Original article

Attitudes of patients with relapsing-remitting form of multiple sclerosis using disease-modifying drugs in Montenegro regarding COVID-19 pandemic

Ljiljana Radulovic[a,b,*], Jevto Erakovic[a], Milovan Roganovic[a,c]

[a] Clinical Centre of Montenegro, Clinic for Neurology, Ljubljanska bb, 81000 Podgorica, Montenegro
[b] University of Montenegro, Faculty of Medicine, Department for Neurology, Krusevac bb, 81000 Podgorica, Montenegro
[c] University of Montenegro, Faculty of Medicine, Department for Medical Biochemistry, Krusevac bb, 81000 Podgorica, Montenegro

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ABSTRACT

Background: In the days of the reorganization of healthcare systems due to SARS-Cov2 pandemic, patients suffering from chronic diseases are being often neglected. The aim of our study was to examine the attitudes and behaviors of patient suffering from relapsing-remitting form of multiple sclerosis using disease-modifying drugs in Montenegro in relation to the current pandemic.
Methods: The research was conducted through an online-generated questionnaire during the peak of the pandemic.
Results: There is a high level of concern about COVID-19 (3.22 ± 1.23), especially about safety behavior intensification (3.80 ± 1.29). Possibility of relapse during pandemic was considered as moderate (2.06 ± 1.42), but relapse symptoms would be reported by the majority of subjects (1.55 ± 1.23). Our unemployed patients statistically more often reported that they had more frequent mood changes, but also that they felt more energy loss. Surprisingly, there was no difference among the subjects according to smoking status. According therapy groups there was significant difference between the groups regarding some variables: patients using ocrelizumab are most concerned about COVID-19; patients using interferon beta 1a i.m. statistically more often have frequent changes in their mood, memory problems, poor appetite, feeling of nausea or upset stomach and patients on fingolimod have bigger afraid of coming to regular visits.
Conclusion: Our patients showed concern about their disease future status in the current epidemic era, but also showed a high degree of trust in physicians and the overall health system.

1. Introduction

At the beginning of 2020, the entire world was caught up in the battle with the SARS-Cov-2 pandemic. The clinical disease termed COVID-19has led to the closure of schools, kindergartens, universities, restriction of movement, self-isolation, the organization of numerous quarantines around the world, and now the subsequent, socioeconomic consequences of the pandemic are being discussed. Medical professionals around the world are involved in the fight against the new virus, with not only infectologists, pulmonologists, microbiologists and epidemiologists included, but also doctors in all professions. In some researches, hospital staff were exposed to stress both physical and psychological in response to this serious infectious public health event. (Phelan et al., 2020) In a situation where fear, anxiety and depression are predominant emotions, when numerous psychological problems can intensify or even appear for the first time in many countries phone-lines for psychological assistance to citizens are organized. Due to above mentioned, health care system is dramatically changed and it is not accessible to chronic patients as before. Regular visits are postponed, but in the case of need patients with chronic diseases can be admitted by adequate specialist.

Several risk factors for COVID-19 infection have been reported so far. Older patients ($\geq$60 years of age) are at higher risk than children who might be less likely to become infected or, if so, may show milder symptoms or even asymptomatic infection. (QS Li et al., 2020) Hypertension, diabetes, respiratory system disease and cardiovascular disease are also reported as risk factors for this new infection. (Yang et al., 2020)

Health systems, on the other hand, should not neglect patients suffering from other diseases. There are many medical emergencies that

need to be addressed even in the days of a pandemic, and certainly chronic patients should not be neglected. Of course, this group also includes patients with multiple sclerosis (MS).As it is well known, MS is an inflammatory demyelinating disease of the central nervous system with a variety of presentations and still unclear pathogenesis. Among these patients, the majority of them suffer from relapsing-remitting form (RR) of the disease. (Lemus et al., 2018)

Seventeen disease-modifying drugs, until now approved, reduce, to various extents the likelihood of developing new white matter lesions, clinical relapses, and stepwise accumulation of disability. (Reich et al., 2018) Side effects of almost all of these drugs are leukocytopenia, neutropenia and lymphopenia, and consequently an increased risk of developing all, including respiratory infections. According to several researches lymphopenia is an effective and reliable indicator of the severity and hospitalization in COVID-19 patients (Tan et al., 2020) and lymphopenia on admission was associated with poor outcome in patients with COVID-19. (Huang and Pranata, 2020) Introduction of 'lymphodepleting' DMTs (ocrelizumab, alemtuzumab, rituximab, cladribine), as well as well as continuing therapy with these drugs should be based on individual circumstances. (Giovannoni et al., 2020) Also, psychiatric symptoms, particularly depression and anxiety, are common in MS patients (Marrie et al., 2015), which can aggravate in such circumstances. This new situation with COVID-19 pandemic has led to the preparation of new protocols for the treatment of patients with MS. (Brownlee et al., 2020)

Clinical center of Montenegro and Clinic for Neurology, as an integral part of it, is the national reference center for the diagnosis, treatment and monitoring of patients with MS in Montenegro. According to available data (register of MS patients is under construction) in Montenegro, about 600 patients suffer from this disease, and about 80% of them suffer from relapsing-remitting form of the disease. The clinic adheres to the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) guidelines for diagnosis and treatment, and all medicines approved by the European Medicine Agency (EMA) for the treatment of MS patients are reimbursed by National Health Found.

The aim of our study was to examine the attitudes and behaviors of RRMS patients on DMD in Montenegro in relation to the current pandemic.

Montenegro is the last country in Europe to register the first case of COVID-19. The first case was registered on March 17, 2020. (Montenegro: WHO Coronavirus Disease (COVID-19) Dashboard. World Health Organization, 2020)

2. Materials and methods

The research was conducted through an original online-generated questionnaire (created for the purpose of this article) that was distributed by telephone to 130 patients with relapsing-remitting form of MS in Montenegro, who are in the databases held by the Clinical Center of Montenegro, who represent one third of all treated patients in our country also the only online available in this period. The research objective, methodology, and especially that participation or refusal to participate in the research would not affect their further treatment were explained to all them. In particular, it was emphasized that the survey is anonymous and that the results obtained would be used solely for scientific and research purposes.

The survey was conducted from April 7 to April 10, 2020, and in that period, according to data from Institute for Public Health of Montenegro (IJZCG [Internet]. Institut za javno zdravlje Crne Gore, 2020; Zvanični sajt Vlade Crne Gore i NKT zazarazne bolesti [Internet] 2020), the epidemiological situation in Montenegro was: 257 patients, 5 recovered, 3 died, with 6–8 newly diagnosed patients daily (population 631,219). The epidemiological situation in Montenegro in the days of conducting the survey is shown in Fig. 1. In the days when the survey was conducted, numerous prohibitions were
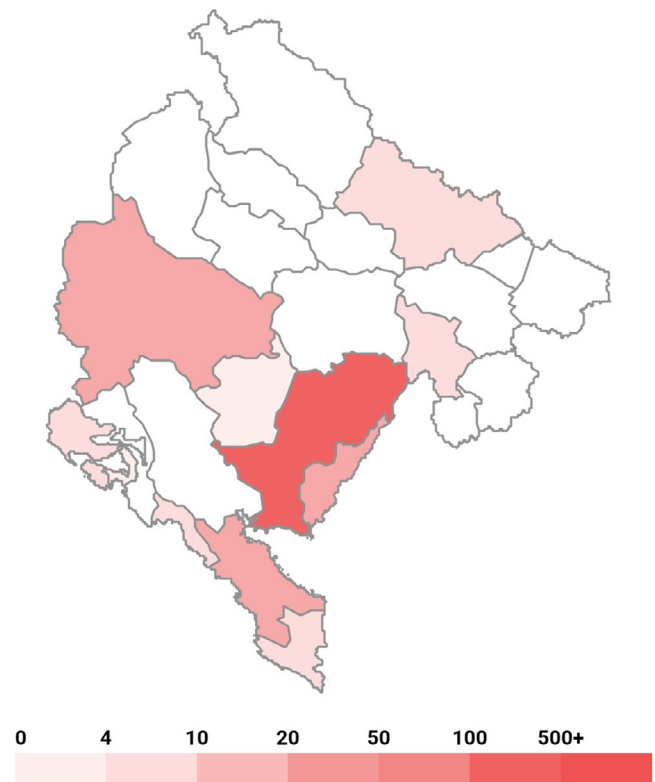

Fig. 1. Epidemiological situation in Montenegro during survey (9).

taken by the Government of Montenegro and the Ministry of Health for 40 days: closed schools, kindergartens and universities, prohibition of movement between cities, ban to be out of house facility from 7 PM to 5AM next day, prohibition of sport and recreating activities in public areas, mandatory physical and social distance, prohibition of traffic for cruisers and air carriers, closure of border crossings, the closure of catering and service facilities, and some settlements and municipalities were quarantined.

Due statistical analysis, our respondents were grouped according to several characteristics: gender, age, DMD, length of illness, level of education, employment status, smoking, presence of diabetes and hypertension, presence of respiratory symptomatology and fever, previous trips abroad of respondents and their family members. Respondents were also asked if they or their family members were quarantined or self-isolated at the time of questioning. In terms of place of residence, respondents were grouped into three groups: region A (Podgorica residents, which at the time of the survey was the focus of the epidemic in Montenegro - the largest number of patients was from this town), followed by region B (respondents from other municipalities in which were reported diseases) and region C (respondents from municipalities in Montenegro where no SARS-Cov-2 disease was recorded).

Participants were asked about personal emotions; about the presence of autonomic symptomatology; and especially about attitudes towards their illness at the time of the epidemic - about whether they think isolation have had a negative impact on them, about their relationship with healthcare professionals at the time of the epidemic, about taking therapy, etc.

We used the chi square test for homogeneity in order to evaluate whether there is a statistically significant difference in the distributions of different populations of respondents. We use a 5% significance level, i.e. we reject the hypothesis that the populations are homogenous if $P < 0.05$. Also, we have calculated the Pearson's correlation coefficients and used linear regression to examine whether there is a statistically significant correlation between patient age/duration of illness and the results obtained.

3. Results

In total, we received 101 responses from our respondents, which means that response rate was 77.69%. The sample was composed of 25 male (24.75%) and 76 female (75.25%) participants with mean age of 39.4 ± 8.7 years. The average duration of illness in our subjects is 7.0 ± 5.1 years. In our study group 2 patients (1.99%) have diabetes and 10 patients (9.90%) have hypertension. There were no patients suffering from chronic pulmonic diseases, although 27 of them (26.73%) are currently consuming cigarettes. From our study population, two patients (1.99%) traveled outside Montenegro within a month before the study. In the 14 days prior to the study, 3 patients (2.97%) experienced fever, 5 patients (4.95%) had lack of breath and 9 of them (8.91%) reported dry cough as a symptom. At the time of filling in the questionnaire, 17 subjects (16.83%) were in self-isolation, 3 of them (2.97%) were quarantined and 1 (0.99%) was under epidemiological surveillance. Regarding the family members of the respondents, in 15 cases (14.85%) it was reported that the family member was in isolation and in 4 cases (3.96%) the family member was in institutional quarantine. In terms of material status, 27 respondents (26.74%) stated that they were unemployed at the time of the survey.

Concerning the DMD that patients use, most of them are on interferon therapy - 35 patients (34.65%) use interferon beta 1b (Betaferon®), 27 (26.73%) use interferon beta 1a sc. (Rebif®) and 16 patients (15.84%) use interferon beta 1a im. (Avonex®). In our group there are 13 patients (12.87%) on fingolimod (Gilenya®) whilst ocrelizumab (Ocrevus®) are receiving 5 patients (4.95%). Other patients receive DMD recently approved in Montenegro: teriflunomide (Aubagio®) – 2 patients (1.98%) and cladribine (Mavenclad®) – 1 patient (0.99%). Also, 2 patients (1.98%) use glatiramer acetate (Copaxone®). The average time of taking therapy is 4.0 ± 3.8 years.

From the large number of data we collected in our research, in three tables (Table 1, 2 and 3) and two figures (Fig. 2 and 3) we presented only those that have statistical significance according to one of the examined variables. The average values for questions for which there were no statistical significance according to any of the examination criteria are (scale 1–5): 3.70 ± 1.30 (for question: To what extent has your worry influenced you to distance yourself from people?); 2.17 ± 1.38 (for feeling of being easily upset or irritated); 1.75 ± 1.17 (for feeling of being afraid in open places); 1.40 ± 1.00 (for feeling of fear of living the house); 1.55 ± 1.23 (for statement that in case of presence of symptoms of relapse due to fear of COVID-19 patient would not contact doctor); 1.50 ± 1.18 (for statement that in the event that the pandemic lasts and that it happens that patient's medicine is missing, he/she would not contact doctor); 1.23 ± 0.80 (for statement that everyday overload with the COVID-19 situation cause misuse of MS drug); 4.30 ± 1.13 (for statement that in case of getting COVID-19 disease patient would require a neurologist to be included in treatment) and 1.95 ± 1.31 for statement that isolation measures have negatively affected patient's condition.

4. Discussion

As can be seen from the introductory columns in all the tables in this manuscript and from results shown in previous paragraph, there is a high level of concern about COVID-19 among our patients (3.22 ± 1.23), especially about safety behavior (hygiene) intensification (3.80 ± 1.29). Among the vegetative symptomatology present in the 14 days back from the day of the test, frequent mood swings (2.19 ± 1.32), a sense of slight irritation (2.17 ± 1.38), and a sense of loss of energy (1.87 ± 1.07) are particularly present. In terms of attitudes toward their own illness, respondents showed a relatively high level of concern about it (2.74 ± 1.44), and the risk of relapse was considered as moderate (2.06 ± 1.42). On the other hand, there are answers that we can explain by the fact that patients with MS in Montenegro are in constant contact with their neurologist, and that

they trust their neurologists, as well as the entire health care system of Montenegro. Thus, there is almost a consensus that in the case of SARS-Cov2 infection, all patients would require a neurologist as a part of medical treating team (4.30 ± 1.13). Also, there is a low level of agreement with the claim that patients had worse compliance due to pandemic (1.23 ± 0.80) or that if they were in the lack of medicine during the pandemic, they would be afraid of seeking it in the health-care system (1.50 ± 1.18). Relapse symptoms would be reported by the largest number of subjects (1.55 ± 1.23), which can be interpreted in two ways - by trusting physicians and the health system, but also by fear of its outcome during the pandemic as well as patients insight in the fact that corticosteroid therapy has best effect only in the first weeks of relapse.

In our study population, the ratio of male and female patients is consistent with the recent knowledge of MS gender distribution (female to male ratio = 2.3–3.5:1). (Harbo et al., 2013) As it was mentioned before, in many, often overemphasized, posts on social networks and in newspaper articles as well as in some scientific researches (LQ Li et al., 2020) it has been reported that men are at higher risk of having SARS-Cov2 infection. Our results, shown in Table 1, show a statistically significant difference in behavior among our patients - men showed that they intensified their safety behavior (hand washing, disinfection), and also they stated that isolation measures had a more negative impact on them than on female patients. We explain the above with the views and populist statements outlined above that men are at risk of getting the new virus.

Smokers are at risk for all respiratory infections, including SARS-Cov2 virus infection. The harmful effects of tobacco smoke, especially on the respiratory tract, are much talked about and efforts of all health systems, especially in the days of a pandemic, are aimed at reducing the number of smokers. The campaign, and especially through the media, is aimed at achieving this goal. However, there was no statistically significant difference on any issue among the subjects in our group according to smoking status (Table 1).

The epidemic days are days of reflection on the future economic status of each individual, family and society as a whole. Many countries have closed many businesses due to the epidemic, and therefore everyone, and especially those who are unemployed, have a fear of the future. Our results show (Table 1) that there is a statistically significant difference in the behavior/results of our patients regarding their employment status. Our unemployed patients statistically more reported that they had more frequent mood changes, that they were crying more easily, but also that they felt more energy loss. On the other hand, the employed population is more concerned about the future course of the disease and is thinking more about consulting with doctor for advice and recommendations regarding its illness due to the current situation with COVID-19. We can explain the above with the fear of the employee patients to lose their current jobs due to progression of disability in the atmosphere of a potential economic crush.

Being in isolation or having a family member who is in isolation is, of course, a stressful moment when it is announced that the whole world is in a state of emergency, a pandemic that affects human lives. In our subjects, no statistical difference was observed in the parameters studied except in the dry mouth sensation.

Patients residing in the regions of Montenegro that have registered cases of SARS-Cov2 patients, and especially those living in the center of the epidemic, the municipality with the most infected, are expected to show greater concern for their disease and are expected to show in greater level vegetative symptomatology. As can be seen in Table 2, statistically significant differences in the feeling of exhaustion, in the attitude that the patient was not understood by others as well as in the difficulties in making decisions were detected. The absence of a statistical difference by the other criteria examined, and especially in the domain of solicitude for illness, we can explain in two ways. Firstly, there is a high degree of responsibility among all citizens of Montenegro, and especially those suffering from chronic diseases - all

Table 1
Patients' attitudes regarding gender, smoking status and employment status.

Question/Statement (scale 1–5)	Total	Criteria (mean value ± standard deviation)										
		Gender			Smoking status				Employment status		
		Male $N = 25$	Female $N = 76$	SR*	Current smoker $N = 28$	Past smoker $N = 23$	Non smoker $N = 50$	SR*	Employed $N = 74$	Unemployed $N = 27$	SR*
How much are you worried about COVID-19?	3.22 ± 1.23	3.36 ± 1.19	3.17 ± 1.24		3.28 ± 1.21	3.43 ± 1.16	3.08 ± 1.28		3.24 ± 1.22	3.15 ± 1.26	
How much has the threat of COVID19 influenced the intensification of safe behavior (hand washing, disinfection …)?	3.80 ± 1.29	3.96 ± 1.06	3.75 ± 1.36	*	3.85 ± 1.30	3.83 ± 1.23	3.76 ± 1.33		3.86 ± 1.20	3.63 ± 1.47	
In the last 14 days, how often have you been feeling…											
frequent changes in your mood	2.19 ± 1.32	2.20 ± 1.22	2.18 ± 1.35		2.32 ± 1.25	2.30 ± 1.29	2.06 ± 1.38		2.09 ± 1.27	2.44 ± 1.42	*
memory problems	1.50 ± 0.93	1.44 ± 1.12	1.53 ± 0.87		1.57 ± 1.07	1.22 ± 0.52	1.60 ± 0.99		1.54 ± 0.91	1.41 ± 1.01	
lack of energy	1.87 ± 1.07	1.84 ± 1.11	1.88 ± 1.07		2.00 ± 1.18	1.91 ± 1.08	1.22 ± 0.68		1.74 ± 0.92	2.22 ± 1.37	*
poor appetite	1.38 ± 0.87	1.64 ± 1.19	1.30 ± 0.73		1.79 ± 1.23	1.26 ± 0.54	1.62 ± 1.21		1.38 ± 0.82	1.41 ± 1.01	
like trapped	1.39 ± 0.87	1.76 ± 1.30	1.82 ± 1.21		2.17 ± 1.39	1.74 ± 0.96	1.42 ± 0.95		1.74 ± 1.16	1.96 ± 1.40	
Sad	1.71 ± 1.07	1.64 ± 0.81	1.74 ± 1.15		1.93 ± 1.09	1.70 ± 1.15	1.48 ± 0.79		1.69 ± 0.99	1.78 ± 1.28	
a sense of exhaustion	1.53 ± 0.88	1.48 ± 0.77	1.55 ± 0.91		1.75 ± 1.04	1.39 ± 0.84	1.36 ± 0.85		1.47 ± 0.74	1.71 ± 1.17	
Scared	1.49 ± 1.00	1.24 ± 0.83	1.58 ± 1.05		1.75 ± 1.21	1.48 ± 1.04	1.58 ± 1.18		1.46 ± 1.00	1.59 ± 1.05	
that people do not understand you	1.69 ± 1.23	1.72 ± 1.28	1.68 ± 1.22		2.07 ± 1.44	1.48 ± 0.99	1.22 ± 0.51		1.49 ± 1.05	2.26 ± 1.51	
nauseous or upset stomach	1.30 ± 0.74	1.28 ± 0.84	1.32 ± 0,72		1.54 ± 1.14	1.22 ± 0.52	1.52 ± 1.09		1.31 ± 0.78	1.30 ± 0.67	
difficulty in making decisions	1.41 ± 0.97	1.40 ± 0.87	1.42 ± 1.01		1.47 ± 1.07	1.13 ± 0.34	1.36 ± 0.78		1.49 ± 1.02	1.22 ± 0.80	
sensation of dry mouth	1.34 ± 0.79	1.12 ± 0.44	1.41 ± 0.87		1.36 ± 0.78	1.26 ± 0.86	1.62 ± 1.07		1.28 ± 0.65	1.48 ± 1.09	
that you can easily cry	1.70 ± 1.16	1.40 ± 0.82	1.80 ± 1.24		1.86 ± 1.30	1.70 ± 1.22	1.62 ± 1.07		1.61 ± 1.04	1.96 ± 1.43	*
To what extent do you agree with the following statements?											
I am worried about the further course of my illness due to the current situation with COVID-19	2.74 ± 1.44	2.92 ± 1.55	2.68 ± 1.41		2.86 ± 1.46	2.70 ± 1.40	2.70 ± 1.47		2.84 ± 1.49	2.48 ± 1.28	*
I am thinking of consulting with my doctor for advice and recommendations regarding my illness due to the current situation with COVID-19	2.83 ± 1.48	3.20 ± 1.41	2.71 ± 1.50		3.25 ± 1.46	2.35 ± 1.11	2.82 ± 1.60		2.97 ± 1.49	2.44 ± 1.42	*
I am afraid of coming to regular check-up with my doctor because of the COVID-19 pandemic	2.49 ± 1.53	2.24 ± 1.30	2.58 ± 1.60		2.68 ± 1.59	2.43 ± 1.70	2.42 ± 1.44		2.50 ± 1.51	2.48 ± 1.63	
I think there is a real risk of relapse due to the current situation with COVID-19	2.06 ± 1.42	1.92 ± 1.29	2.10 ± 1.47		2.21 ± 1.55	2.39 ± 1.62	1.82 ± 1.22		2.05 ± 1.45	2.07 ± 1.36	

χ^2 test, $p < 0,05$, SR = statistically relevant .

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Table 2
Patients' attitudes regarding self-isolation and place of resident.

Question/Statement (scale 1–5)	Total	Criteria (mean value ± standard deviation)												
		Patients in self-isolation			Patient's family member in self-isolation			Place of resident			
		Yes N = 17	No N = 84	SR*	Yes N = 16	No N = 85	SR*	Region A N = 61	Region B N = 45	Region C N = 19	SR*
How much are you worried about COVID-19?	3.22 ± 1.23	3.24 ± 0.97	3.21 ± 1.28		3.12 ± 0.89	3.24 ± 1.29		3.27 ± 1.17	3.27 ± 1.30	3.00 ± 1.20	
How much has the threat of COVID19 influenced the intensification of safe behavior (hand washing, disinfection ...)?	3.80 ± 1.29	3.76 ± 1.25	3.81 ± 1.30		3.50 ± 1.26	3.86 ± 1.29		4.00 ± 1.31	3.67 ± 1.22	3.74 ± 1.41	
In the last 14 days, how often have you been feeling…											
frequent changes in your mood	2.19 ± 1.32	1.76 ± 1.15	2.27 ± 1.34		1.81 ± 1.17	2.26 ± 1.34		1.89 ± 1.17	2.38 ± 1.47	2.32 ± 1.16	
memory problems	1.50 ± 0,93	1.24 ± 0.44	1.56 ± 1.00		1.25 ± 0.45	1.55 ± 0.99		1.49 ± 0.90	1.51 ± 1.01	1.53 ± 0.84	
lack of energy	1.87 ± 1.07	1.76 ± 1.15	1.89 ± 1.06		1.81 ± 1.17	1.88 ± 1.06		1.65 ± 0.92	2.02 ± 1.23	1.95 ± 0.91	
poor appetite	1.38 ± 0.87	1.29 ± 0.59	1.40 ± 0.92		1.31 ± 0.60	1.40 ± 0.92		1.30 ± 0.88	1.42 ± 0.97	1.47 ± 0.61	
like trapped	1.39 ± 0.87	1.41 ± 0.71	1.88 ± 1.29		1.50 ± 0.73	1.86 ± 1.29		1.59 ± 1.01	1.96 ± 1.26	1.84 ± 1.50	
Sad	1.71 ± 1.07	1.53 ± 0.94	1.75 ± 1.10		1.56 ± 0.96	1.74 ± 1.09		1.43 ± 0.77	1.80 ± 1.22	2.05 ± 1.13	
a sense of exhaustion	1.53 ± 0.88	1.59 ± 0.87	1.52 ± 0.88		1.62 ± 0.89	1.52 ± 0.88		1.19 ± 0.40	1.60 ± 0.89	2.05 ± 1.22	*
Scared	1,49 ± 1.00	1.29 ± 0.59	1.54 ± 1.07		1.31 ± 0.60	1.53 ± 1.06		1.27 ± 0.69	1.62 ± 1.25	1.63 ± 0.83	
that people do not understand you	1.69 ± 1.23	1.47 ± 0.94	1.74 ± 1.28		1.50 ± 0.97	1.73 ± 1.28		1.13 ± 0.59	1.96 ± 1.33	2.16 ± 1.54	*
nauseous or upset stomach	1.30 ± 0.74	1.29 ± 0.59	1.31 ± 0.78		1.31 ± 0.60	1.31 ± 0.77		1.16 ± 0.44	1.40 ± 0.96	1.37 ± 0.60	
difficulty in making decisions	1.41 ± 0.97	1.06 ± 0.24	1.49 ± 1.05	*	1.06 ± 0.25	1.48 ± 1.04		1.22 ± 0.58	1.58 ± 1.27	1.42 ± 0.69	*
sensation of dry mouth	1.34 ± 0.79	1.71 ± 0.92	1.26 ± 0.75		1.62 ± 0.89	1.28 ± 0.77	*	1.27 ± 0.77	1.33 ± 0.77	1.47 ± 0.90	
that you can easily cry	1.70 ± 1.16	1.76 ± 1.25	1.69 ± 1.15		1.81 ± 1.28	1.68 ± 1.15		1.65 ± 1.01	1.76 ± 1.30	1.68 ± 1.16	
To what extent do you agree with the following statements?											
I am worried about the further course of my illness due to the current situation with COVID-19	2.74 ± 1.44	2.41 ± 1.32	2.81 ± 1.46		2.37 ± 1.36	2.81 ± 1.45		2.76 ± 1.32	2.69 ± 1.49	2.84 ± 1.61	
I am thinking of consulting with my doctor for advice and recommendations regarding my illness due to the current situation with COVID-19	2.83 ± 1.48	3.00 ± 1.54	2.80 ± 1.48		3.06 ± 1.44	2.79 ± 1.50		2.62 ± 1.46	2.84 ± 1.46	3.21 ± 1,58	
I am afraid of coming to regular check-up with my doctor because of the COVID-19 pandemic	2.49 ± 1.53	2.82 ± 1.59	2.43 ± 1.52		2.87 ± 1.63	2.42 ± 1.51		2.70 ± 1.68	2.33 ± 1.48	2.47 ± 1.39	
I think there is a real risk of relapse due to the current situation with COVID-19	2.06 ± 1.42	2.12 ± 1.62	2.05 ± 1.39		2.19 ± 1.64	2.04 ± 1.38		1.97 ± 1.42	2.24 ± 1.51	1.79 ± 1.18	

χ^2 test, $p < 0,05$, SR = statistically relevant.
Region A – Podgorica residents (focus of the epidemic in Montenegro).
Region B - respondents from other municipalities in which were reported diseases.
Region C - respondents from municipalities in Montenegro where no SARS-Cov-2 disease was recorded.

Table 3
Patients' attitudes regarding the type of therapy .

Question/Statement (scale 1–5)	Total	Type of therapy (mean value ± standard deviation)						SR*
		Interferon beta 1b (Betaferon®) N = 35	Interferon beta 1a sc. (Rebif®) N = 27	Interferon beta 1a im. (Avonex®) N = 16	Fingolimod (Gilenya®) N = 13	Ocrelizumab (Ocrevus®) N = 5	Other N = 5	
How much are you worried about COVID-19?	3.22 ± 1.23	2.91 ± 1.20	3.11 ± 1.12	3.94 ± 1.24	2.92 ± 1.38	4.20 ± 0.45	3.40 ± 1.14	*
How much has the threat of COVID19 influenced the intensification of safe behavior (hand washing, disinfection ..)?	3.80 ± 1.29	3.26 ± 1.31	4.04 ± 1.34	4.56 ± 0.63	3.62 ± 1.39	4.00 ± 1.23	4.20 ± 0.84	
In the last 14 days, how often have you been feeling…								
frequent changes in your mood	2.19 ± 1.32	2.00 ± 1.28	2.19 ± 1.18	2.81 ± 1.64	2.15 ± 1.46	1.80 ± 1.10	2.00 ± 0.71	*
memory problems	1.50 ± 0,93	1.31 ± 0.53	1.48 ± 0.94	1.94 ± 1.61	1.77 ± 0.83	1.00 ± 0.00	1.40 ± 0.55	*
lack of energy	1.87 ± 1.07	1.94 ± 1.03	1.59 ± 0.75	2.25 ± 1.53	1.85 ± 1.21	2.20 ± 1.10	1.40 ± 0.55	
poor appetite	1.38 ± 0.87	1.37 ± 0.60	1.19 ± 0.56	2.12 ± 1.41	1.15 ± 0.38	1.00 ± 0.00	1.20 ± 0.45	*
like trapped	1.39 ± 0.87	1.57 ± 0.95	1.70 ± 1.20	2.62 ± 1.67	1.77 ± 1.17	2.00 ± 1.41	1.20 ± 0.45	
Sad	1.71 ± 1.07	1.71 ± 1.02	1.70 ± 1.20	1.81 ± 1.28	1.92 ± 1.50	1.40 ± 0.89	1.20 ± 0.45	
Scared	1.49 ± 1.00	1.31 ± 0.63	1.11 ± 0.42	2.00 ± 1.67	1.54 ± 1.33	1.00 ± 0.00	1.20 ± 0.45	
that people do not understand you	1.69 ± 1.23	1.54 ± 1.20	1.70 ± 0.91	2.44 ± 1.59	1.69 ± 1.11	1.40 ± 0.89	1.20 ± 0.45	
nauseous or upset stomach	1.30 ± 0.74	1.49 ± 0.74	1.56 ± 0.93	1.62 ± 1.36	1.08 ± 0.28	1.00 ± 0.00	1.20 ± 0.45	*
difficulty in making decisions	1.41 ± 0.97	1.31 ± 0.76	1.56 ± 0.80	1.62 ± 1.36	1.77 ± 1.54	1.20 ± 0.45	1.20 ± 0.45	
sensation of dry mouth	1.34 ± 0.79	1.37 ± 0.73	1.59 ± 1.15	1.50 ± 1.21	1.54 ± 0.88	1.00 ± 0.00	1.20 ± 0.45	
that you can easily cry	1.70 ± 1.16	1.69 ± 1.13	1.07 ± 0.27	1.31 ± 0.79	2.31 ± 1.65	1.80 ± 1.10	1.20 ± 0.45	
To what extent do you agree with the following statements?								
I am worried about the further course of my illness due to the current situation with COVID-19	2.74 ± 1.44	2.54 ± 1.44	2.70 ± 1.59	3.37 ± 1.63	2.31 ± 1.44	3.40 ± 1.67	2.60 ± 0.89	
I am thinking of consulting with my doctor for advice and recommendations regarding my illness due to the current situation with COVID-19	2.83 ± 1.48	2.57 ± 1.42	2.70 ± 1.59	3.25 ± 1.65	2.92 ± 1.44	3.60 ± 1.34	3.00 ± 1.00	
I am afraid of coming to regular check-up with my doctor because of the COVID-19 pandemic	2.49 ± 1.53	2.20 ± 1.28	2.56 ± 1.58	2.62 ± 1.96	3.08 ± 1.44	2.20 ± 1.64	2.60 ± 1.82	*
I think there is a real risk of relapse due to the current situation with COVID-19	2.06 ± 1.42	2.00 ± 1.41	1.85 ± 1.26	2.62 ± 1.71	2.31 ± 1.65	1.80 ± 1.10	1.40 ± 0.55	

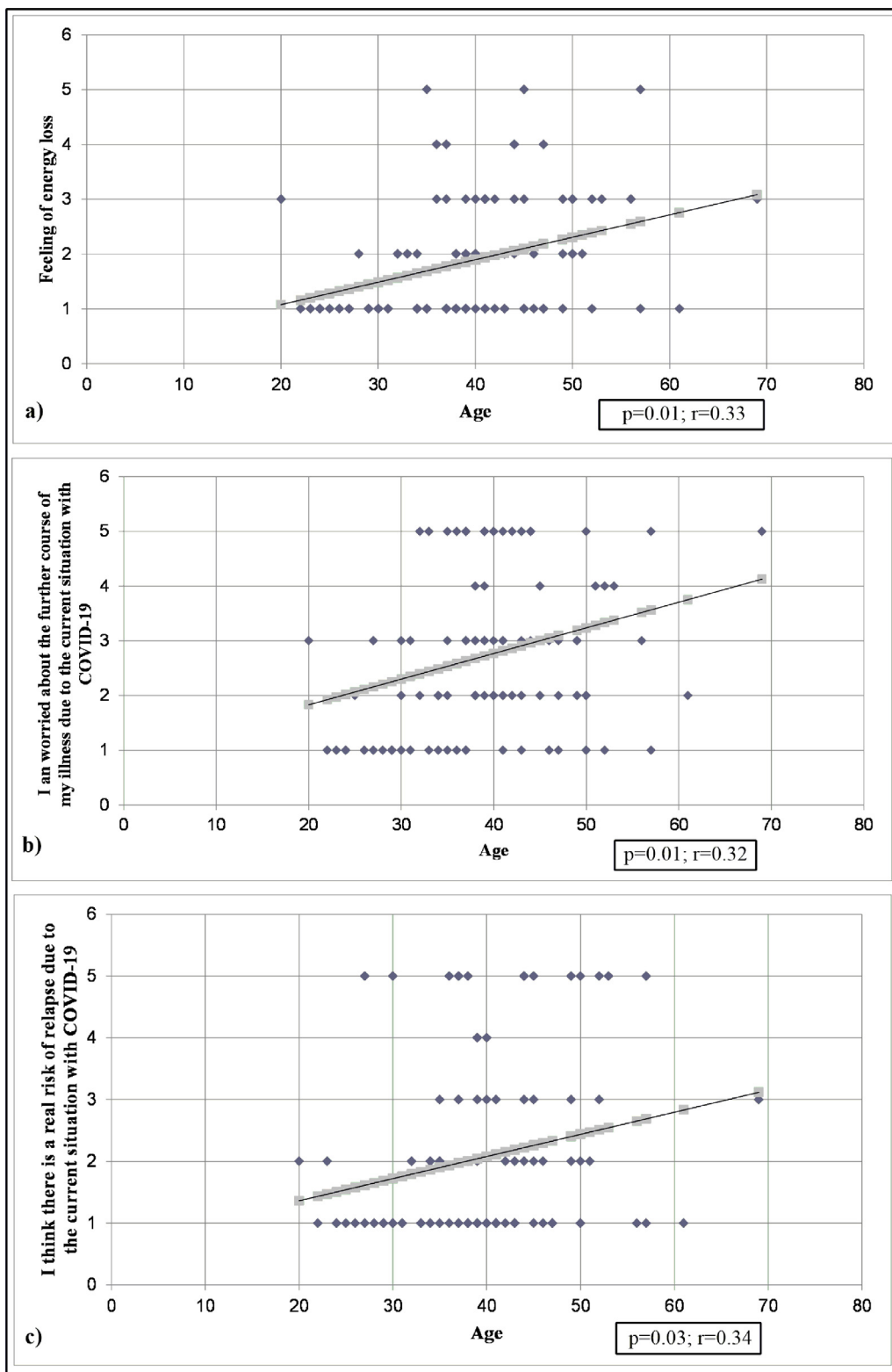χ^2 test, $p < 0,05$, SR = statistically relevant.

Fig. 2. Statistically relevant correlations between age of patients and parameters examined.

epidemiological measures prescribed by the competent institutions are respected. Secondly, patients with MS in Montenegro are aware of the risk of the new virus and therefore have taken additional measures to protect against it.

Many epidemiological measures have been focused particularly on the elderly population, and through a media campaign conducted in both Montenegro and countries in the region, it has been emphasized

that the SARS-Cov2 virus is particularly fatal for the elderly population (Liu et al., 2020). In our results (Fig. 2), a positive correlation was found between age with the following: feelings of lack of energy ($r = 0.33$; $p = 0.01$), concern for the further course of the disease ($r = 0.32$; $p = 0.01$), and feeling of the possibility of relapse due to COVID-19($r = 0.34$; $p = 0.03$).

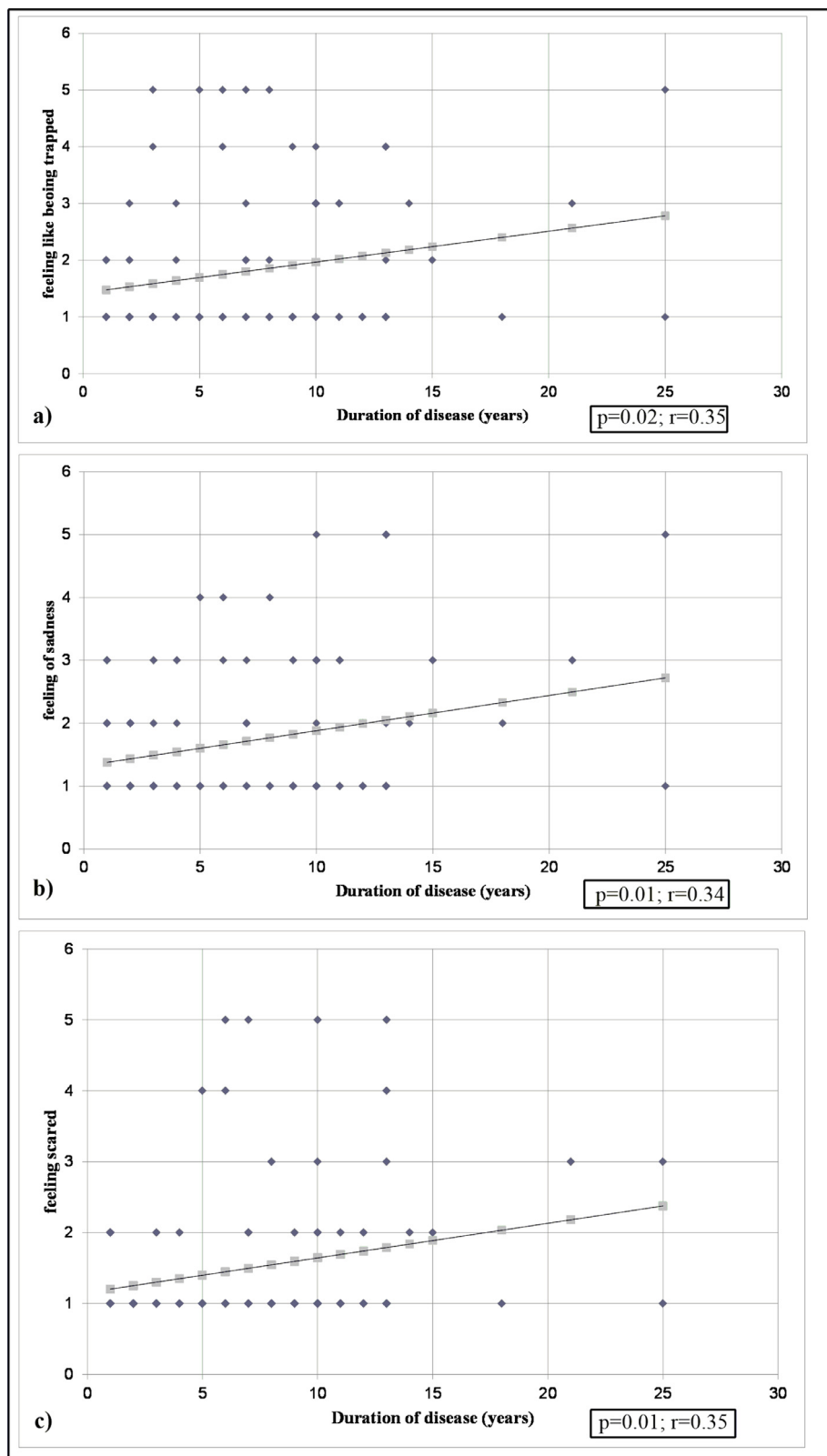With regard to the treatment that patients receive, questions from

Fig. 3. Statistically relevant correlations between duration of disease and parameters examined.

patients in daily clinical practice about the mechanism of action of the drug, side effects, expected efficacy of the drug, the possibility of developing new relapse, etc. are common. Patients with MS are generally well aware of the above. In the days of a pandemic, it is not expected that patients with MS use therapy regularly, and that they do not think about the risk of relapse. As our data in Table 3 shows, there was a statistically significant difference between the treatment groups regarding COVID-19 concerns, more frequent mood swings, memory problems, low appetite, and nausea. The same has been proven with regard to the fear of coming to regular check-ups with neurologists.

Patients using ocrelizumab are, compared to others, most concerned about COVID-19 whilst patients using interferon beta 1a i.m. statistically more often have frequent changes in their mood, memory problems, poor appetite, feeling of nausea or upset stomach. Patients on fingolimod have bigger afraid of coming to regular check-up because of the COVID-19 pandemic, when compared to other treatment groups.

When we concern disease duration as a test parameter, a positive correlation was obtained by analyzing data on disease duration (Fig. 3) and feelings of: being trapped ($r = 0.35$, $p = 0.02$), sadness($r = 0.34$, $p = 0.01$) and fearfulness ($r = 0.35$, $p = 0.01$). Thus, no statistically significant correlation was found with respect to questions about trust in the healthcare system, which means that all our patients, to a greater or lesser extent, have confidence in their medical professionals.

In our respondents, there was no significant number of patients with comorbidities (with hypertension, diabetes or chronic pulmonary disease), and therefore we were unable to perform the relevant statistical analysis according to these parameters. The same situation is with the reported symptomatology of SARS-Cov2 (fever, cough, etc.).

5. Conclusion

Montenegrin patients suffering from RR MS using DMD, generally, show concern about their disease and their future status in the era of the current epidemic. Older MS patients show higher level of solicitude due to COVID-19 pandemic. Female MS patients are not as worried about COVID-19 as male patients. Patients using ocrelizumab are most concerned about COVID-19 whilst those using interferon beta 1a i.m. statistically more often have frequent changes in their mood, memory problems, poor appetite, feeling of nausea or upset stomach. Patients on fingolimod have bigger afraid of coming to regular check-ups. On the other hand, patients show a high degree of trust in physicians and the overall health system. This obliges healthcare professionals to continue to pay a special attention to vulnerable patient groups, especially in emergency situations such as the current one. MS patients certainly belong to this group.

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CRediT authorship contribution statement

Ljiljana Radulovic: Conceptualization, Data curation, Methodology, Supervision, Writing - original draft, Writing - review & editing. **Jevto Erakovic:** Conceptualization, Supervision, Writing - original draft, Writing - review & editing. **Milovan Roganovic:** Conceptualization, Data curation, Methodology, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

X The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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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.2020.102380.

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