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Describing post-traumatic stress disorder and its associations with depression, anxiety and insomnia: a descriptive study in Italian adults with Marfan syndrome during the COVID-19 third wave

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ABSTRACT

Objective The evaluation of post-traumatic stress disorder (PTSD), depression, anxiety and insomnia in patients with Marfan syndrome (MFS) during the third wave of the COVID-19 pandemic in a region of northern Italy (Lombardy) and the investigation of which mental health, sociodemographic and clinical factors were associated with PTSD.

Design Descriptive observational design with cross-sectional data collection procedure.

Setting A single Italian MFS-specific specialised and reference centre in Lombardy (Italy) between February and April 2021.

Participants 112 adults with MFS. The majority of participants were female (n=64; 57.1%), with a high school diploma (n=52; 46.4%) and active workers (n=66; 58.9%). The mean age was 41.89 years (SD=14.00), and the mean time from diagnosis was 15.18 years (SD=11.91).

Primary and secondary outcomes Descriptive statistics described PTSD, which was the primary outcome, as well as depression, anxiety and insomnia, which were the secondary outcomes. Four linear regression models described the predictors of PTSD total score and its three domains: avoidance, intrusion and hyperarousal.

Results One out of 10 patients with MFS had mild psychological symptoms regarding depression, anxiety and insomnia, and scores of PTSD that indicated clinical worries about the mental health status. The presence of PTSD was mainly predicted by anxiety (β=0.647; p<0.001), being older, taking psychoactive medication and being unemployed.

Conclusion Depression, anxiety and insomnia should be monitored in patients with MFS in order to minimise PTSD insurgence. Specific psychosocial interventions should be developed and tested for this population and adopted in clinical practice, given the relevance of mental health outcomes during the pandemic.

INTRODUCTION

The COVID-19 pandemic has been particularly burdening for the general public and specific groups of patients.[1–3] In this regard,

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study addressed the paucity of research on mental health outcomes in patients with Marfan syndrome.
⇒ The assessed self-report measurements are based on established, valid and reliable tools.
⇒ Some unmeasured variables, such as health engagement, health literacy and self-efficacy, might have an influence in mitigating the investigated associations.
⇒ The cross-sectional nature of the investigation limits the understanding of the investigated associations over time.

several studies focused on describing post-traumatic stress disorder (PTSD),[4 5] depression, anxiety[4] and insomnia,[5] highlighting the alarming levels of these conditions and how these psychological symptoms and some demographics are interassociated.[5] Earlier studies showed that 57.1% of individuals had poor sleep quality, 32.1% had high anxiety, 41.8% had severe distress and 7.6% had PTSD symptoms associated with COVID-19.[4 5]

The COVID-19 pandemic triggered additional difficulties for the specific subgroup of patients with Marfan syndrome (MFS) because of their need to have access to care services, which determined the additional burdens to the ones required by managing their chronic condition.[6] MFS is a rare hereditary systemic connective tissue disease determined by a mutation in the Fibrillin-1 gene that codes for the protein.[7] MFS has an autosomal dominant transmission and an incidence of 1–5/10 000 in the general population; it can become symptomatic at any age and exhibits a wide range of symptoms, even within families.[8] Major symptoms of this systemic condition might be

seen in the cardiovascular and ocular systems as well as other organs and systems, including the bones, lungs and skin. Leading cardiovascular problems include the development of thoracic aortic aneurysms, valve diseases and myocardial dysfunction, which decide high mortality and abysmal survival rates.[9]

Mental health for patients with MFS is crucial to maximising their participation in care plans. Due to the multisystemic nature of the disease and the complexity of the care needed for individuals with MFS, this syndrome needs lifetime management and therapies.[10] In this regard, understanding accurate population-based information regarding specific periods during the COVID-19 pandemic is relevant to implementing public health initiatives and adjusting some emerging issues within the delivered care.

In Italy and other European countries, the third wave of the COVID-19 pandemic (winter 2021) was a meaningful period to gather relevant information on patients with MFS, because during the third wave the patients had the possibility to be vaccinated. There was special attention to developing and sustaining services for patients with chronic conditions during this wave, because in the previous two waves services were limited due to the need to prioritise a response to patients with COVID-19.[11] In other words, information from the third wave of the COVID-19 pandemic might be considered a proxy assessment of data gathered in a period where the management of the pandemic shifted towards a long-term response, trying to normalise the services for people with chronic conditions, such as patients with MFS.

Although acknowledging the relevance for clinical practice of describing how the COVID-19 pandemic impacted mental health, including PTSD and the psychological symptoms of depression, anxiety and sleep disorders, in patients with chronic conditions,[12] the available knowledge on the specific population of patients with MFS is still highly limited as the available research mainly focused on describing the adverse clinical episodes of these patients during the COVID-19 pandemic.[6] Thus far, the literature on PTSD, depression, anxiety and insomnia in patients with MFS during the COVID-19 pandemic is highly limited.[7–10] This gap undermines the possibility of determining which aspect has to be prioritised in supporting patients with MFS by enhancing educational and motivational activities, accounting for data derived from context-specific descriptions. For this reason, this study aimed at describing PTSD, depression, anxiety and insomnia in patients with MFS during the third wave of the COVID-19 pandemic in a region of northern Italy (Lombardy) and investigating which mental health, sociodemographic and clinical factors were associated with PTSD.

METHODS
Design
This study used a cross-sectional data collection procedure with a descriptive observational design in a single Italian MFS-specific specialised and reference centre. The study was carried out in Lombardy (Italy) between February and April 2021 during the third wave of the COVID-19 pandemic. The study conduction and reporting followed the 'Strengthening the Reporting of Observational Studies in Epidemiology' checklist for cross-sectional studies (see research checklist).

Setting, sample and procedure
The involved Marfan centre uses a multidisciplinary strategy involving cardiologists, clinical geneticists, nurse practitioners and psychologists to offer clinical care for patients with MFS during yearly (or planned) follow-ups at the outpatient MFS clinic. Between February and April 2021, the number of eligible patients with MFS followed at the involved MFS-specific specialised and reference centre and who met the inclusion criteria was 154, and 112 agreed to participate in the study (response rate: 74%). All 112 participants completed the study. The inclusion criteria were being at least 18 years of age during recruitment, an MFS diagnosis[13] and proficiency in speaking, reading and writing Italian. Cognitive impairments were considered exclusion criteria, and their presence was determined by accessing the patient's health records, in which cognitive assessments were routinely performed in the MFS clinic. In this regard, information regarding a previous assessment of cognitive functioning performed in the last 2 years was available for all eligible patients with MFS.

Although acknowledging that the study was based on a single-centre and convenience sampling approach, an estimate to determine which sample size might adequately represent patients with MFS living in Lombardy (Italy) was performed by using the one proportion from a finite population approach.[14] The sample size had to be minimally estimated as the population size (roughly 1500 patients in Lombardy)*X/(X+population size−1), where X=$Z_{\alpha/2}^{2}$*(sample proportion of 8%: which was the rate of mental health patients under the 75th percentile assessed in a previous study using the 12-item Short Form Survey[10])*(1−sample proportion)/(margin of error).[2] Therefore, considering a CI of 95%, the required minimum sample size to reflect the target population with the characteristics indicated in the sample proportion was 106 patients. This estimate indicates that the enrolled sample size of 112 patients with MFS was adequate to represent the population living in Lombardy.

Enrolled patients (n=112) were asked to complete the self-report questionnaires to assess PTSD, depression, anxiety and insomnia and provide sociodemographic, clinical and anamnestic data using a web-based application provided by the hospital that complied with the General Data Protection Regulation. The self-reported clinical or anamnestic data that the patients provided to the web-based application were verified and validated with a cross-check by a clinician who had access to the electronic medical records of enrolled patients.

Table 1 Characteristics of the responders (n=112)

	n	%
Sex		
Male	48	42.9
Female	64	57.1
Education		
Lower than secondary	28	25
High school diploma	52	46.4
University	32	28.6
Occupation		
Active worker	66	58.9
Non-active worker	46	41.1
Age		
Years (mean; SD)	41.89	14
Years from diagnosis		
Years (mean; SD)	15.18	11.91
Cardiovascular comorbidities		
Yes	89	79.5
Previous abdominal surgeries		
Yes	47	42
On treatment with cardiovascular drugs		
Yes	81	72.3
Respiratory comorbidities		
Yes	20	17.9
Other comorbidities		
None	107	95.5
Thyroid	3	2.7
Neuropathies	2	1.8
Previous psychotherapy		
Yes	31	27.7
Psychiatric or psychological support during the COVID-19 pandemic		
Yes	17	12.8
Prescribed psychoactive drugs		
Yes	19	17.4
Prescribed psychoactive drugs during the pandemic		
Yes	6	7.1
Having reported at least one positive test for COVID-19		
Yes	13	11.9
Having downloaded the Italian tracking system (Immuni)		
Yes	30	27.5
COVID-19 vaccine hesitancy		
Yes	26	23.9
Great concerns about being infected by COVID-19		
Yes	43	39.4

Measurements

The characteristics of responders included sex (male, female, other), education (lower than secondary school, high school diploma and university), occupation (active vs non-active worker), age (years), years from diagnosis (years), cardiovascular comorbidities (yes, no), previous abdominal surgeries (yes, no), active treatment with cardiovascular drugs (yes, no), respiratory comorbidities (yes, no), other comorbidities (none, thyroid, neuropathies), previous psychotherapy (yes, no), psychiatric or psychological support during the COVID-19 pandemic (yes, no), prescribed psychoactive drugs (yes, no), prescribed psychoactive drugs during the pandemic (yes, no), having reported at least one positive test for COVID-19 (yes, no), having downloaded the Italian tracking system (as a proxy of health engagement) (yes, no), COVID-19 vaccine hesitancy (yes, no) and great concerns about being infected by COVID-19 (yes, no).

PTSD was assessed using the Italian version of the Impact of Event Scale-Revised (IES-R).[15] The IES-R is a self-report scale with 22 items for assessing subjective distress brought on by a specific traumatic situation or event. It has three subscales, each reflective of one of the main post-traumatic stress symptom clusters: intrusion, avoidance or hyperarousal. Unwanted and distressing memories, nightmares, flashbacks, mental anguish and/or bodily response on exposure to reminders are all intrusion symptoms. Activities intended to stop the onset of unpleasant emotions, such as fear, grief or guilt, are referred to as avoidance. Being constantly agitated, furious and paranoid is a hyperarousal symptom that profoundly impacts the mood and quality of life. Total scores over 24 indicate PTSD as a clinical concern.

Psychological symptoms of depression were assessed using the Italian version of the Patient Health Questionnaire-9 (PHQ-9).[16] PHQ-9 encompasses the criteria for depression with other depressive symptoms in a brief self-report tool (nine items), and scores equal to or higher than 10 indicate sensitivity and specificity of 88% for major depression.

Anxiety was assessed using the Italian version of the General Anxiety Disorder-7 (GAD-7) scale.[16] It is a brief self-report tool useful for assessing the severity of anxiety in clinical practice and research. It showed evidence of validity and reliability in several contexts. Adopting a cut-off of 8 is recommended to maximise sensitivity without reducing specificity and detect clinically relevant anxiety, acknowledging that scores 0–4 indicate minimal anxiety, scores 5–9 are associated with mild anxiety, scores 10–14 with moderate anxiety and scores greater than 14 severe anxiety.[17]

Insomnia was assessed using the Italian version of the Insomnia Severity Index (ISI),[18] which is a brief, reliable and valid scale aimed at facilitating screening for insomnia in general practice. Scores equal to or higher than 14 indicate moderate insomnia, and scores equal to or higher than 22 indicate severe insomnia with acceptable sensitivity and specificity derived from several studies summarised in a recent systematic review.[19]

Data analysis

The frequency distribution analysis was used to first check the data for any potential errors, outliers or missing

Table 2 Self-report assessments

	n	%
Patient Health Questionnaire-9		
Score (mean; SD)	6.48	5.32
Scores 0–4: no depression	42	37.5
Scores 5–9: mild symptoms	43	38.4
Scores 10–14: moderate symptoms	15	13.4
Scores >14: moderately severe symptoms	12	10.7
General Anxiety Disorder-7		
Score (mean; SD)	5.59	5.05
Scores 0–4 (minimal anxiety)	54	48.2
Scores 5–9 (mild anxiety)	38	33.9
Scores 10–14 (moderate anxiety)	11	9.8
Scores >14 (severe anxiety)	9	8
Insomnia Severity Index		
Score (mean; SD)	6.62	6.03
Scores 0–7 (no insomnia)	68	60.7
Scores 8–14 (subthreshold insomnia)	31	27.7
Scores 15–21 (moderate insomnia)	12	10.7
Scores 22–28 (severe insomnia)	1	0.9
Post-traumatic stress disorder (PTSD)		
Avoidance		
Score (mean; SD)	5.05	5.25
Intrusion		
Score (mean; SD)	5.52	6.09
Hyperarousal		
Score (mean; SD)	3.39	4.43
IES-R total		
Score (mean; SD)	13.96	14.78

Depression was assessed by using Patient Health Questionnaire-9 (PHQ-9), anxiety with General Anxiety Disorder-7, insomnia with Insomnia Severity Index and post-traumatic stress disorder with the Impact of Event Scale-Revised (IES-R).

information. Before performing the Kolmogorov-Smirnov test, each quantitative variable was examined for skewness and kurtosis. For normally distributed data, continuous variables were reported as mean and SD, whereas non-normally distributed variables were expressed using their median and IQR. Categorical variables have been compiled using numbers and percentages. The description of PTSD, depression, anxiety and insomnia in patients with MFS was therefore achieved using descriptive statistics.

A bivariate analysis was carried out to select the potential independent variables that might have an influence on explaining the variance of PTSD.[20] The independent variables were preliminary checked for possible collinearity using correlation analysis. In the case of highly intercorrelated potential independent variables, only one variable would be included based on a choice determined

by a theoretical rationale. Only the variables showing a significant bivariate relationship with PTSD were simultaneously included in a linear regression model performed to determine which elements had an influence on PTSD. The model estimated the regression coefficients using the least squares estimate method. The regression coefficients were standardised for the reporting, and F-statistics were used to determine the adequacy of the model in explaining sample statistics. The null hypotheses of inferential tests were two tailed with alpha set at 5%. Analytics were performed using IBM SPSS Statistics for Windows V.27 (IBM).

Patient and public involvement
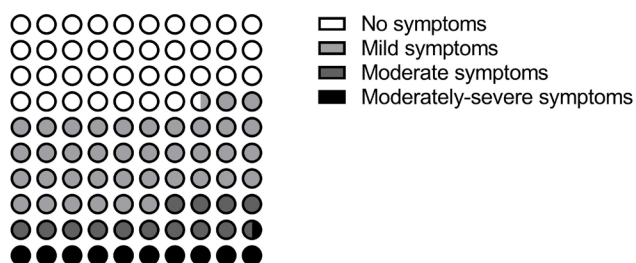Patients and members of the public were not involved in the design of this study.
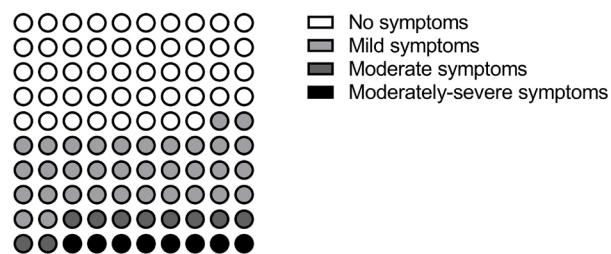
RESULTS
Sample characteristics
Table 1 summarises the sample characteristics (n=112). The majority of patients with MFS included in the sample were female (n=64; 57.1%), with a high school diploma (n=52; 46.4%) and active workers (n=66; 58.9%). The mean age was 41.89 years (SD=14.00), and the mean time from diagnosis was 15.18 years (SD=11.91). The majority of the patients had cardiovascular comorbidities (n=89; 79.5%) on treatment with cardiovascular drugs (n=81; 72.3%). Forty-seven patients (42%) reported at least one previous abdominal surgery, and 20 patients had respiratory comorbidities (17.9%). Roughly 3 out of 10 patients (n=31; 27.7%) experienced previous psychotherapy, 17 patients started psychiatric or psychological support during the COVID-19 pandemic (12.8%) and 19 patients were making use of psychoactive drugs during the data collection period (7.1%). Thirteen patients reported at least one positive test for COVID-19 (11.9%), and only 30 patients downloaded the Italian tracking system (27.5%). The levels of vaccine hesitancy were computed considering the answers of those with doubts about the safety of receiving the vaccine and those who did not want to be vaccinated, and vaccine hesitancy was found in 23.9% of the responders (n=26). Four out of 10 (n=43) patients reported great concerns about being infected (n=39.4%).

PTSD and psychological symptoms of depression, anxiety and insomnia
The mean score of the PHQ-9 (psychological symptoms of depression) was 6.48 (SD=5.32); 15 patients (13.4%) resulted to having moderate symptoms (between 10 and 14) and 12 patients (10.7%) demonstrated moderately severe symptoms (>14). The mean score of the GAD-7 (anxiety) was 5.59 (SD=5.05), with 11 patients (9.8%) exhibiting moderate anxiety (between 10 and 14) and 9 (8%) resulting to having moderately severe anxiety (>14).

Patient Health Questionnaire-9

□ No symptoms
▨ Mild symptoms
▨ Moderate symptoms
■ Moderately-severe symptoms

Total=112

General Anxiety Disorder-7

□ No symptoms
▨ Mild symptoms
▨ Moderate symptoms
■ Moderately-severe symptoms

Total=112

Insomnia severity index

□ No symptoms
▨ Mild symptoms
▨ Moderate symptoms
■ Moderately-severe symptoms
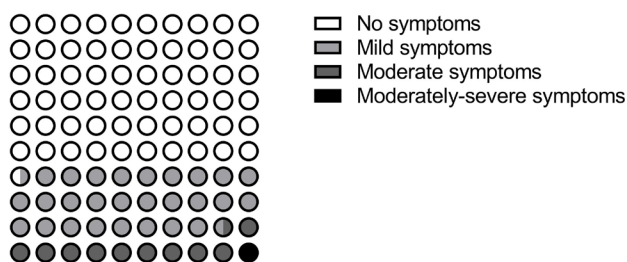
Total=112

Posttraumatic stress disorder

□ No symptoms
▨ Mild symptoms
▨ Moderate symptoms
■ Moderately-severe symptoms
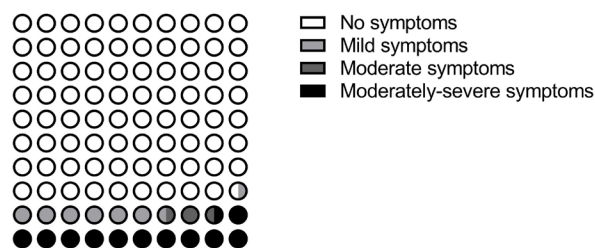
Total=112

Figure 1 Distribution of symptom dimensions.

The mean score of the ISI (insomnia) was 6.62 (SD=6.03), with 12 patients (9.8%) exhibiting moderate insomnia (between 15 and 21) and only one patient showing severe insomnia (score >22) (0.9%).

The mean total score of the IES-R (PTSD) was 13.96 (SD=14.78), the mean score of the avoidance was 5.05 (SD=5.25), intrusion was 5.52 (SD=6.09) and hyperarousal was 3.39 (SD=4.43). Overall, 23 patients (20.5%) reported IES-R scores higher than 24, indicating that PTSD is a clinical concern.

The descriptive statistics regarding PTSD, depression, anxiety and insomnia are more specifically summarised in table 2, and figure 1 shows the distribution of symptoms.

PTSD and its correlations with sample characteristics

All the correlation coefficients between PTSD (IES-R total score, avoidance, intrusion and hyperarousal) with the sample characteristics are shown in table 3.

Females exhibited higher scores of total IES-R, avoidance and intrusion; correlations were respectively r_{pb}=0.205 (p=0.030), r_{pb}=0.192 (p=0.043) and r_{pb}=0.208 (p=0.028). Higher age was significantly positively correlated with higher IES-R, intrusion and hyperarousal, and coefficients were respectively r=0.192 (p=0.043), r=0.246 (p=0.033) and r=0.153 (p=0.049). Non-active workers reported higher scores of IES-R, avoidance, intrusion and hyperarousal; coefficients were respectively r=0.340 (p<0.001), r=0.221 (p=0.003), r=0.381 (p<0.001) and r=0.350 (p<0.001).

Patients without respiratory comorbidities had lower scores of IES-R, avoidance, intrusion and hyperarousal; coefficients were respectively r_{pb}=−0.278 (p=0.003), r_{pb}=−0.187 (p=0.009), r_{pb}=−0.299 (p<0.001) and r_{pb}=0.297 (p<0.001). Patients without other comorbidities had lower scores of IES-R, intrusion and hyperarousal; coefficients were respectively r_{pb}=−0.186 (p=0.013), r_{pb}=−0.222 (p=0.016) and r_{pb}=0.232 (p=0.015). Patients with previous psychotherapy experience had higher scores of IES-R, intrusion and hyperarousal; coefficients were respectively r_{pb}=−0.216 (p=0.017), r_{pb}=−0.194 (p=0.026) and r_{pb}=0.257 (p=0.005). Patients with previously prescribed psychoactive drugs had higher scores of IES-R, avoidance, intrusion and hyperarousal; coefficients were respectively r_{pb}=−0.551 (p<0.001), r_{pb}=−0.482 (p<0.001), r_{pb}=−0.523 (p<0.001) and r_{pb}=0.544 (p<0.001). Patients with previously prescribed psychoactive drugs during the COVID-19 pandemic had higher scores of IES-R, avoidance, intrusion and hyperarousal, and coefficients were respectively r_{pb}=−0.437 (p<0.001), r_{pb}=−0.361 (p<0.001), r_{pb}=−0.366 (p<0.001) and r_{pb}=0.523 (p<0.001). Patients with great concerns about being infected by COVID-19 had higher scores of IES-R, avoidance, intrusion and hyperarousal; coefficients were respectively r_{pb}=−0.265 (p<0.001), r_{pb}=−0.272 (p<0.001), r_{pb}=−0.248 (p<0.001) and r_{pb}=0.250 (p<0.001). Psychological symptoms of depression, anxiety and insomnia were significantly positively correlated with IES-R, avoidance, intrusion and hyperarousal.

Table 3 Correlations between PTSD (IES-R total score, avoidance, intrusion and hyperarousal) with the sample characteristics

	IES-R	Avoidance	Intrusion	Hyperarousal
Sex (0=male; 1=female)	0.205*	0.192*	0.208*	0.171
Age	0.192*	0.135	0.246**	0.153*
Education	−0.032	0.014	−0.065	−0.035
Occupation (0=active worker; 1=non active worker)	0.340**	0.221*	0.381**	0.350**
Years from diagnosis	0.016	−0.001	0.062	−0.032
Cardiovascular comorbidities (0=yes; 1=no)	−0.099	−0.115	−0.076	−0.09
Previous abdominal surgeries (0=yes; 1=no)	0.059	0.026	0.058	0.088
On treatment with cardiovascular drugs (0=yes; 1=no)	−0.068	−0.128	−0.036	−0.023
Respiratory comorbidities (0=yes; 1=no)	−0.278**	−0.187*	−0.299**	−0.297**
Other comorbidities (0=yes; 1=no)	−0.186*	0.07	−0.222*	−0.232*
Previous psychotherapy (0=yes; 1=no)	−0.216*	−0.165	−0.194*	−0.257**
Psychiatric or psychological support during the COVID-19 pandemic (0=yes; 1=no)	−0.136	−0.075	−0.143	−0.168
Prescribed psychoactive drugs (0=yes; 1=no)	−0.551**	−0.482**	−0.523**	−0.544**
Prescribed psychoactive drugs during the COVID-19 pandemic (0=yes; 1=no)	−0.437**	−0.361**	−0.366**	−0.523**
Having reported at least one positive test for COVID-19	0.045	0.078	0.022	0.028
Having downloaded the Italian tracking system (Immuni) (0=yes; 1=no)	−0.054	−0.095	−0.03	−0.025
Vaccine hesitancy (0=yes; 1=no)	−0.015	−0.025	−0.009	−0.008
Great concerns about being infected by COVID-19 (0=yes; 1=no)	−0.265**	−0.272**	−0.248**	−0.250**
PHQ-9 score	0.634**	0.746**	0.718**	0.751**
GAD-7 score	0.689**	0.803**	0.760**	0.818**
ISI score	0.504**	0.573**	0.566**	0.537**

*P<0.05; **p<0.01.
Variables in bold reported at least two significant correlations with a minimum of three out of four domains of PTSD, which have been selected as independent variables for the linear regression models aimed at investigating the elements explaining the variance of PTSD.
GAD-7, General Anxiety Disorder-7; IES-R, Impact of Event Scale-Revised; ISI, Insomnia Severity Index; PHQ-9, Patient Health Questionnaire-9; PTSD, post-traumatic stress disorder.

Determinants of IES-R, avoidance, intrusion and hyperarousal

The included independent variables selected from the bivariate analysis explained 75.3% of the variance of the IES-R score, and the model adequately fitted the sample statistics ($F_{(12)}=18.081$; p<0.001). Older patients had higher IES-R ($\beta=0.145$; p=0.027) as well as non-active workers ($\beta=0.143$; p=0.034). Having a prescription of at least one psychoactive drug was slightly negatively associated with IES-R ($\beta=−0.180$; p=0.033). Anxiety (GAD-7) was the strongest positive predictor of the IES-R score ($\beta=0.647$; p<0.001).

The selected independent variables explained 54.7% of the variance accounted for the avoidance, and the model adequately fitted the sample statistics ($F_{(12)}=7.147$; p<0.001). Anxiety (GAD-7) was the only predictor of the avoidance score, where the higher the anxiety, the higher the avoidance ($\beta=0.546$; p<0.001).

The selected independent variables explained 74.3% of the variance of the intrusion score, and the model adequately fitted the sample data ($F_{(12)}=17.110$; p<0.001).

Older patients had higher intrusion ($\beta=0.196$; p=0.004) as well as non-active workers ($\beta=0.218$; p=0.002). Having a prescription of at least one psychoactive drug was slightly negatively associated with intrusion ($\beta=−0.192$; p=0.026). Anxiety (GAD-7) was the strongest positive predictor of the IES-R score ($\beta=0.640$; p<0.001).

76.6% of the variance of the hyperarousal score was explained by the selected independent variables and the model adequately fitted the sample statistics ($F_{(12)}=19.419$; p<0.001). Non-active workers had higher hyperarousal scores ($\beta=0.146$; p=0.027). Anxiety (GAD-7) was the strongest positive predictor of the IES-R score ($\beta=0.631$; p<0.001).

All the performed models are summarised in table 4.

DISCUSSION

This study focused on answering the current gap of the paucity of literature aimed at describing PTSD and the psychological symptoms of depression, anxiety and

Table 4 Determinants of IES-R, avoidance, intrusion and hyperarousal

	IES-R		Avoidance		Intrusion		Hyperarousal	
	β	P value	β	P value	β	P value	β	P value
Sex (0=male; 1=female)	0.035	0.576	0.033	0.697	0.042	0.520	0.022	0.724
Age	**0.145**	**0.027**	0.100	0.257	**0.196**	**0.004**	0.100	0.116
Occupation (0=active worker; 1=non-active worker)	**0.143**	**0.034**	0.029	0.748	**0.218**	**0.002**	**0.146**	**0.027**
Respiratory comorbidities (0=yes; 1=no)	−0.057	0.407	−0.021	0.826	−0.068	0.339	−0.075	0.270
Other comorbidities (0=yes; 1=no)	−0.018	0.778	−0.100	0.26	0.029	0.669	0.019	0.765
Previous psychotherapy (0=yes; 1=no)	0.056	0.380	0.079	0.362	0.065	0.318	0.005	0.936
Prescribed psychoactive drugs (0=yes; 1=no)	**−0.18**	**0.033**	−0.174	0.127	**−0.192**	**0.026**	−0.132	0.106
Prescribed psychoactive drugs during the COVID-19 pandemic (0=yes; 1=no)	0.067	0.408	0.067	0.543	0.137	0.100	−0.040	0.606
Great concerns about being infected by COVID-19 (0=yes; 1=no)	−0.070	0.291	−0.096	0.284	−0.053	0.434	−0.046	0.470
PHQ-9 score	0.099	0.452	0.101	0.573	0.053	0.692	0.137	0.287
GAD-7 score	**0.647**	**<0.001**	**0.546**	**0.001**	**0.640**	**<0.001**	**0.631**	**<0.001**
ISI score	−0.056	0.560	0.010	0.938	−0.052	0.594	−0.126	0.180
Model								
Test F	$F_{(12)}=18.081$; p<0.001		$F_{(12)}=7.147$; p<0.001		$F_{(12)}=17.11$; p<0.001		$F_{(12)}=19.419$; p<0.001	
R^2	0.753		0.547		0.743		0.766	

*Bold values are the statistically significant estimates.

GAD-7, General Anxiety Disorder-7; IES-R, Impact of Event Scale-Revised; ISI, Insomnia Severity Index; PHQ-9, Patient Health Questionnaire-9.

insomnia in patients with MFS during the COVID-19 pandemic. Precisely, the study was conducted during the third epidemic wave in Italy (between February and April 2021). The third pandemic wave was a specific phase in managing the challenges of COVID-19 where patients had availability of vaccines against the COVID-19 infection, and healthcare systems were trying to prioritise the needs of patients with chronic conditions, such as per the MFS.[21]

Overall, the levels of PTSD and the psychological symptoms of depression, anxiety and insomnia were consistent with those described in other populations of patients with and without chronic conditions.[22–24] Specifically, the assessed aspects might be considered as proxies of mental health, and one out of 10 patients with MFS in the specific setting of the investigation (Lombardy, Italy) suffered from moderate psychological symptoms of depression, anxiety and insomnia, and exhibited clinical concerns regarding PTSD. These results confirm the triple global public mental health challenge posed by the COVID-19 pandemic, as it is pivotal in preventing an associated rise in mental disorders and decline in mental well-being across populations, especially patients with frailty, safeguarding those with previous mental disorders from COVID-19 and

offering suitable public mental health interventions.[25] In this scenario, specific public mental health interventions are also required for patients with MFS due to poor mental health outcomes assessed through PTSD, depression, anxiety and insomnia and are expected within the range of 10%−20%, based on the results of this study.

It is plausible that hyperarousal symptoms might account for the strong contribution of anxiety in determining PTSD. Additionally, the cross-sectional design did not allow the researchers to perform additional analyses to track the changes and the inter-relationship between anxiety and hyperarousal symptoms over time. Overall, the current study portrayed that what mainly influenced PTSD was the presence of higher anxiety scores. This information completes the descriptive data sustaining the need for public mental health interventions, as these interventions might focus primarily on reducing anxiety levels in patients with MFS. For this reason, some approaches corroborated by research in other chronic populations[26] should be tested among patients with MFS and implemented in practice. In other words, there is a double challenge: one for researchers and one for clinicians. On the one hand, researchers should determine which set of psychosocial and public interventions is more effective in

reducing anxiety levels or preventing poor mental health outcomes in the specific population of patients with MFS. On the other hand, clinicians have to start working on integrating psychosocial and public interventions in the daily clinical activities of MFS clinics. The possible strategies described in other chronic populations[26] include a wide range of evidence-based possibilities,[27] which might be summarised in generic approaches, such as the therapeutic alliance, the clinician's empathy and the patient's aspirations, and theory-driven approaches, such as cognitive–behavioural therapy.[28]

Specific attention should be paid to older patients, non-active workers (retired or unemployed) and patients already treated with psychoactive drugs, indicating that they have a pre-existing psychological/psychiatric condition. These individual-level characteristics seem to be associated with frailer profiles showing higher levels of PTSD. Therefore, greater attention to screening mental health outcomes and planning interventions is required in these specific subgroups of patients.

Limitations

There are some limitations that require to be considered when interpreting the results from this study. Although the sample size was sufficient to reflect the MFS community in Lombardy adequately, the sampling process was based on a single-centre data collection approach; therefore, caution is required when generalising the results in populations different from the one represented in this study. Another limitation is due to the uncontrolled impact of some potentially unmeasured characteristics, such as health engagement, health literacy and self-efficacy. The most important limit regards the cross-sectional data collection, as no longitudinal trajectories are available to define the measured constructs over time. For instance, patients treated with psychoactive drugs in this study were associated with higher levels of PTSD; however, it is reasonable that symptomatic patients receiving proper treatment might report a steady or improving longitudinal curve over time.

CONCLUSION

One out of 10 patients with MFS reported moderate psychological symptoms of depression, anxiety and insomnia and clinical concerns regarding PTSD. For this reason, more studies on the specific population of patients with MFS are required to gather an in-depth epidemiological description of mental health outcomes in this rare genetic disease. Clinicians should pay great attention to the mental health of patients with higher levels of anxiety, who are older and non-active workers (retired or unemployed) and who are already treated with psychoactive drugs. Psychosocial and public interventions should be specifically tested in this population and implemented in clinical practice to prevent PTSD and psychological symptoms of depression, anxiety and insomnia in patients with MFS and optimise their mental health.

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