	0.346
Diabetes, n	2	1	1	0.399
Smoking, n	5	5	0	0.160
Body mass index, mean (SD)	23.2 (3.2)	23.2 (3.4)	22.9 (2.8)	0.808
Vaccinated against COVID-19	15 (45.4)	11 (45.8)	4 (50.0)	0.838

MS = multiple sclerosis; EDSS = Expanded Disability Status Scale; IQR = interquartile range; SD = standard deviation; DMT = disease modifying therapy

with those who died, but the difference did not reach statistical significance. Two out of 8 patients who died were treated with ocrelizumab (total number of patients treated with ocrelizumab was 5). Demographic and clinical characteristics of each patient who died from COVID-19 are listed in Table 2.

Regarding the symptoms of COVID-19, fever was the most frequently reported symptom in both groups (Fig. 1). Fatigue, shortness of breath, pain (joint, bone, muscle) and chills were more prominent in the group of patients who died, while anosmia, sore throat, headache and diarrhea were more frequently reported in the group of patients who survived.

All eight patients who died were admitted to the ICU and required artificial ventilation in comparison to none of those who survived ($p<0.001$). Out of those requiring artificial ventilation, 7/8 patients required assist-control mode of ventilation and one was in pressure supported spontaneous mode of ventilation.

Patients who died in comparison with those who survived had longer hospital stay (mean 20.9±8.5

Table 2. Characteristics of MS patients who died from COVID-19

Case No.	Age	Sex	Course of disease	EDSS score	Comorbidity	DMT
1	63	F	PPMS	6.5	No	Ocrelizumab
2	55	M	RRMS	5.0	Cardiovascular disease, hypertension	Ocrelizumab
3	75	F	PPMS	6.5	Cardiovascular disease, hypertension	No
4	68	F	PPMS	7.0	Cardiovascular disease, hypertension	No
5	73	F	SPMS	8.5	Depression, epilepsy, diabetes, hypertension	No
6	49	F	SPMS	6.5	Epilepsy	No
7	42	F	PPMS	8.5	Epilepsy	No
8	72	M	PPMS	6.0	Cardiovascular disease	No

MS = multiple sclerosis; F = female; M = male; RRMS = relapsing-remitting multiple sclerosis; PPMS = primary progressive multiple sclerosis; SPMS = secondary progressive multiple sclerosis; EDSS = Expanded Disability Status Scale; DMT = disease modifying therapy

Table 3. Risk factors for COVID-19-related death in multiple sclerosis

	Univariate analysis			Multivariate analysis		
Variable	OR	95% CI	p	OR	95% CI	p
Sex	0.81	0.13-5.03	0.821			
Age	0.92	0.85-0.99	0.046			
MS phenotype	4.88	1.30-18.31	0.019	7.66	1.08-60.6	0.044
Duration of MS	1.01	0.95-1.07	0.750			
EDSS >6.0	9.80	1.04-19.70	0.046			
DMTs	0.84	0.16-4.35	0.835			
Ocrelizumab	2.33	0.31-17.35	0.408			
Comorbidities	2.88	0.30-7.97	0.361			
Cardiovascular comorbidities	7.0	1.11-14.06	0.038			
Vaccination	1.18	0.24-5.86	0.838			
Length of hospital stay	0.77	0.64-0.93	0.006	0.76	0.61-0.94	0.013

OR = odds ratio; CI = confidence interval; MS = multiple sclerosis; EDSS = Expanded Disability Status Scale; DMT = disease modifying therapy

vs. 9.9±4.9 days, p<0.001). Finally, all patients who developed sepsis had lethal outcome.

Results of univariate logistic regression analyses demonstrated that older age, EDSS higher than 6.0, progressive forms of MS, cardiovascular comorbidities, and longer duration of hospital stay statistically significantly increased the risk of COVID-19-related death in MS patients (Table 3). Treatment with ocrelizumab was associated with more than 2-fold increased death risk (OR=2.33; 95% CI 0.31-17.35, p=0.408), but this finding did not reach statistical significance. Increased death risk was not shown in those treated with any other DMT (data not shown). Finally, it has to be emphasized that admission to ICU

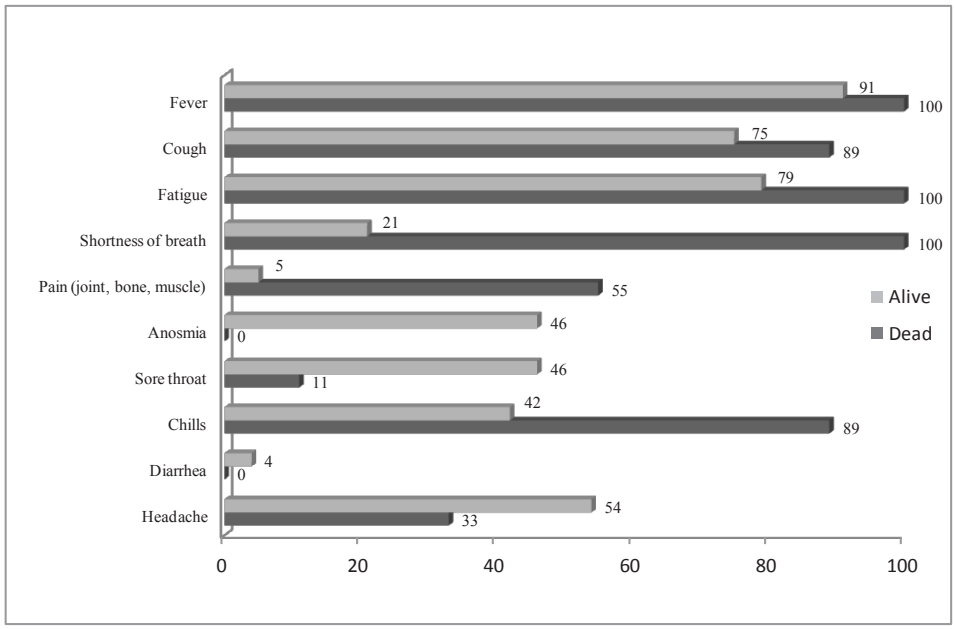

Fig. 1. Proportion (percentage) of patients with multiple sclerosis with COVID-19 symptoms.

and mechanical ventilation were present in all patients who died.

It has been shown by the multivariate logistic regression analysis that progressive forms of MS (OR=7.66, 95% CI 1.08-60.6, p=0.044) and longer hospital stay (OR=1.30, 95% CI 1.08-1.57, p=0.006) significantly increased the risk of death in our MS cohort.

Discussion

In this case series, all MS patients hospitalized due to severe COVID-19 came from a single referral center for COVID-19 disease and SARS-CoV-2 infection was laboratory confirmed in all cases. To the best of our knowledge, the outcomes of COVID-19 exclusively in PwMS hospitalized due to the severe infection have not been analyzed until now. Serious outcomes were frequent in our MS cohort. The requirement for intensive care and artificial ventilation was recorded in 25% of the patients. It has to be emphasized that it could have had a significant impact on a very high CFR (25%) detected in our cohort of demographically and clinically well-defined PwMS with severe COVID-19 (Table 2). In the MuSC-19 cohort, MS patients had a risk of severe events including death, which was about twice the risk in the age- and sex-matched Italian population[2]. Statistically significant odds ratio (OR) was obtained for hospitalization, ICU admission, and death (p<0.001).

Univariate regression analysis showed that older age, EDSS higher than 6.0, progressive MS forms, cardiovascular comorbidities, and longer duration of hospital stay statistically significantly increased the risk of COVID-19-related death in PwMS who developed severe infection warranting hospitalization. In the multivariate model, only progressive forms of MS and longer hospital stay were shown to be independent risk factors for death in our study.

The excess of CFR in our MS patients could at least in part be attributed to the generally accepted risk factors for COVID-19-related death in general population, such as older age (mean age in those who died was 62.1 *vs.* 51.3 years in MS patients who survived), comorbidities being reported in the majority of those who died (87.5%), and the presence of cardiovascular disorders being statistically significantly (p=0.026) more frequent in those who died (50%) *versus* those who survived (12.5%). It was demonstrated in Italy that COVID-19 deaths were mainly observed among older male patients who also had multiple comorbidities[7]. Apart from these risk factors shared with the general population, several MS-specific determinants influencing the lethality of COVID-19 were also identified in our hospitalized MS cohort, i.e., EDSS higher than 6.0 and progressive disease course were associated with an increased risk of

death. This is in line with the results of studies conducted in 2020 and 2021 that found higher disability and/or progressive MS to be risk factors for developing more severe COVID-19[8-10].

The association of DMTs and their various classes with COVID-19 severity has not yet been clearly defined. Especially, it remains unknown whether hospitalized PwMS who are treated with DMTs are at an increased risk of COVID-19-related death. The majority of studies did not find any association between specific DMTs and COVID-19 severity or lethality[3,8-13]. Very recently, it has been demonstrated that veteran patients with MS hospitalized for COVID-19 were less likely to die when taking DMTs[14]. Having in mind that it has been reported that increased mortality occurred in PwMS taking ocrelizumab[15], it should be noted that in this study, none of the patients was treated with this agent. The potential detrimental role of ocrelizumab in the outcome of COVID-19 PwMS treated with this drug may be due to the mechanism of action of anti-CD20 agents which lead to prolonged B-cell depletion. An increased risk of death due to COVID-19 in PwMS treated with ocrelizumab was not confirmed in a number of small studies, probably due to the low statistical power to explore rare events[3]. In line with this notion, in our study, 2 out of 5 PwMS treated with ocrelizumab died during hospitalization (OR 2.33), but this finding did not reach statistical significance.

Although our sample was small, which was the key limitation of our study, we demonstrated that our MS patients hospitalized due to severe COVID-19 had a high risk of death and that progressive forms of the disease and higher level of disability, as MS-specific determinants, significantly contributed to the increased mortality risk.

Having in mind all the above mentioned, it should be considered that increased lethality of COVID-19 is possible in MS cases of advanced age, presence of comorbidity, and progressive disease course. Additionally, more intense monitoring and risk mitigation plans may be used by healthcare providers in PwMS treated with anti-CD20 agents.

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Sažetak

POVEĆANA SMRTNOST KOD BOLESNIKA S MULTIPLOM SKLEROZOM HOSPITALIZIRANIH ZBOG TEŠKOG OBLIKA COVID-19

M. Budimkić Stefanović, J. Ivanović, O. Tamaš, N. Veselinović, N. Momčilović, M. Ždraljević, Š. Mesaroš, T. Pekmezović i *J. Drulović*

Cilj ove studije bio je procijeniti smrtnost (*case fatality ratio*, CFR) kod osoba s multiplom sklerozom (MS) hospitaliziranih zbog teškog oblika COVID-19 i ispitati ulogu čimbenika rizika za smrtni ishod u ovoj dobro definiranoj kohorti. Ova studija serije slučajeva obuhvatila je sve osobe s MS (N=32) s teškim oblikom COVID-19 koji su bili hospitalizirani u referentnom centru za COVID-19 u Beogradu od siječnja 2021. do siječnja 2022. godine. Osam od 32 bolesnika je umrlo od COVID-19 (CFR 25%). Uzrok smrti je bila sepsa kod 7 bolesnika i plućna embolija kod jednog bolesnika. Rezultati univarijatne logističke regresijske analize su pokazali da starija životna dob, EDSS viši od 6,0, progresivni oblici MS, kardiovaskularne supostojeće bolesti i duže trajanje hospitalizacije statistički značajno povećavaju rizik od smrti uzrokovane COVID-19 kod bolesnika s MS. Liječenje okrelizumabom je bilo povezano s više od 2 puta većim rizikom od smrti (p=0,408). Multivarijatna logistička regresijska analiza je pokazala da su progresivni oblici MS (p=0,044) i duža hospitalizacija (p=0,006) značajno povećali rizik od smrti u našoj kohorti bolesnika s MS. U ovoj studiji su starija dob, prisustvo supostojećih bolesti i progresivni tijek bolesti bili nezavisni prediktori povećane smrtnosti od COVID-19 kod osoba s MS. Intenzivnije praćenje je indicirano kod osoba s MS koje se liječe anti-CD20 lijekovima.

Ključne riječi: *Multipla skleroza; Težak oblik COVID-19; Smrtnost; Rizični čimbenici*