Post-traumatic stress disorder and post-traumatic stress symptoms in patients with systemic autoimmune diseases during the COVID-19 pandemic

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Abstract

Objective
The COVID-19 outbreak led to an increase in mental disorders, particularly post-traumatic stress disorder (PTSD), in the general population and especially in high-risk populations such as patients with rheumatologic conditions. Although these latters are considered vulnerable to developing PTSD, few specific data have been particularly reported in the framework of the pandemic. The aim of the present study was to investigate PTSD and posttraumatic stress symptoms (PTSS) in a sample of patients with systemic autoimmune disease (SAD), followed in the framework of a prospective observational study during the pandemic.

Methods
The PERMAS project is a prospective observational study including patients with SAD and involving the Rheumatology and the Psychiatric Clinics of the Azienda Ospedaliero Universitaria Pisana (AOUP, Pisa, Italy) and the Institute of Management of the Scuola Superiore Sant'Anna (Pisa, Italy). The assessments included: a data-sheet for sociodemographic and clinical characteristics; the Trauma and Loss Spectrum-Self Report (TALS-SR) and the Impact of Event Scale-Revised (IES-R), for PTSD and PTSS; the 36-item Short Form Survey (SF-36) to assess quality of life.

Results
The total sample consisted of 252 patients with SAD, including 131 with connective tissue disease, 101 with arthritis and 20 with systemic vasculitis. The diagnostic groups differed significantly in age (p<0.001), gender (p<0.001), prevalence of full-blown and partial PTSD (p=0.001), and other psychopathologic variables. Connective tissue disease and SF-36 were significantly associated with the TALS-SR scores in both univariate (p<0.001) and multivariate (p<0.025; p<0.001) analyses.

Conclusion
Patients with SAD, and, in particular, patients with connective tissue diseases reported an increased risk of developing stress-related psychopathological symptoms, indicating the need for special psychological monitoring of this high-risk group.

Key words
COVID-19, post-traumatic stress disorder, systemic autoimmune diseases

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What is already known on this topic
- *The COVID-19 pandemic, with its related lockdown and social distancing measures, had a dramatic impact on people's daily lives and were associated with high rates of anxiety, depressive and post-traumatic stress symptoms, particularly in more vulnerable populations*
- *Patients with rheumatic diseases represent a risk group for the development of psychopathological symptoms after traumatic experiences.*
- *Lifelong post-traumatic stress symptoms are associated with worsening of rheumatic disease and poorer quality of life in patients with rheumatic disease*

What this study adds
- *In the context of the COVID-19 pandemic, patients with systemic autoimmune diseases (SAD) had a high prevalence of posttraumatic symptoms, with differences between diagnostic groups. A particularly high risk was found in individuals with connective tissue diseases*

How this study might affect research, practice or policy
- *Clinical treatment pathways for patients with SAD should include psychopathological risk stratification and mental health care to improve outcomes and quality of life in these patients*

Introduction

The COVID-19 pandemic has represented an unprecedented event that has been associated with the development of anxiety, depressive and post-traumatic stress symptoms (PTSS) with high prevalence rates also being reported when compared to other mass trauma (1-4). Pandemic-related PTSS rates were found to be around 15% in the general population in the early phases of the pandemic (5) and predisposing factors that may increase the risk for developing PTSS have been explored. In particular, women have been confirmed to be more vulnerable to developing PTSS (6) also when exposed to pandemic related trauma, besides reporting greater symptoms of re-experiencing, hyperarousal and negative mood alterations when exposed to lockdown measures (7). Other socio-demographic variables, such as younger age, living alone in the absence of family support and precarious financial conditions due to the pandemic (7-10) have also been reported to favor the onset of PTSS and lower level of education was related to pandemic induced post-traumatic stress disorder (PTSD) (11).

Pandemic-related PTSS and PTSD have also been suggested to affect specific clinical populations that may have been more severely exposed to the risks related to a possible COVID contagion or to the effects of the restrictive containment measures adopted by governments worldwide. Patients affected by rheumatic diseases represent a population at risk of developing psychopathological symptoms in the aftermath of traumatic exposures (12, 13), besides showing both a worsening of the rheumatic disease severity and worse quality of life have been reported in pre-pandemic studies (14, 15). During the Pandemic, several studies confirmed a greater vulnerability to mental health disturbances in patients affected by rheumatic diseases (16-22). Indeed, patients with a pre-existing rheumatological disease experienced higher levels of anxiety and depression compared to healthy controls (20), and existing anxiety-depressive symptoms increased (22). Likewise, in a sample of 771 patients with rheumatic diseases, Ingegnoli *et al.* (18) reported PTSD in 28% of the sample. In addition, difficulties in accessing care, especially in the first phase of lockdown as well as the higher risk of severe COVID-19 complications due to the underlying condition and immunosuppressive treatments have been identified as contributors to the psychological distress of these patients (16).

The aim of the present study was to investigate the occurrence of PTSD and PTSS related to the Pandemic, besides their associated features, in a sample of patients with systemic autoimmune disease (SAD) followed in the outpatient Rheumatologic Unit of a major university hospital in Italy.

Materials and methods

The present analysis is part of the PERMAS project, an observational study foreseeing prospective enrolment of patients and collection of clinical, psychological and socio-economic data related to the COVID-19 pandemic. PERMAS was performed in accordance with the directives issued by the declaration of Helsinki and the Nuremberg Code and approved by Regional Ethics Committee for Experimentation Clinic of the Tuscany Region, Area Vasta Nord Ovest section on 11/02/2021, protocol no. 19233.

The study sample included adult subjects diagnosed with systemic autoimmune disease (SAD) consecutively enrolled at the outpatients Rheumatology Unit of the AOUP from May 2021 to June 2022 after signing a written informed consent.

Exclusion criteria were any limitation in verbal communication that compromised the subject's ability to follow the protocol assessment (for example a poor knowledge of the Italian language) and/or lack of collaboration skills. Patients enrolled were divided into three subgroups upon the specific Rheumatologic diagnosis: connective tissue disease, inflammatory arthritis, and systemic vasculitis.

Instruments and assessment

Patients enrolled were asked to fill a dedicated questionnaire including ad-

Table I. Descriptive data and comparisons between diagnosis groups.

	Connective tissue disease n=131	Arthritis n=101	Systemic vasculitis n=20	Overall n=252	*p*-value
Age, years	49.18 ± 13.28*§	55.40 ± 12.65	51.15 ± 12.27	51.83 ± 13.23	**<0.001**
Sex, female (%)	118 (90.1%)*§	61 (60.4%)	7 (35.0%)	186 (73.8%)	**<0.001**
IES-R Total score	20.91 ± 14.93	19.56 ± 15.95	21.40 ± 17.51	20.41 ± 15.51	0.774
IES-R Avoidance	0.966 ± 0.634	0.939 ± 0.769	0.856 ± 0.617	0.95 ± 0.69	0.617
IES-R Intrusive thought	0.895 ± 0.795	0.798 ± 0.757	0.938 ± 0.919	0.86 ± 0.79	0.588
IES-R Hyperarousal	1.004 ± 0.860	0.944 ± 0.845	1.175 ± 1.082	0.99 ± 0.87	0.547
TALS-SR Loss events	4 ± 2.21	3.38 ± 2.08	4.5 ± 2.27	3.76 ± 2.18	0.079
TALS-SR Grief reactions	10.55 ± 4.98	9.41 ± 5.25	10.5 ± 6.06	10.11 ± 5.18	0.274
TALS-SR Potentially traumatic events	3.40 ± 2.52	2.59 ± 2.49†	4.53 ± 4.33	3.16 ± 2.72	**0.009**
TALS-SR Reaction to losses and PTE	5.42 ± 3.91	4 ± 3.96	4.3 ± 4.19	4.76 ± 4	**0.023**
TALS-SR Re-experiencing	1.80 ± 2.06*	1.15 ± 1.81	1.8 ± 2.71	1.54 ± 2.03	**0.044**
TALS-SR Avoidance and numbing	2.34 ± 2.54	1.63 ± 2.37	2.3 ± 3.44	2.06 ± 2.57	0.102
TALS-SR Maladaptive coping	0.39 ± 0.77	0.19 ± 0.50†	0.7 ± 1.17	0.33 ± 0.73	**0.007**
TALS-SR Arousal	1.43 ± 1.60	1.09 ± 1.52	1.35 ± 1.81	1.29 ± 1.59	0.256
TALS-SR Global	30.07 ± 16.08*	23.54 ± 25.70	30.35 ± 22.22	27.48 ± 16.73	**0.009**
PTSD symptomatological diagnosis (partial + full blown)	81 (61.8%)*	40 (39.6%)	7 (35.0%)	128 (0.51%)	**0.001**
No PTSD diagnosis	50 (38.2%)	61 (60.4%)	13 (65.0%)	124 (0.49%)	
Relative COVID - yes	42 (32.06%)	29 (28.71%)	6 (30%)	77 (30.56%)	0.854
Caught COVID - yes	18 (13.74%)	7 (6.93%)	5 (25%)	30 (11.9%)	**0.044**
Hospitalised COVID - yes	0 (0%)	1 (14.29%)	0 (0%)	1 (3.33%)	0.400
Quarantine - yes	28 (21.37%)	19 (18.81%)	7 (35%)	54 (21.43%)	0.279
Ongoing psychiatric therapy - yes	9 (6.87%)	4 (3.96%)	2 (10%)	15 (5.95%)	0.339
Started psychiatric therapy - yes	1 (11.11%)	1 (25%)	1 (50%)	3 (20%)	0.499
Modified psychiatric therapy - yes	3 (33.33%)	0 (0%)	2 (100%)	5 (33.33%)	0.075
Suspended rheumatic treatment - yes	20 (15.27%)	27 (26.73%)	7 (35%)	54 (21.43%)	**0.031**
Disease flare - yes	37 (28.24%)	35 (34.65%)	9 (45%)	81 (32.14%)	0.266
Hospitalised because of flare - yes [1] [2]	6 (16.22%)	0 (0%)	2 (22.22%)	8 (9.88%)	**0.015**

TALS-SR: Trauma and Loss Spectrum-Lifetime version; PTE: potentially traumatic events.
The results are presented in mean and standard deviation for continuous variables and as frequency and percentage for categorical ones.
*p<0.05 for *post-hoc* comparisons of arthritis *vs*. connective tissues disease.
§p<0.05 for *post-hoc* comparisons of connective tissues disease *vs*. systemic vasculitis.
†p<0.05 for *post-hoc* comparisons of arthritis *vs*. systemic vasculitis.

hoc developed questions as well as validated instruments to collect information about demographics, experience during the COVID-19 pandemic, quality of life (QoL), fatigue, sleep quality, anxiety and depression, a psychological evaluation to assess the impact of the pandemic as well as facts related to the use of healthcare services, and need for assistance in the six months preceding the assessment.

Psychological assessments included: the Impact of Events Scale Revised (IES-R), and Trauma and Loss Spectrum-Self Report (TALS-SR), to examine acute and lifetime post-traumatic stress symptoms, respectively.

The IES-R (23) is a self-assessment questionnaire used as PTSD screening, which refers to the last seven days prior to filling out the survey. It is a 22-item Likert scale ranging from 1 (never) to 5 (very often) and divided into 3 subscales: intrusion symptoms, avoidance, and hyperarousal. A final IES-R score higher than 23 identified patients with Post-Traumatic Stress Symptoms, while a score higher than 32 detected a probable PTSD diagnosis.

The TALS-SR (24, 25) investigates the typical, atypical, attenuated and subthreshold symptoms of the Post-Traumatic Stress Spectrum providing a complete dimensional approach to the psychophysiology of the individual. This self-assessment questionnaire includes 116 items with a dichotomous response (yes/no) organised in nine domains: (1) loss events, (2) grief reactions, (3) potentially traumatic events, (4) reactions to losses or upsetting events, (5) re-experiencing, (6) avoidance and numbing, (7) maladaptive coping, (8) arousal, (9) personal characteristics/risk factors.

The TALS-SR was adapted for the COVID-19 pandemic. In line with previous studies (26-28) symptomatological PTSD prevalence rates according to the DSM-5 criteria, were assessed by means of a matching between the TALS-SR and the DSM PTSD symptoms. In particular, in the present study, a symptomatological DSM-5 diagnosis of PTSD was assessed by using the following matching between each of the DSM-5 symptoms criteria and the corresponding TALS-SR item:
DSM-5 Criterion B (B1*=80°; B2* =77°; B3* =79°; B4* =78°; B5* =81°);
DSM-5 Criterion C (C1* =86°; C2* =87° and/or 88° and/or 89°);
DSM-5 Criterion D (D1* =90°; D2* =95°; D3* =85°; D4* =96°; D5* =91°; D6* =93°; D7* =92°);
DSM-5 Criterion E (E1* =108°; E2* =99° and/or 100° and/or 102° and/or

Table II. Descriptive data and comparisons between genders within each diagnosis group.

	Gender group	Connective tissue disease n=131	Arthritis n=101	Systemic vasculitis n=20
IES-R Total score	Female	22.15 ± 16.80	21.53 ± 15.18	19.43 ± 11.24
	Male	*15.63 ± 13.67*	*15.23 ± 11.42*	*22.46 ± 20.47*
	p-value	0.086	**0.035**	0.674
IES-R Avoidance	Female	1.05 ± 0.80	0.99 ± 0.64	0.875 ± 0.53
	Male	*0.778 ± 0.69*	*0.740 ± 0.52*	*0.846 ± 0.68*
	p-value	0.132	0.079	0.918
IES-R Intrusive thoughts	Female	0.90 ± 0.81	0.91 ± 0.81	0.77 ± 0.55
	Male	*0.65 ± 0.65*	*0.721 ± 0.64*	*1.03 ± 1.08*
	p-value	0.333	0.096	0.482
IES-R Hyperarousal	Female	0.70 ± 0.67	0.59 ± 0.67	1.24 ± 1.23
	Male	*0.778 ± 0.69*	*0.740 ± 0.52*	*0.846 ± 0.68*
	p-value	**0.036**	**0.012**	0.676
TALS-SR Global	Female	30.36 ± 15.92	28.23 ± 15.88	30 ± 16.69
	Male	*27.46 ± 17.91*	*16.4 ± 12.54*	*30.54 ± 22.35*
	p-value	0.585	**<0.001**	0.955
TALS-SR Loss events	Female	4.08 ± 2.20	3.61 ± 2.11	4.28 ± 2.14
	Male	*3.31 ± 2.25*	*3.05 ± 2.02*	*4 ± 2.42*
	p-value	0.260	0.187	0.790
TALS-SR Grief reactions	Female	10.61 ± 4.93	10.62 ± 5.58	9.71 ± 2.87
	Male	*10.08 ± 5.54*	*7.39 ± 3.97*	*11 ± 7.54*
	p-value	0.745	**0.002**	0.612
TALS-SR Potentially traumatic events	Female	3.42 ± 2.61	2.85 ± 2.48	4.29 ± 3.90
	Male	*3.23 ± 1.79*	*3.21 ± 2.48*	*4.7 ± 4.81*
	p-value	0.742	0.226	0.845
TALS-SR Reaction to losses and PTE	Female	5.49 ± 3.89	5.04 ± 4.36	4.14 ± 4.34
	Male	*4.77 ± 4.26*	*2.40 ± 2.58*	*4.38 ± 4.29*
	p-value	0.565	**<0.001**	0.907
TALS-SR Re-experiencing	Female	1.69 ± 2.06	1.87 ± 2.08	1.71 ± 2.36
	Male	*0.32 ± 0.83*	*1.15 ± 1.62*	*1.84 ± 2.96*
	p-value	0.168	**<0.001**	0.915
TALS-SR Avoidance and numbing	Female	2.16 ± 2.64	2.41 ± 2.54	2.29 ± 3.59
	Male	*0.82 ± 1.60*	*1.69 ± 2.56*	*2.31 ± 3.50*
	p-value	0.349	**0.002**	0.990
TALS-SR Maladaptive coping	Female	0.23 ± 0.49	0.36 ± 0.72	0.71 ± 1.25
	Male	*0.13 ± 1.60*	*0.69 ± 2.56*	*0.69 ± 3.50*
	p-value	0.305	0.315	0.970
TALS-SR Arousal	Female	1.44 ± 1.74	1.47 ± 1.61	1 ± 1.53
	Male	*0.55 ± 0.88*	*1.08 ± 1.50*	*1.54 ± 1.98*
	p-value	0.381	**0.001**	0.510

TALS-SR: Trauma and Loss Spectrum-Lifetime version; PTE: potentially traumatic events.
The results are presented in mean and standard deviation for continuous variables and as frequency and percentage for categorical ones.
Lower age, female gender, rheumatic disease diagnosis (connective tissue disease), marital status (widow), occupation level (housewife, retired), ongoing psychiatric therapy, disease flare-up and SF-36 MCS were significantly associated with the TALS-SR (2 classes= no PTSD diagnosis *vs*. partial and full-blown PTSD diagnosis) at univariate analysis, *s*ee Table III.

103° and/or 104°; E3* =106°; E4* =107°; E5* =105°; E6* =109°).
*DSM-5 symptom; °n of TALS-SR item.

According to previous literature on DSM-5 criteria, a partial PTSD diagnosis was also considered by means of the fulfillment of 3 out of 4 of the B-E symptomatological criteria (29). The TALS-SR presented good intra-class correlation coefficients (from 0.934 to 0.994) with SCI-TALS, the interview version used for assessing post-traumatic stress symptomatology. Similarly, SCI-TALS showed a good internal consistency (Kuder-Richardson coeffi-cient exceeding the minimum standard of 0.50 for each domain).

The Quality of life (QoL) (30) was assessed using 36-Item Short Form Survey (SF-36v2), a well-established and validated instrument composed of 36 questions grouped into eight domains of health which also allow derivation of two different composite scores to evaluate physical and mental health (PCS and MCS).

An electronic version of the questionnaire was implemented using the EU-survey and dedicated workstations with tablets were arranged at the Rheumatologic Unit of the AOUP, to allow patients complete self-assessments during the waiting time for the usual follow-up visit. On the same day, clinical rheumatological evaluation was then performed to assess specific aspects of current disease activity, previous organ involvement, ongoing therapies, and hospitalisation.

Statistical analysis
All data were analysed using R statistical software version 4.2.0 (31).
Patients' characteristics are described as numbers and percentage or mean and standard deviation for categorical and continuous variables respectively. The prevalence of PTSD was calculated using the aforementioned cut-off for both IES-R and TALS and comparisons of patients' characteristics between and among subgroups were performed using Chi-square test or Fisher test and independent-sample t-test or one-way analysis of variance (ANOVA) as appropriate. Tukey's range test was used for the *post-hoc* comparisons.
To explore potential patients' characteristics associated with psychiatric symptoms (according to the TALS-SR), univariate and multivariate binary logistic regression were used as appropriate. In both cases, with the exception of age, gender and marital status that were forced in multivariate models, only variables with $p<0.1$ at univariate analysis were considered to be included in multivariate models and variables causing collinearity were excluded on the basis of the variance inflation factor (VIF). Results from models were presented in terms of odds-ratio (OR) and 95% con-

Table III. Univariate logistic regression for TALS-SR.

	OR (95%CI)	*p*-value
Age	0.970 (0.950-0.989)	**0.002**
Female	3.502 (1.934-6.550)	**<0.001**
Diagnosis		
Inflammatory arthritis	(ref)	
Connective tissue disease	2.470 (1.457-4.232)	**0.001**
Systemic vasculitis	0.821 (0.287-2.187)	0.700
Marital status		
Single	(ref)	
Married or cohabitant	0.573 (0.293-1.095)	0.096
Divorced	0.720 (0.258-2.024)	0.529
Widow	0.171 (0.024-0.800)	**0.039**
Educational level		
Middle school or less	(ref)	
High school diploma	0.961 (0.536-1.721)	0.895
College degree or more	0.980 (0.488-1.967)	0.954
Occupation level		
Employed	(ref)	
Housewife	2.451 (1.092-5.929)	**0.036**
Unemployed	1.079 (0.391-3.024)	0.883
Unable to work	1.918 (0.180-41.812)	0.590
Retired	0.346 (0.165-0.693)	**0.004**
Student	-	-
Diagnosed psychiatric disease - yes	2.044 (0.985-4.442)	0.061
Relative COVID - yes	0.992 (0.580-1.698)	0.976
Caught COVID - yes	0.520 (0.229-1.126)	0.103
Ongoing psychiatric therapy - yes	4.172 (1.286-18.654)	**0.030**
Suspended immunosuppressive treatment - yes	0.723 (0.392-1.321)	0.293
Disease flare-up - yes	1.783 (1.0.46-3.072)	**0.035**
Hospitalised after flare-up - yes	0.622 (0.137-2.821)	0.525
Quarantined	1.160 (0.635-2-131)	0.630
SF36 Physical Component Score	0.979 (0.952-1.006)	0.125
SF 36 Mental Component Score	0.921 (0.893-0.948)	**<0.001**

fidence interval (CI). The level of significance was set for *p*-value<0.05. The SF-36 health survey summary scores were calculated using PRO CoRE 2.1, Smart Measurement® System.

Results

A total of 252 patients were consecutively enrolled, 186 females and 66 males, with a mean age of 51.83±13.23. Mean age for females was 50.76±13.74 years and for males 54.82±11.28 (*p*=0.019). The sample included 131 patients with connective tissue diseases (systemic lupus erythematosus, Sjögren syndrome, undifferentiated connective tissue disease, systemic sclerosis, idiopathic inflammatory myopathy); 101 patients with inflammatory arthritis (rheumatoid arthritis or spondyloarthritis); and 20 patients with systemic vasculitis (Behçet's disease, giant cell arteritis, ANCA-associated vasculitis). A detailed description of patients' characteristics is reported in Table I.

Age and gender significantly differed among diagnostic groups (*p*<0.001 for both), see Table I. In particular, age was significantly higher in the arthritis group (mean age 55.40±12.65 years old) when compared with the connective tissue disease group (mean age 49.18±13.28 years old, *p*=0.001) and the prevalence of female gender was significantly higher in the connective tissue disease group (90.1%) compared with both the systemic vasculitis (35.0%) and arthritis (60.4%) groups.

Diagnostic groups differed significantly in the psychological variables including the TALS-SR Potentially traumatic events (*p*=0.009), Reaction to losses and potentially traumatic events (*p*=0.023), Re-experiencing (*p*=0.044) and Maladaptive coping (*p*=0.007) domains, in the TALS-SR total score (*p*=0.009), as well as in the prevalence

of Full-blown and partial PTSD as evaluated through the TALS-SR (*p*=0.001), See Table I. *Post-hoc* analyses showed that the arthritis group showed lower scores in the TALS-SR potentially traumatic events (mean score 2.59±2.49) TALS-SR Maladaptive coping domain (mean score 0.39±0.77) than the systemic vasculitis group (mean score = 4.53±4.33, *p*=0.018 and 0.70±1.17, *p*=0.011, respectively). Likewise, the arthritis group showed significantly lower scores in the TALS-SR *Re-experiencing* domain (mean score = 1.15±1.81) and total score (mean score 23.54±25.70) compared with the connective tissue disease group (mean score = 1.80±2.06, *p*=0.040 and mean score 30.07±16.08, *p*=0.027, respectively). Consistently, the prevalence of full-blown and partial PTSD, as evaluated through the TALS-SR, was significantly lower in the arthritis (39.6%) vs connective tissue disease (61.8%) groups (*p*=0.003), see Table I.

Gender differences also emerged in psychopathological variables across the three different diagnostic groups (Table II). In details, significant gender differences were found in the arthritis group with females reporting significantly higher scores in the IES-R Total (*p*=0.035) and Hyperarousal domain (*p*=0.012) scores, as well as in the TALS-SR total (*p*<0.001) and Grief reactions (*p*=0.002), Reaction to losses and potentially traumatic events (*p*<0.001), Re-experiencing (*p*<0.001), Avoidance and numbing (*p*=0.002) and *Arousal* (*p*=0.001) domains scores. In the arthritis group, males generally showed significantly lower scores than females, except for the IES-R Hyperarousal domain, the only variable in which males showed higher scores than females. In the group of connective tissue disease, significant gender differences emerged only for IES-R Hyperarousal (*p*=0.036), with males having higher scores than females. In the systemic vasculitis group, no significant gender differences were found. At multivariate analysis only being diagnosed with connective tissue disease and having lower SF36 MCS remained significantly associated with the TALS-SR (2 classes = no PTSD diagnosis *vs.*

Table IV. Multivariate logistic regression for TALS-SR.

	OR (95%CI)	*p*-value
Age	0.996 (0.964-1.030)	0.827
Female	1.704 (0.766-3.844)	0.193
Diagnosed rheumatic disease		
Arthritis	(ref)	
Connective tissue disease	2.154 (1.106-4.260)	**0.025**
Systemic vasculitis	0.567 (0.138-2.069)	0.407
Marital status		
Single	(ref)	
Married or Cohabitant	0.488 (0.190-1.229)	0.130
Divorced	0.840 (0.224-3.120)	0.794
Widow	0.175 (0.018-1.262)	0.101
Occupation level		
Employed	(ref)	
Housewife	2.568 (0.972-7.232)	0.064
Unemployed	0.880 (0.272-2.870)	0.830
Unable to work	-	-
Retired	0.723 (0.252-2.045)	0.541
Student	-	-
Diagnosed psychiatric disease - yes	0.979 (0.351-2.749)	0.967
Caught COVID - yes	0.484 (0.174-1.281)	0.151
Ongoing psychiatric therapy - yes	3.198 (0.675-18.315)	0.157
Disease flare-up - yes	1.491 (0.755-2.965)	0.250
SF 36 Mental Component Score	0.917 (0.883-0.950)	**<0.001**

partial and full-blown PTSD diagnosis), see Table IV.

Discussion

To the best of our knowledge, this is the first study aimed at comparing COVID-19 pandemic related PTSD and PTSS across patients with different rheumatic diseases, namely: inflammatory arthropathies, connective tissue disease, and systemic vasculitis. Our results showed a higher prevalence of full-blown and partial PTSD diagnosis in the connective tissue disease group. As expected, statistically significant younger age and higher prevalence of females emerged in the connective tissue disease group compared with the arthritis group, suggesting a possible more severe impact on the psychological effects of the COVID-19 pandemic. Indeed, previous studies have demonstrated that younger age and female gender represent important predictors for PTSD development (4, 11, 32-34). Likewise, several studies performed during the pandemic reported higher levels of PTSS among adolescents and young adults (7, 8) as well as women (6-35). Consistently, among patients with rheumatic diseases, such as inflammatory arthritis, connective tissue disease, primary fibromyalgia,

and miscellaneous disease, women and young adults showed elevated levels of PTSS during the Pandemic (16, 22). Furthermore, Maguire & O'Shea 2020 (36) found significantly higher rates of decline in general health, mood disturbance, and increased disease activity during the period of social isolation in a cohort of females with arthritis. Among the factors that may increase the susceptibility to PTSS in the female gender, it has been proposed that women tend to be more reactive to stress and have an anxious temperament that may predispose them to the development of PTSD (6). Similarly, younger age could have favored the risk of stress symptomatology due to the greater accessibility to the web and the interruption of routine and sociability (8).

Nevertheless, it is important to highlight that in our study we found that the connective tissue disease group was associated with an increased prevalence of full or partial PTSD compared to the arthritis group, even in regression models adjusted for gender and age, by which this difference may not be only attributed to demographic factors (age and gender).

Interestingly, previous studies reported that resilience levels achieved in patients

with inflammatory arthritis immediately after the first wave of COVID-19 pandemic were significantly higher than in controls (37). Ciaffi *et al*., 2020 (37) hypothesise that patients with inflammatory arthritis implement cognitive, behavioural, emotional, and active coping responses against the stress and challenges related to the disease, thus they might be better equipped to deal with the stress caused by the COVID-19 pandemic when compared to healthy controls. However, in our study differences emerged between the arthritis and the connective tissue disease groups, suggesting that even if both are chronic diseases, the latter could be at higher risk to develop stress-related disorders.

Previous studies found a high prevalence of stress-related psychological symptoms in connective tissue diseases; 38.7% of systemic lupus erythematosus patients screened positive for PTSD during the COVID-19 pandemic in a nationwide survey using the Post-Traumatic Stress Disorder (PTSD) Checklist for DSM-5. Recently, Moroni *et al*. (12) found 31% of patients with PTSD with the TALS-SR in a sample of 99 subjects with systemic lupus erythematosus. As a matter of fact, there is a growing body of evidence linking psychosocial trauma and associated stress responses and systemic lupus erythematosus onset and course (38).

The CTDs represent a group of systemic autoimmune conditions that share some common aspects: they are rare or low prevalence diseases with multiorgan involvement. In these diseases, infective complications are one of the major causes of mortality and morbidity; the infection risk is strictly related to the chronic use of steroid and immunosuppression as well as the underlying immune-system dysfunction. Thus, it is not surprising that this group of patients perceived a higher risk of severe COVID-19 complications due to their underlying condition, thus experiencing the pandemic as a particularly stressful situation. For the same reasons, it can also be assumed that doctors themselves have transferred a greater sense of risk and uncertainty to this type of patient than to others. Moreover, the younger age of the CTDs group could have been

responsible for higher COVID-19 exposure risk due to the need to continue with their daily activities, possibly increasing fear and uncertainty. Lastly, the low prevalence of connective tissue diseases with respect to the inflammatory arthritis group could have played a role. Indeed, it has been shown that COVID-19 had significant personal and social impact especially on people living with rare rheumatic diseases such as connective tissue diseases as it exacerbates the many challenges the patients have to face in their daily living (39-41). Moreover, in the first phase of the pandemic, knowledge of the impact of the disease in rare diseases was few and fragmented; in the complete absence of guidelines, even medical decisions had to be based on the experience of the individual, generating further disorientation and insecurity in the patient. The study has some limitations; first of all, the sub-group of patients with a diagnosis of vasculitis is very small and clinically heterogeneous, thus some specific aspects of their response to the stress could have not been properly captured by the analysis. Moreover, our study did not include a healthy control group, but only literature-based comparisons could be made.

However, our study provided a large comparison between different diagnoses, highlighting the importance of disease-specific factors that can contribute to psychological response to stressful events. Other points of strength of this study are the prospective patients' enrollment, with face-to-face clinical data collection and assessments and the use of different, complementary instruments for a better understanding of the multifaceted aspect of the stress-related psychopathology.

Conclusion

The COVID-19 pandemic resulted in a severe burden for patients with systemic autoimmune diseases causing a high psychological distress. In particular, our study demonstrated a higher risk of stress-related psychopathology in patients with connective tissue diseases, suggesting the need for special psychological monitoring in this high-risk group.

Better understanding of the psychological impact of stressful events on these patients will allow for better prevention and care in times of crisis.

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