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Original article

Mental health status of relapsing-remitting multiple sclerosis Italian patients returning to work soon after the easing of lockdown during COVID-19 pandemic: A monocentric experience



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ABSTRACT

Background: The prolonged lockdown related to COVID-19 pandemic determined disruption of lifestyle and social isolation.

Methods: To assess the mental health status of Relapsing-Remitting Multiple Sclerosis (RRMS) patients regularly followed at the MS center of Catania (Italy) and returning to work after the easing of lockdown during COVID-19 pandemic. Then, to identify any variables associated to psychological distress. RRMS patients returning to work during the COVID-19 pandemic were invited to answer a telephonic interview consisting of the administration of the Short-Screening-Scale for DSM IV (SSS-DSM-IV), the Depression, Anxiety, Stress Scale- 21 (DASS-21) and the Insomnia Severity Index (ISI). Other information was extracted from electronic medical records.

Results: Valid and complete interviews were obtained from 432 patients (response rate 64.3%). Out of them, 277 (64.1%) were female, mean age 40.4 (SD 12.4) years. One-hundred thirty-seven (31.7%) RRMS patients received a score ≥ 4 at the SSS-DSM-IV, indicating clinically significant PTSD-like symptoms. About DASS-21, moderate-to-severe anxiety was reported by 210 RRMS patients (48.6%), moderate-to-severe depression, and moderate-to-severe stress were respectively reported by 95 (22%) and 220 (50.9%) RRMS patients. Insomnia was reported by 128 patients (29.6%). Factors associated with major severity of symptoms were: marital status, previous diagnosis of mood disorders, switching/starting Disease-Modifying Therapies in the last 12 months, and a higher level of disability measured with Expanded Disability Status Scale (for all, $p < .05$).

Conclusions: Our findings highlight the need to provide psychological support to MS patients facing the delicate phase of returning to work and to normal activities.

1. Introduction

In December 2019, the Coronavirus Disease 2019 (COVID-19) pandemic infection firstly occurred in China and, after three months, it became ubiquitous with hundreds of thousands of confirmed cases worldwide. Italy was the first European country to deal with the effects of the COVID-19 pandemic.

Prolonged lockdown and business closure determined disruption of lifestyle, social isolation, and loss on personal incomes. For people with multiple sclerosis (MS), the situation carries additional reasons for concern, due to the use of immunosuppressive therapies.

Indeed, patients affected by Relapsing Remitting MS (RRMS) are specifically vulnerable to the neuropsychiatric impact of the COVID-19

pandemic. Hence, the relationship between MS and immediate COVID-19 neuropsychiatric impact must not be neglected in this population of patients. As a matter of fact, variable degrees of neuropsychiatric involvement already exist in MS patients. Depression and anxiety result in a lower quality of life, increased fatigue and disability scores, and a more aggressive MS course (Patel et al., 2018). Notably, the neuropsychiatric correlates of MS relate to disease exacerbations and decreased treatment adherence (Mohr and Cox, 2001).

The neuropsychiatric effects of the viral pandemic on the general population have been previously demonstrated in China. In a cross-sectional study conducted during COVID-19 pandemic, 53.8% of the 1210 respondents reported a moderate-to-severe psychological impact of the outbreak (Wang et al., 2020). Another research showed anxiety

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and stress disorder rates to be 23% and 27% respectively among the medical staff of a hospital in China (Huang et al., 2020).

In Italy since May 4th, 2020 the government approved the gradual return to work and to normal activities.

The primary aim of this study was to assess the mental health status of a sample of Relapsing-Remitting Multiple Sclerosis (RRMS) patients regularly followed at the MS center of Catania (Italy) and returning to work after the easing of lockdown during COVID-19 pandemic. The secondary aim was to identify any variables associated to psychological distress that could inform clinical practice.

2. Methods

2.1. Participants

After the government approval of gradual return to work, patients with RRMS regularly followed at the tertiary MS center of Catania (Italy) were invited to participate in the study, conducted from 4 May to 22 May 2020. The short recruitment period allowed to measure the psychological distress experienced by RRMS patients in the immediacy of their return to work during COVID-19 pandemic.

Specific questionnaires were administered via telephonic interviews, since face-to-face encounters were reserved to emergencies only, in accordance with the local regulations seeking to limit the spread of COVID-19 pandemic.

2.2. Protocol approvals standard, registrations, and patient consents

The study protocol was approved by the local ethics committee (Comitato Etico Catania 1, n.85/2020/PO) Patients provided written informed consent. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and with the appropriate national regulations.

2.3. Inclusion and exclusion criteria

Patients with RRMS were selected through the consultation of the electronic medical records registered in the iMed© (Merck-Serono, Geneva) software (Trojano et al., 2019), routinely used in our MS center.

Key eligibility criteria were: 1) having a diagnosis of RRMS according to the revised 2010 McDonald criteria (Polman et al., 2011) and 2) being employed in a job before the outbreak of the pandemic.

The exclusion criteria consisted in the inability to complete the telephonic interview and the presence of a previously diagnosed cognitive impairment.

In clinical practice, patients are classified as having cognitive impairment when they fail at least three neuropsychological tests belonging to the Brief Repeatable Battery (BRB) of Neuropsychological Tests (Rao, 1990) and Stroop test (Stroop, 1935), in the light of previous studies using the same neuropsychological battery and reporting that less than 5% of healthy controls failed more than three tests (Amato et al., 2014; Amato et al., 2010; Amato et al., 2008).

2.4. Measures and outcomes

The following sociodemographic data were collected: age, gender, marital status, type of occupation, weekly working hours. The considered clinical data were: disease duration, line of prescribed Disease Modifying Treatment (DMT), starting/switching DMTs in the last year, experiencing relapses in the last 12 months, level of disability measured with Expanded Disability Status Scale (EDSS). DMTs were classified to first and second line according to the Italian regulations.

A previous diagnosis of mood or anxious disorder was recorded as a comorbidity. The following diagnostic codes, based on the 10th revision of the International Statistical Classification of Diseases and related

Health Problems (ICD-10) criteria, were considered: F31.3 Bipolar disorder, current episode depressed, mild or moderate severity, F32 Major Depressive Disorder–single episode, F33 Major depressive disorder–recurrent episodes, F41 other anxiety disorders including generalised anxiety disorder, panic disorder, and F41.8 mixed anxiety and depressive disorder.

The telephonic interview consisted in the administration of the following structured questionnaires: Short Screening Scale for DSM-IV (Bohnert and Breslau, 2011; Kimerling et al., 2006); Depression, Anxiety and Stress Scale (DASS-21) (Le et al., 2019); Insomnia Severity Index (ISI) (Tan et al., 2020; Wang et al., 2020).

The Short Screening Scale for DSM-IV (SSS DSM-IV) (Bohnert and Breslau, 2011; Kimerling et al., 2006), still reliable although not updated to DSM 5, is a brief and easy-to-administer tool assessing the presence of Post-Traumatic Stress Disorder (PTSD) symptoms. It consists of seven questions with “yes” or “no” response options. A score ≥ 4 is considered indicative of PTSD.

The presence of anxious-depressive symptoms and complaints of distress was assessed using the Depression, Anxiety, and Stress Scale (DASS-21), whereby the calculation of scores was based on previous studies (14). DASS-21 has been demonstrated to be a valid measure of mental health during COVID-19 pandemic (Tan et al., 2020; Wang et al., 2020).

The sleep quality of respondents was measured through the Insomnia Severity Index (ISI) (18). The total ISI score was divided into: no clinically significant insomnia (0–7), subthreshold insomnia (Stroop, 1935; Amato et al., 2014; Amato et al., 2010; Amato et al., 2008; Bohnert and Breslau, 2011; Kimerling et al., 2006; Le et al., 2019), moderately severe clinical insomnia (Tan et al., 2020; Wang et al., 2020; Bastien et al., 2001; Amato et al., 2019; Butler et al., 2016; Feinstein et al., 2014) and severe clinical insomnia).

2.5. Statistical analysis

The categorical variables were reported as number and percentage (%), while the continuous ones were expressed in terms of mean \pm standard deviation (SD) or median with interquartile range (IQR). The proportions were compared through chi-square test. The level of significance was set at 0.05. Multiple linear regression with a backward selection method was used to examine the association between the outcome variables (SSS-DSM-IV, DASS-21 and ISI scores) and both demographic and clinical variables. All the analyses were conducted using IBM SPSS Statistics 21.

2.6. Data availability

Anonymised data will be shared upon request from any qualified investigator for the sole purpose of replicating procedures and results presented in the report, provided that data transfer is in agreement with EU legislation on the general data protection regulation.

3. Results

3.1. Response rate, demographics and occupational characteristics

From a total cohort of 1350 patients with RRMS, 672 fulfilled the inclusion criteria. Valid and complete interviews were obtained from 432 patients, with a response rate of 64.3%.

The mean age was 40.4 (SD 12.4) years, and the majority of respondents were female ($n = 277$; 64.1%). A total of 70.3% patients were married, 17.4% were single, and 12.3% were divorced or widowed.

Concerning the occupational characteristics, 77.5% of the respondents were employees or self-employed, while 22.5% were executives and with management roles.

The mean prepandemic working hours was 41.3 (SD 4.2) hours/per

week (in Italy the average working hours per week is 40 h) All the enrolled patients had returned to work for a maximum of 10 days after the easing of lockdown and mean working hours was reduced to a mean of 36.2 (SD 3.2) hours per week.

3.2. Clinical characteristics of the enrolled RRMS patients

The mean disease duration of the enrolled patients was 64 (SD: 38.1) months. The median EDSS at last visit was 1.5 (IQR 1.00–2.5). In the last 12 months, 112 (25.9%) had experienced at least one relapse. About DMTs, all patients were treated with DMTs. Out of them, 248 patients (63.4%) were on first-line DMTs and 143 (36.6%) were on second-line DMTs. In the last 12 months, 60 (13.8%) RRMS patients switched DMTs and 52 (12.0%) started the first DMT. Concerning the considered comorbidities, 91 (21.1%) of the RRMS patients had received a diagnosis of mood disorder fitting the previously mentioned classification.

3.3. Mental health status of the patients returning to work during COVID-19 pandemic

The mean SSS-DSM IV score was 3.5 (SD: 1.0) (Table 1). One-hundred thirty-seven (31.8%) RRMS patients received a score ≥ 4 , indicating with the presence of clinically significant PTSD-like symptoms. Regarding the DASS-21, moderate-to-severe anxiety was reported by

210 RRMS patients (48.6%), while moderate-to-severe depression and moderate-to-severe stress were respectively reported by 95 (22%) and 220 (50.9%) patients. Moderate and severe clinical insomnia was reported by 128 patients (29.6%) (Table 1).

Comparing the proportion of RRMS patients with and without previous psychiatric comorbidities for each questionnaire, no differences were found at chi-square test, except for DASS-21 depression. For this item, out of 95 RRMS patients referring depression, 91 (95.7%, $p < .001$) had a previous diagnosis of mood disorder according to ICD-10.

3.4. Demographics and clinical characteristics associated with scores at multiple linear regression analysis

Demographics and clinical predictors of the score at each questionnaire are showed in Table 2.

For demographics, divorced or widowed patients had a significantly higher score at DASS-21 stress ($p = .00$) when compared to single or married respondents.

Patients with psychiatric comorbidities showed higher scores at SSS DSM IV ($p = .00$), DASS-21 depression ($p = 0.00$), DASS-21 stress ($p = .00$) and ISI ($p = .001$).

A higher EDSS was predictive of higher scores at SSS DSM IV ($p = .00$).

Patients who had started their first DMT or had switched DMT

Table 1

The SSS-DSM IV, DASS-21 and ISI scores of RRMS patients after they were approved to return to work.

	All RRMS patients (n = 432)
Short Screening Scale for DSM IV (SSS-DSM IV)	
Mean SSS-DSM IV score (SD)	3.5 (1.0)
Presence of PTSD symptoms	
No PTSD like symptoms (3 or below)	295 (68.3%)
Presence of PTSD like symptoms (≥ 4)	137 (31.8%)
Depression, anxiety and stress scale (DASS-21)	
Mean DASS-21 Anxiety score (SD)	9.3 (0.7)
DASS-21 (Anxiety)	
No (0–7)	190 (44%)
Mild (Stroop, 1935; Amato et al., 2014)	32 (7.4%)
Moderate (Amato et al., 2010; Amato et al., 2008; Bohnert and Breslau, 2011; Kimerling et al., 2006; Le et al., 2019)	150 (34.7%)
Severe (TAN et al., 2020; WANG et al., 2020; WANG C et al., 2020; Bastien et al., 2001; Amato et al., 2019)	60 (13.9%)
Extremely Severe (20+)	0 (0%)
Mean DASS-21 Depression score (SD)	10.9 (5.3)
DASS-21 (Depression)	
No (0–9)	225 (52.1%)
Mild (Amato et al., 2010; Amato et al., 2008; Bohnert and Breslau, 2011; Kimerling et al., 2006)	112 (25.9%)
Moderate (Le et al., 2019; TAN et al., 2020; WANG et al., 2020; WANG C et al., 2020; Bastien et al., 2001; Amato et al., 2019; Butler et al., 2016)	80 (18.5%)
Severe ((Feinstein et al., 2014-27)	15 (3.5%)
Extremely Severe (28+)	0 (0%)
Mean DASS-21 Stress score (SD)	20.2 (4.9)
DASS-21 (Stress)	
No (0–14)	167 (38.6%)
Mild (TAN et al., 2020; WANG et al., 2020; WANG C et al., 2020; Bastien et al., 2001)	45 (10.4%)
Moderate (Amato et al., 2019; Butler et al., 2016; Feinstein et al., 2014; https://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/DMT_Consensus_MS_Coalition.pdf ; https://www.aism.it/fase_2_aggiornate_le_raccomandazioni_globali_sul_covid_19_le_persone_con_sclerosi_multipla , https://www.aism.it/international_musc_19_platform_multiple_sclerosis_and_covid_19 , Sormani, 2020)	150 (34.7%)
Severe (26–33)	70 (16.2%)
Extremely Severe (34+)	0 (0%)
Insomnia Severity Index (ISI)	
Mean ISI score (SD)	7.2 (4.8)
No clinically significant insomnia (0–7)	
Subthreshold insomnia (Stroop, 1935; Amato et al., 2014; Amato et al., 2010; Amato et al., 2008; Bohnert and Breslau, 2011; Kimerling et al., 2006; Le et al., 2019)	180 (41.7%)
Moderately severe clinical insomnia (TAN et al., 2020; WANG et al., 2020; WANG C et al., 2020; Bastien et al., 2001; Amato et al., 2019; Butler et al., 2016; Feinstein et al., 2014)	103 (23.8%)
Severe clinical insomnia (https://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/DMT_Consensus_MS_Coalition.pdf -28)	25 (5.8%)

PTSD, post traumatic stress disorders; RRMS, relapsing remitting multiple sclerosis.

Table 2Multiple linear regression analysis between demographic, clinic characteristics and immediate mental health of RRMS patients returning to work ($n = 432$).

Variables	SSS DSM IV (Mean score) β (95% CI)	DASS – 21 Anxiety (Mean score) β (95%CI)	DASS– 21 Depression (Mean score) β (95%CI)	DASS – 21 stress (Mean score) β (95%CI)	ISI (Mean score) β (95% CI)
Marital status*	Non-significant	Non-significant	Non-significant	1.7 (1.8–2.6), $p = .000$	Non-significant
Age	Non-significant	Non-significant	Non-significant	Non-significant	Non-significant
Psychiatric comorbidity	1.4 (1.3–1.7), $p = .000$	3.1 (2.5–3.7), $p = .000$	12.4 (11.7–13.2), $p = .000$	5.0 (3.9–6.1), $p = .000$	1.2 (1.5–1.9), $p = .001$
EDSS score	2.3 (1.5–2.5), $p = .000$	Non-significant	Non-significant	Non-significant	Non-significant
Disease duration	Non-significant	Non-significant	Non-significant	Non-significant	Non-significant
n. relapses in the year before	Non-significant	Non-significant	Non-significant	Non-significant	Non-significant
Starting or changing DMT in the last 12 months	2.3(2.2–2.5), $p = .000$	3.8(3.4–4.4), $p = .000$	2.3 (1.7–2.9), $p = .000$	6.4 (5.4–7.4), $p = .000$	11.0 (10.5–11.6), $p = .000$
Line of DMT actually taken**	Non-significant	Non-significant	Non-significant	Non-significant	Non-significant

*reference group, separated/divorced/widowed; ** reference group, second line DMT. DMT, disease modifying therapy; EDSS, Expanded Disability Status Scale.

within the last 12 months had significantly higher scores at the SSS DSM IV ($p = .00$), DASS-21 anxiety ($p = 0.00$), DASS-21 depression ($p = .00$), DASS-21 stress ($p = .00$) and ISI ($p = .00$).

4. Discussion

In our cohort of RRMS patients the return to work was associated with the presence of psychiatric concerns that were higher in patients who have started /switched DMTs in the last 12 months or in those with higher levels of disability. Notably, symptoms were exacerbating in RRMS patients with previous diagnosis of psychiatric comorbidity.

Patients with MS are known to undertake cognitive impairment and maladaptive coping strategies (Amato et al., 2019; Patti, 2010) which make them even more susceptible to the detrimental neuropsychiatric effects of the outbreak. As a matter of fact, regardless to the pandemic, anxiety and depression have been reported in up to 57% (Butler et al., 2016) and 40% (Feinstein et al., 2014) of MS patients respectively and these rates are highly above those recorded in general population (Marrie, 2015).

Additionally, RRMS therapy has drastically changed in the last years, with many DMTs of increased efficacy but with a broad spectrum of action on the immune system. RRMS patients have a theoretically increased risk of being infected and they are aware of it (https://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/DMT_Consensus_MS_Coalition.pdf D'Amico, 2015, 2019). The return to normal activities is perceived as a risk, even assuming the connotations of a traumatic event, due to a sense of helplessness and inadequacy.

These feelings as reported during the interviews with the patients, have been triggered by the loss of social support during lockdown due to the suspension of physical rehabilitation therapies or group therapies and were accentuated in patients perceiving their disease as unstable due to a recent starting/switching of DMT.

With the aim of understanding the most pressing needs of MS patients during this pandemic, the Italian Multiple Sclerosis Society (AISM), the Italian Multiple Sclerosis Foundation (FISM), and the Multiple Sclerosis Study Group of the Italian Neurological Society have set up a program to help with these crucial elements in the response to COVID-19 in patients with MS (22; 23; 24).

A recent study reported more than 232 cases of COVID-19 infection among people with MS reported by Italian neurologists through a specifically designed web-based case report form (Sormani, 2020). Out of them, six were critical patients. These results must be considered only preliminary, also in the light of the speculations about the potentially protective role of some DMTs against COVID-19 infection (Sormani, 2020).

Questions about the long-term effect of this pandemic on psychiatric comorbidities, as well as on the patient–physician relationship need further investigation.

The study has some limitations. Firstly, the generalizability of the

results, because of the response rate and the telephonic modality of administration that did not permit to recur to more extended and self-reported questionnaires.

Despite the increased use of telephonic interviews in research, it is unknown whether they are as valid as diagnostic face-to-face interviews, so caution is required in assuming comparability of in-person and telephonic results of administered questionnaires.

Furthermore, the response rate does not allow us to be sure of the reported percentages. A selection bias is possible; 35,7% of patients did not participate to the study. Among them, more than 25% did not answer to telephone during the short recruitment period; about the others, approximately 10%, refused the interview because they referred to have not enough time. We cannot be sure the real reason they refused the interview, especially if this was related to a mood disorder.

However, since the telephonic interviews were administered when RRMS patients had just returned to work during COVID-19 pandemic, they did not have recall bias about their mental state, and it is an important element in PTSD evaluation.

In conclusion, MS patients, already burdened in physical and psychological terms, may be more vulnerable to the concerns and neuropsychiatric consequences related to COVID-19 pandemic, also in the light of their awareness of being potentially more likely to contract infections.

Considering the rapid spread of the disease, MS specialists should monitor MS patients for neuropsychiatric complications and implement strategies to offer psychological support when needed.

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The researchers were independent from funders and sponsors. All researchers could access all the data.

Declaration of Competing Interest

Dr. Aurora Zanghi has nothing to disclose related to this manuscript
Dr. Emanuele D'Amico has nothing to disclose related to this manuscript
Dr. Maria Luca has nothing to disclose related to this manuscript
Dr. Marco Ciaorella has nothing to disclose related to this manuscript
Dr. Lucia Basile has nothing to disclose related to this manuscript.
Dr. Francesco Patti has nothing to disclose related to this manuscript

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