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Title page

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Post-Traumatic Stress Disorder in Patients with Rheumatic Disease during the COVID-19 Outbreak

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Shortened title:

PTSD in RD Patients during the COVID-19 Outbreak

Abstract

Objective: The COVID-19 pandemic is not only a traumatic event, but a collective stressor unfolding over time, causing devastating implications for the mental health. This study aimed to shed light on the mental health status of patients with rheumatic disease (RD) during the massive outbreak of COVID-19 in China, especially the prevalence and severity of post-traumatic stress disorder (PTSD) compared with healthy individuals.

Methods: A total of 486 RD patients and 486 age- and sex-matched healthy individuals were recruited into the study. For each participant, we collected demographic and clinical characteristics data. The PTSD Checklist for DSM-5 (PCL-5) and 4 items from the Pittsburgh Sleep Quality Index (PSQI) were used to investigate the prevalence and severity of PTSD and sleep quality, respectively.

Results: Compared with healthy control subjects (n=486), RD patients (n=486) had a higher prevalence of PTSD (12.1% vs. 4.1%; $p<0.001$). Higher total scores on the PCL-5 and on all four items from the PSQI ($p\leq 0.001$) were also observed. Female, old age, poor sleep quality, long duration of RD, poor subjective evaluation of the disease and pessimistic subjective perception of the epidemic were identified as risk factors of PTSD in RD patients during the COVID-19 epidemic.

Conclusion: During the COVID-19 outbreak, RD patients presented a higher prevalence and severity of PTSD and showed more sleep disturbances. Our findings confirm the importance of psychological assessment and mental health care out of regular clinical care for RD patients during the pandemic.

Keywords

COVID-19, Mental health, Post-traumatic stress disorder, Sleep disorders, Rheumatic diseases

Strengths and limitations of this study

First, we adopted a case-control study to compare the prevalence and severity of PTSD in patients with rheumatic disease (RD) and healthy controls. Secondly, the sample size of this study was large, and two groups were matched in age and gender, which has high promotion value. Thirdly, this study was carried out during the massive outbreak of COVID-19 in China and compared the different psychological reactions to COVID-19 of RD patients and healthy controls. Finally, the main limitation of this study was a cross-sectional study, which cannot indicate whether the high prevalence and severity of PTSD in RD patients due to the different reactions to the epidemic of COVID-19 or the rheumatic disease.

Introduction

COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread throughout the world, causing a pandemic. By Jan 2021, it had spread across 207 countries with more than 99 million confirmed cases and exceeded 2 million deaths worldwide. The outbreak of COVID-19 unleashed public panic and fuelled psychological problems, especially fear, depression, anxiety, stress, irritability, insomnia, confusion, boredom, and stigma associated with quarantine[1]. Thereinto, the post-traumatic stress disorder (PTSD) arising from exposure to trauma needs of wide attention urgently[2]. Many patients and medical staff experienced PTSD during the outbreaks of SARS, MERS, and Ebola[3-5]. Even ordinary residents in epidemic areas became high-risk populations of PTSD. Several studies revealed that 6-14% of the general population experienced PTSD during the SARS outbreak,[6] while the PTSD rate during the COVID-19 pandemic has been estimated at 7-32%[7,8], a statistic that includes indirect victims of the contagion. Thus, PTSD should be given more focus during the outbreak of COVID-19.

Patients with rheumatic diseases (RDs), such as ankylosing spondylitis (AS), rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), had a high prevalence of mental health disorders, especially anxiety, depression, and cognitive impairment[9]. The negative impacts of these mental illnesses in the context of RD included increased disease activity, suboptimal treatment adherence, reduced treatment response, and decreased quality of life. Furthermore, due to disease activity, comorbidities, and immunosuppressive therapy, patients with RD might be more susceptible to COVID-19 than the general population[10]. They were also more nervous and expressed more hypochondria on account of the many similarities in clinical symptoms between RDs and COVID-19, such as fever, anaemia and elevated C-reactive protein (CRP) levels[11]. As a result, the psychological problems of RD patients during the

COVID-19 epidemic need to be particularly addressed, while few studies have examined so far. This study aimed to shed light on the mental health status of RD patients during the COVID-19 epidemic in China, especially the prevalence and severity of PTSD compared with healthy individuals.

Methods

Study design and subjects

A cross-sectional case-control study was conducted with 490 consecutive RD patients who received regular clinical follow-up in the Rheumatology and Immunology Department of Shanghai Changzheng Hospital from February to April 2020 which was the worst period of COVID-19 in China, The exclusion criteria for the RD patients included (1) patients ≤ 18 years old, (2) patients with hearing or cognitive impairment or an inability to fill out the questionnaire, (3) patients who spent more than 30 minutes or less than 2 minutes answering the questionnaire, and (4) patients previously diagnosed with PTSD. In addition, age- and sex-matched healthy individuals were volunteered as controls. They completed the same questionnaire online, excluding volunteers under the age of 18 and those who were unable to understand and complete the questionnaire or who had been previously diagnosed with RD or PTSD. This study was approved by the Human Research Ethics Committee of Changzheng Hospital (2017SL046), and informed consent was obtained from all participants.

Demographic and clinical characteristics

Demographic variables included gender, age, occupation, education level, income, quarantine status, and marital status. Clinical variables included clinical diagnosis, disease duration, patient global assessment visual analogue scale (PGA-VAS) score, sleep quality and disorders, weekly exercise frequency, and

subjective perception of the COVID-19 epidemic. Subjective perception of the COVID-19 epidemic was assessed via the following three questions: 1) "How dangerous is COVID-19 to life and health?"; 2) "How much does COVID-19 affect life, work or study?"; and 3) "How confident are you in defeating COVID-19?". Responses were given on a five-point Likert scale from 1 (nothing at all) to 5 (highest)[12].

Measurement of PTSD

The PTSD checklist for DSM-5 (PCL-5) was used to assess PTSD symptoms[13]. There are 20 items including 4 symptom clusters: intrusion symptoms (Criterion B, items 1-5), avoidance symptoms (Criterion C, items 6, 7), negative alterations in cognition or emotional symptoms (Criterion D, items 8-14), and hyper-arousal symptoms (Criterion E, items 15-20). Each item was scored on a five-point Likert scale from 0 (nothing at all) to 4 (extremely), representing the degree to which an individual has been bothered by PTSD-related symptoms during the past month. The overall score and the sum of each symptom were both investigated. A score of 33 or greater is suggested as a probable diagnosis of PTSD. The Chinese version of the PCL-5 has psychometric properties that are similar to those of the original version and is widely used in trauma-related research and practice[14].The COVID-19 epidemic put the Chinese population at risk of a deadly pandemic. According to PCL-5's DSM-5 Life Events List (LEC-5)[15], this public health disaster is a traumatic event. Therefore, PCL-5 was used to assess PTSD symptoms.

Measurement of sleep quality

Self-reported sleep quality was measured based on 4 questions extracted from the Pittsburgh Sleep Quality Index (PSQI)[16], including "subjective sleep quality", "unable to fall asleep within 30 minutes", "easily waking up at night or in the early morning" and "sleep time lasting for one month". Each item was scored from 0 to 3, with higher scores indicating more severe sleep disorders.

Statistical Analysis

Statistical analysis was performed using IBM SPSS version 21.0. A two-tailed test was used, and $p<0.05$ was considered as statistically significant. Descriptive and frequency statistics (mean, [SD] and percentages) were used to describe baseline demographic information and clinical information. First, descriptive statistics were calculated for the demographic variables, clinical diagnosis data, disease duration data, and subjective evaluation scores of the RD patient population. Then, the chi-squared test and t test were used to analyse the prevalence of PTSD, the PTSD symptoms and sleep quality of the rheumatic group and the control group. Then, one-way analysis of variance (ANOVA) was used to analyse the difference in the PCL-5 scores between different disease courses and clinical diagnoses in the RD group. Last, hierarchical regression analysis was used to determine the independent variables related to PTSD in the RD group.

Results

Demographic and clinical information of the RD patients

A total of 490 RD patients were recruited to complete the survey. Of the 490 respondents, 4 participants were removed due to illogical answers (for example, all choices were one or zero). Therefore, 486 participants were included in this analysis. As illustrated in Table 1, the sample comprised 301 males and 185 females with an average age of 40.03 years (SD, 14.70 years). Regarding the diagnosis, there were 289 (59.5%) patients with AS, 79 (16.3%) patients with RA, 15 (3.1%) patients with SLE, 10 (2.1%) patients with osteoarthritis (OA), 10 (2.1%) patients with osteoporosis (OP), 33 (6.8%) patients with gout, 10 (2.1%) patients with Sjogren's syndrome (SS), 11 (2.3%) patients with psoriatic arthritis (PsA) and 33 (6.8%) with other rheumatic diseases. In terms of the classification of the course of their RD, 39 (8.0%) patients were diagnosed less than 1 year ago, 205 (42.2%) patients were diagnosed between 1 and 5 years

ago, and 242 (49.8%) patients were diagnosed more than 5 years ago. A total of 292 (60.1%) patients had PGA-VAS scores between 1 and 5, and 194 (39.9%) patients had PGA-VAS scores between 6 and 10. The subjective perception of the COVID-19 epidemic scores (1-5) were as follows: Q1 (2.52±1.18), Q2 (3.26±1.10), and Q3 (4.38±0.81).

The difference of PTSD symptoms and sleep quality between RD patients and healthy controls

The PTSD symptoms and sleep quality of two groups were then analysed (Table 2). The mean PCL-5 score of the patients with RD (18.40 ± 11.47) was significantly higher than that of the healthy controls (11.07 ± 10.04) ($p<0.001$), with all four criteria rated significantly higher for RD patients than healthy respondents ($p<0.001$), indicating that all four types of symptoms (intrusion, avoidance, negative changes in cognition or mood, hyper-arousal) are more severe in rheumatic patients. A total of 12.1% (59/486) of RD patients and 4.1% (20/486) of healthy controls scored 33 or higher and met the diagnostic criteria for PTSD. Compared with the number of healthy controls, there were significantly more RD patients who fulfilled the diagnostic criteria for PTSD ($p<0.001$).

In terms of the diagnostic classification, although there were no significant differences between the subgroups, the Criterion B (intrusion symptoms) scores of the SLE patients were significantly higher than those of the RA patients ($p<0.05$) (see Figure 1).

Regarding sleep quality and disorders, the scores of the four items from the PSQI ("subjective sleep quality", "unable to fall asleep within 30 minutes", "easily waking up at night or in the early morning" and "sleep time") were significantly higher in the RD patients than the healthy control group. The results indicated that during the COVID-19 pandemic, the prevalence and severity of PTSD were significantly higher in RD patients than healthy controls, and the sleep quality of PD patients was also worse.

Factors related to PTSD in RD patients

With the PCL-5 score as the dependent variable and related variables as independent variables, the results of the hierarchical regression analysis were listed in Table 3.

In the first step, the demographic variables included accounted for 2.3% of the variance in PTSD symptoms. In the second step, the clinical characteristics of the RD patients were included in the model, and the subjective assessment of the disease had a significant effect on the PCL-5 scores. For the course of the RD, we defined "1-5 years" as a dummy variable and found that the PCL-5 scores in the "<1 year" group were significantly higher than those in the reference group ($p<0.05$) (see Figure 2). These features related to RD accounted for 5.8% of the unique variance. In the third step, two questions on the subjective perception of the COVID-19 epidemic (Q2 and Q3) were also statistically significant ($p<0.001$), accounting for 7.9% of the difference in the results. The sleep quality score was added to the final step of the hierarchical regression, thereby increasing the variance by 5.8%.

In the final model, gender ($\beta=0.147$, $p=0.001$), subjective assessment of the disease ($\beta=0.112$, $p=0.014$), and Q2 regarding the subjective perception of the COVID-19 epidemic ($\beta=0.110$, $p=0.046$) were positively correlated with the severity of PTSD symptoms, whereas age ($\beta=-0.155$, $p=0.001$) and Q3 ($\beta=-0.194$, $p<0.001$) were negatively correlated with PTSD symptoms. In summary, the total variation contribution of these variables to the PCL-5 score was significant ($R^2=21.7\%$, $F=10.899$, $p<0.001$).

Discussion

Although the disease status and the treatment of RD patients have been widespread concerned[17], almost nothing is known with certainty about the psychological impact of the COVID-19 pandemic on RD patients. In fact, RD patients are more susceptible to mental disorders during this COVID-19 outbreak. It was demonstrated that RD patients suffered more from PTSD and sleep disorders than healthy controls

and had significantly higher PCL-5 scores and individual criteria scores. That is to say, RD patients have higher odds of developing PTSD in the context of the COVID-19 pandemic. Our findings confirm the importance of psychological assessment and care for RD patients during the pandemic.

Fears had risen in RD patients because of the higher risks of COVID-19 infection[10], as a result of high similarity in clinical symptoms between RDs and COVID-19. A significant bidirectional relationship between autoimmune diseases and PTSD was observed[18]. That is, PTSD patients were prone to comorbidity with autoimmune disease[19], and vice versa[20]. It was hypothesised that psychoneuroimmunity (PNI) imbalance was the leading cause. PTSD was characterized by abnormal activation of the hypothalamus-pituitary-adrenal axis (HPA axis), which was thought to communicate with the immune system in a two-way manner[21]. On the one hand, it had been suggested that dysregulation of the HPA axis will exacerbate systemic inflammation, which may be involved in the pathogenesis of chronic inflammatory autoimmune diseases such as SLE and RA[22]. On the other hand, the chronic inflammatory state caused by RD will aggravate the dysregulation of the HPA axis, which will further disturb the physiological stress response of RD patients and make them more susceptible to PTSD[9]. Circulating cytokines may also be involved in making RD patients more susceptible to PTSD. Some recent reports demonstrated that serum interleukin-1 (IL-1), IL-6, tumour necrosis factor (TNF) and interferon (IFN)-γ levels were increased in patients with PTSD[23]. These factors were also involved in the pathogenesis of RDs, such as RA and SLE[24].

As expected, the sleep of RD patients was disturbed, in accordance with the results of previous studies. Psychosocial variables, steroid use, and chronic pain were possible psychobiological factors[25]. Sleep disorders also seemed to be a core feature of PTSD[26], suggesting that PTSD symptoms may be worse in RD patients.

Although no significant difference was observed in the PCL-5 scores among different diagnosis subgroups, all standard scores of patients with SLE and OP tended to be higher. SLE patients may be more stressed due to severe systemic involvement and drug shortages. They were concerned that chloroquine will become a specific drug for COVID-19[27], resulting in a higher Criterion B (intrusion symptom) score for SLE patients than for other RA patients. Consistent with previous findings, patients with OP may be more sensitive to PTSD due to age[28]. However, future studies with more samples should be carried out to verify and expand such results.

It is not lightweight to explore the psychological impact of COVID-19 in different groups of RD patients. Consequently, female, old age, poor sleep quality, long duration of RD, poor subjective evaluation of the disease and a pessimistic subjective perception of the epidemic were identified as risk factors for PTSD in RD patients during the COVID-19 epidemic.

In the current study, females were at higher risk to develop PTSD, in line with previous studies that explored predictors of PTSD during the COVID-19 epidemic.[7] It has been shown that females usually tended to present depression, physical anxiety sensitivity, and helplessness which were all proven to be PTSD-related risk factors[29]. As expected, age and sleep quality were predictive factors of PTSD and have been widely explored in relevant studies[30,31].

It is important to note that long duration and poor subjective assessment of RD determined the risk of PTSD to a certain extent. Patients with longer disease course were more likely to suffer from psychological problems caused by chronic stress[32]. Among people with different disease durations, those in "1-5 years" group had significantly higher PTSD levels than those in "<1 year" group. However, inconsistent with the hypothesis, the difference between the "1-5 years" and ">5 years" group was not significant. One possible reason is that patients who were diagnosed as more than 5 year ago have adapted

to their disease and have even become more resilient to other health-related stressors. Chronic pain usually determines the subjective assessment of the disease in RD patients, which is usually complicated by PTSD[33]. Obviously, during the pandemic of a life-threatening infectious disease, patients with a long disease duration and chronic pain should be regarded as at risk of PTSD.

Regarding the subjective perception of the epidemic, the symptoms of PTSD caused by pessimism and fear were more severe, which was consistent with research on the psychological impact of SARS[12]. Media reports emphasized that COVID-19 is a unique threat, which further exacerbates the possibility of panic, stress hysteria and fear. Fear is an adaptive response that triggers defensive behaviours to protect ourselves. If the fear is not managed properly, PTSD will develop[34]. Thus, applying psychological interventions to reduce pandemic fears and instilling emotional adaptability during the COVID-19 pandemic may help prevent the development of PTSD.

Currently, several limitations are worth considering. First, this study lacked research data on the prevalence of PTSD before the epidemic in both RD patients and controls. As a result, it is difficult to determine whether the high prevalence of PTSD in the RD group is due to COVID-19. In addition, to guarantee a reliable subgroup analysis, larger samples are warranted in the future.

Conclusion

In the context of COVID-19, the present study will provide references not only rheumatologically but also psychologically. It is suggested that, compared to healthy controls, RD patients present a higher prevalence and severity of PTSD and more sleep disturbances. Under such future life-threatening infectious epidemics, as regular clinical care, the importance of mental health in RD patients is nothing to sneeze at.

Contributorship statement

XW, XG, ZS contributed to the writing of this article and the statistical analysis of this article, who are co-first authors, HM, WL and HX leaded the whole study, including putting forward this study, carrying out the study, and was the co-corresponding author. ZW and HL contributed to perform the investigation and collection of all data and part of the statistical analysis of this article.

Competing interests

The authors declare that they have no conflicts of interest.

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Data sharing statement

Data can be provided after the Article is published through the email address of the corresponding authors for communication. The corresponding authors have the right to decide whether to share the data or not based on the research objectives and plan provided. With the permission of the corresponding authors, we can provide participant data without names and identifiers.

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Tables

	RD patients	
	N	%
Age		
18-34	223	45.9
35-60	203	41.8
>60	60	12.3
Gender		
Male	301	61.9
Female	185	38.1
Clinical diagnosis		
Rheumatoid arthritis, RA	79	16.3
Ankylosing spondylitis, AS	289	59.5
Systemic lupus erythematosus, SLE	15	3.1
Osteoarthritis, OA	10	2.1
Osteoporosis, OP	10	2.1
Gout	33	6.8
Sjogren's syndrome, SS	10	2.1
Psoriatic arthritis, PsA	11	2.3
Other	29	6.0
Duration of disease		
<1 year	39	8.0

1-5 years	205	42.2
>5 years	242	49.8
PGA-VAS scores		
1-5	292	60.1
6-10	194	39.9
Perception of the COVID-19 epidemic situation	MEAN	SD
Q1: How dangerous is COVID-19 to life and health?	2.52	1.18
Q2: How much does COVID-19 affect life, work or study?	3.26	1.10
Q3: How confident are you in defeating COVID-19?	4.38	0.81

Table 1: Demographic information and clinical information for all the RD patients

Note: RD=rheumatic diseases. PGA-VAS scores=Patient Global Assessment Visual Analogue Scale scores.

	RD patients		Control		Chi-square/t	p-value
	Mean/N	SD/%	Mean/N	SD/%		
Total	486	100.00	486	100.00		
Age						
18-34	223	45.90	213	43.80	3.418	0.181
35-60	203	41.80	227	46.70		
>60	60	12.30	46	9.50		
Gender						
Male	301	61.90	302	62.10	0.004	0.947
Female	185	38.10	184	37.90		
PCL-5 Scores						
Total scores	18.40	11.47	11.07	10.01	-10.601	<0.001

Criterion B	4.86	3.40	3.22	3.34	-7.577	<0.001
Criterion C	2.21	1.97	0.89	1.46	-11.978	<0.001
Criterion D	6.20	4.59	3.58	3.93	-7.617	<0.001
Criterion E	5.12	3.66	3.58	3.46	-10.601	<0.001
Sleep quality						
Subjective sleep quality	1.19	0.77	0.78	0.76	-8.424	<0.001
Difficulty falling asleep	1.07	1.09	0.51	0.88	-8.782	<0.001
Frequent nocturnal or early morning awakening	1.41	1.16	0.82	1.06	-8.269	<0.001
Sleep duration	0.95	0.85	0.77	0.85	-3.217	0.001

Table 2: Group differences in demographic information, PCL-5 scores and sleep quality between the RD patient group and the control group

Note: RD=rheumatic diseases. PCL-5=PTSD checklist for DSM-5.

Variables	PCL-5 score				R Square	R Square Change	F	p-value
	B	β	t	p-value				
Step 1								
Age	-0.064	-0.081	-1.762	0.079	0.023	0.023	5.576	0.004
Female vs. Male	3.452	0.146	3.166	0.002				
Step 2								
Age	-0.100	-0.127	-2.719	0.007	0.080	0.058	8.381	<0.001
Female vs. Male	4.253	0.180	3.940	0.000				
Duration of disease <1 year vs. 1-5 years	-4.339	-0.103	-2.243	0.025				
Duration of disease >5 years vs. 1-5 years	0.170	0.007	0.156	0.876				
PGA-VAS scores	1.055	0.210	4.612	<0.001				
Step 3								

	Age	-0.088	-0.112	-2.491	0.013	0.159	0.079	11.260	<0.001
	Female vs. Male	3.797	0.161	3.579	<0.001				
	Duration of disease <1 year vs. 1-5 years	-3.847	-0.091	-2.061	0.040				
	Duration of disease >5 years vs. 1-5 years	0.182	0.008	0.174	0.862				
	PGA-VAS scores	0.905	0.180	4.014	<0.001				
	Q1: How dangerous is COVID-19 to life and health?	0.457	0.047	0.964	0.336				
	Q2: How much does COVID-19 affect life, work or study?	1.816	0.175	3.544	<0.001				
	Q3: How confident are you in defeating COVID-19?	-3.086	-0.217	-4.970	<0.001				
Step 4									
	Age	-0.121	-0.155	-3.412	0.001	0.217	0.058	10.899	<0.001
	Female vs. Male	3.471	0.147	3.323	0.001				
	Duration of disease <1 year vs. 1-5 years	-2.351	-0.056	-1.286	0.199				

Duration of disease >5 years vs. 1-5 years	0.556	0.024	0.546	0.586
PGA-VAS scores	0.561	0.112	2.473	0.014
Q1: How dangerous is COVID-19 to life and health?	0.520	0.053	1.130	0.259
Q2: How much does COVID-19 affect life, work or study?	1.331	0.128	2.642	0.009
Q3: How confident are you in defeating COVID-19?	-2.754	-0.194	-4.545	<0.001
Subjective sleep quality	1.627	0.110	1.999	0.046
Difficulty falling asleep	0.954	0.090	1.678	0.094
Frequent nocturnal or early morning awakening	0.715	0.072	1.401	0.162
Sleep duration	0.878	0.065	1.371	0.171

Table 3: Regression analyses with the PCL-5 score as the dependent variable in all RD patients (n=486)

Note: B =unstandardized beta; β =standardized regression weight. The duration of disease was transformed into two dummy variables (<1 year vs. 1-5 years, >5 years vs. 1-5 years), with 1-5 years as the reference group.

Figures

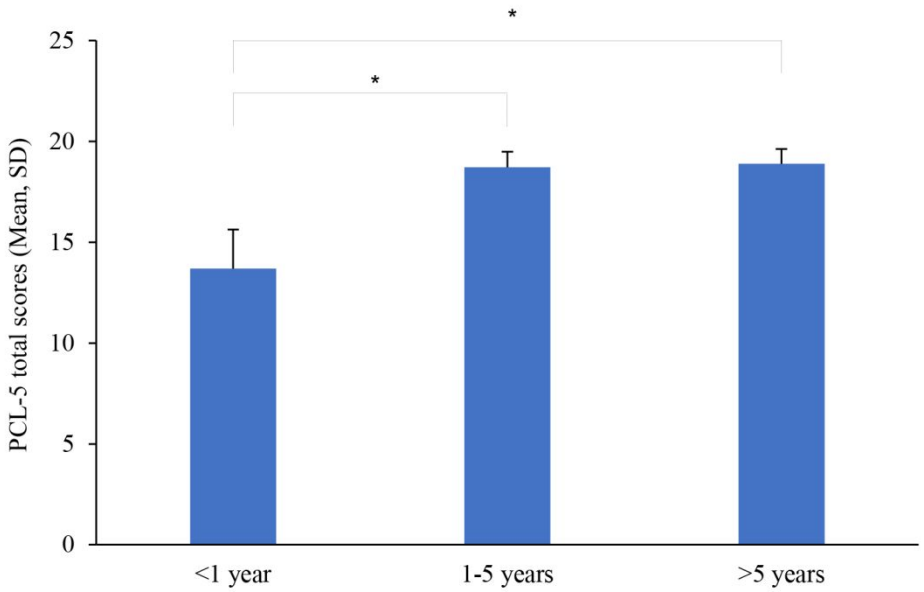

Figure 1: Group differences in all the PCL-5 criteria between the different subgroups of RD

Note: * p-value<0.05. PCL-5=PTSD checklist for DSM-5. All 4 criteria (B, C, D, E) are components of the PCL-5.

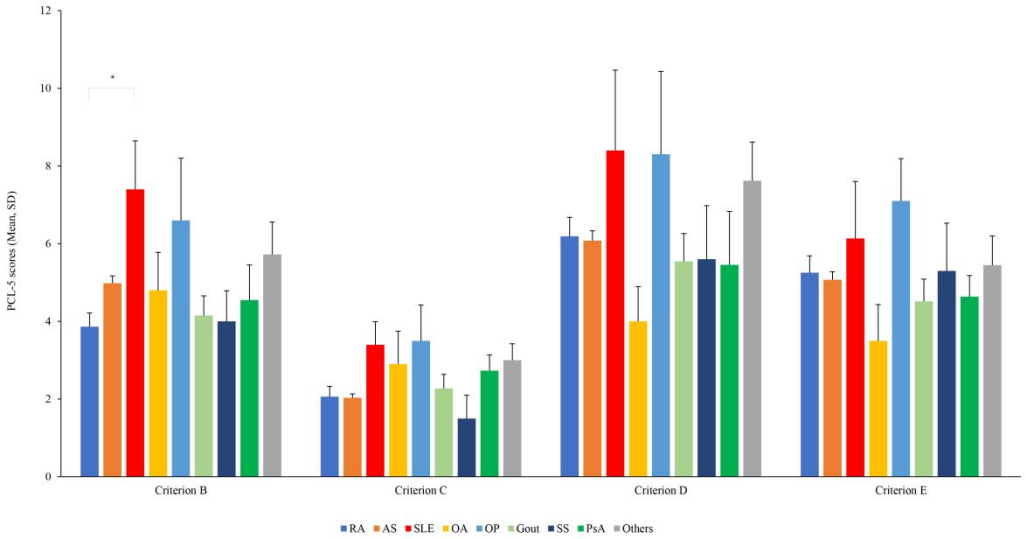

Figure 2: Differences in the PCL-5 scores between different disease duration groups

Note: * p-value<0.05. The duration of disease was transformed into three groups (< 1 year, 1-5 years, > 5 years).

Figure legends

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Title page

Title:

Post-Traumatic Stress Disorder in Patients with Rheumatic Disease during the COVID-19 Outbreak: a cross-sectional case-control study in China

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Shortened title:

PTSD in RD Patients during the COVID-19 Outbreak

Abstract

Objective: The COVID-19 pandemic is not only a traumatic event, but a collective stressor unfolding over time, causing devastating implications for the mental health. This study aimed to shed light on the mental health status of patients with rheumatic disease (RD) during the massive outbreak of COVID-19 in China, especially the prevalence and severity of post-traumatic stress disorder (PTSD) compared with healthy individuals.

Methods: A total of 486 RD patients and 486 age- and sex-matched healthy individuals were recruited into the study. For each participant, we collected demographic and clinical characteristics data. The PTSD Checklist for DSM-5 (PCL-5) and 4 items from the Pittsburgh Sleep Quality Index (PSQI) were used to investigate the prevalence and severity of PTSD and sleep quality, respectively.

Results: Compared with healthy control subjects (n=486), RD patients (n=486) had a higher prevalence of PTSD (12.1% vs. 4.1%; $p<0.001$). Higher total scores on the PCL-5 and on all four items from the PSQI ($p\leq 0.001$) were also observed. Female, old age, poor sleep quality, long duration of RD, poor subjective evaluation of the disease and pessimistic subjective perception of the epidemic were identified as risk factors of PTSD in RD patients during the COVID-19 epidemic.

Conclusion: During the COVID-19 outbreak, RD patients presented a higher prevalence and severity of PTSD and showed more sleep disturbances. Our findings confirm the importance of psychological assessment and mental health care out of regular clinical care for RD patients during the pandemic.

Strengths and limitations of this study

► This is the first case-control study to explore the prevalence of post-traumatic stress disorder (PTSD) in patients with rheumatic disease (RD) and general Chinese residents during the massive outbreak of

COVID-19 in China.

► This study is one of the first to compare the different psychological reactions to COVID-19 of RD patients and healthy controls.

► This study is a cross-sectional study, which limited to indicate whether the high prevalence and severity of PTSD in RD patients due to the different reactions to the epidemic of COVID-19 or the rheumatic disease.

► Findings relied on a self-reported survey which may question the authenticity of responses and give consideration to social desirability bias.

► To guarantee a reliable subgroup analysis, larger samples are warranted in the future.

Keywords

COVID-19, Mental health, Post-traumatic stress disorder, Sleep disorders, Rheumatic diseases

Introduction

COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread throughout the world, causing a pandemic. By Jan 2021, it had spread across 207 countries with more than 99 million confirmed cases and exceeded 2 million deaths worldwide. The outbreak of COVID-19 unleashed public panic and fuelled psychological problems, especially fear, depression, anxiety, stress, irritability, insomnia, confusion, boredom, and stigma associated with quarantine.[1] Thereinto, the post-traumatic stress disorder (PTSD) arising from exposure to trauma needs of wide attention urgently.[2] Many patients and medical staff experienced PTSD during the outbreaks of SARS, MERS, Ebola and COVID-19.[3-7] Even ordinary residents in epidemic areas became high-risk populations of PTSD. Several studies revealed that 6-14% of the general population experienced PTSD during the SARS outbreak,[8] while the PTSD rate during the COVID-19 pandemic ranged at 4-35%,[9 10] a statistic that includes indirect victims of the contagion. Thus, PTSD should be given more focus during the outbreak of COVID-19.

Patients with rheumatic diseases (RDs), such as ankylosing spondylitis (AS), rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), had a high prevalence of mental health disorders, especially anxiety, depression, and cognitive impairment.[11 12] The negative impacts of these mental illnesses in the context of RD included increased disease activity, suboptimal treatment adherence, reduced treatment response, and decreased quality of life. Furthermore, due to disease activity, comorbidities, and immunosuppressive therapy, patients with RD might be more susceptible to COVID-19 than the general population.[13] They were more nervous and suffering from hypochondria on account of the many similarities in clinical symptoms between RDs and COVID-19, such as fever, anaemia and elevated C-reactive protein (CRP) levels.[14] As a result, the psychological problems of RD patients during the COVID-19 epidemic need to be particularly addressed, while few studies have examined so far. This

study aimed to shed light on the mental health status of RD patients during the COVID-19 epidemic in China, especially the prevalence and severity of PTSD compared with healthy individuals.

Methods

Study design and subjects

According to previous studies, the PTSD rate of the general Chinese residents during the COVID-19 pandemic has been estimated at 4.6-7.4%.[9 15] It was revealed that 12-18% of patients with ankylosing spondylitis (AS) and rheumatoid arthritis (RA) presented PTSD,[16 17] which were the main components of our recruitments, although lacking large-scale epidemiological data. We estimated the sample size with a 6% prevalence of PTSD in the general population and a 12% prevalence of rheumatic patients. By calculation, the minimum sample size was 353. A cross-sectional case-control study was conducted with 490 consecutive RD patients who received regular clinical follow-up in the Rheumatology and Immunology Department of Shanghai Changzheng Hospital from February to April 2020 which was the worst period of COVID-19 in China. All patients completed standardized questionnaire under the guidance of physicians, which took about 10 to 15 minutes and included demographic and clinical characteristics, measurements of PTSD and sleep quality. The exclusion criteria for the RD patients included (1) patients ≤ 18 years old, (2) patients with hearing or cognitive impairment or an inability to fill out the questionnaire, (3) patients who spent more than 30 minutes or less than 2 minutes answering the questionnaire, and (4) patients previously diagnosed with PTSD. At the same time, we also recruited healthy volunteers from the community in Shanghai who had similar demographic characteristics of patients with RD as comparison group. All the participants completed the same questionnaire online. We

also excluded volunteers under the age of 18 and those who had been previously diagnosed with RD or other complex disease. Finally, 486 age- and sex-matched healthy individuals entered the analysis as controls. This study was approved by the Human Research Ethics Committee of Changzheng Hospital (2017SL046), and informed consent was obtained from all participants.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Demographic and clinical characteristics

Demographic variables included gender, age, occupation, education level, income, quarantine status, and marital status. Clinical variables included clinical diagnosis, disease duration, patient global assessment visual analogue scale (PGA-VAS) score, sleep quality and disorders, weekly exercise frequency, and subjective perception of the COVID-19 epidemic. Subjective perception of the COVID-19 epidemic was assessed via the following three questions: 1) "How dangerous is COVID-19 to life and health?"; 2) "How much does COVID-19 affect life, work or study?"; and 3) "How confident are you in defeating COVID-19?". Responses were given on a five-point Likert scale from 1 (nothing at all) to 5 (highest).[18]

Measurement of PTSD

The PTSD checklist for DSM-5 (PCL-5) was used to assess PTSD symptoms.[19] There are 20 items including 4 symptom clusters: intrusion symptoms (Criterion B, items 1-5), avoidance symptoms (Criterion C, items 6, 7), negative alterations in cognition or emotional symptoms (Criterion D, items 8-14), and hyper-arousal symptoms (Criterion E, items 15-20). Each item was scored on a five-point Likert scale from 0 (nothing at all) to 4 (extremely), representing the degree to which an individual has been bothered by PTSD-related symptoms during the past month. The overall score and the sum of each

symptom were both investigated. A score of 33 or greater was suggested as a probable diagnosis of PTSD. The Chinese version of the PCL-5 has psychometric properties that are similar to those of the original version and is widely used in trauma-related research and practice.[20] The COVID-19 epidemic put the Chinese population at risk of a deadly pandemic. According to PCL-5's DSM-5 Life Events List (LEC-5),[21] this public health disaster is a traumatic event. Therefore, PCL-5 was used to assess PTSD symptoms.

Measurement of sleep quality

Self-reported sleep quality was measured based on 4 questions extracted from the Pittsburgh Sleep Quality Index (PSQI),[22] including "subjective sleep quality", "unable to fall asleep within 30 minutes", "easily waking up at night or in the early morning" and "sleep time lasting for one month". Each item was scored from 0 to 3, with higher scores indicating more severe sleep disorders.

Statistical Analysis

Statistical analysis was performed using IBM SPSS version 21.0. A two-tailed test was used, and $p<0.05$ was considered as statistically significant. Descriptive and frequency statistics (mean, [SD] and percentages) were used to describe baseline demographic information and clinical information. First, descriptive statistics were calculated for the demographic variables, clinical diagnosis data, disease duration data, and subjective evaluation scores of the RD patient population. The differences in the PTSD symptoms and sleep quality between the two groups were examined. If the data met normality, t-test was used; otherwise, Mann-Whitney U test was used. Logistic regression analysis was used to estimate the odds of experiencing PTSD symptoms among patients with RD compared to healthy people. Last, hierarchical regression analysis was used to determine the independent variables related to PTSD in the RD group.

Results

Demographic and clinical information of the RD patients

A total of 490 RD patients were recruited to complete the survey. Of the 490 respondents, 4 participants were removed due to illogical answers (for example, all choices were one or zero). Therefore, 486 participants were included in this analysis. As illustrated in Table 1, the sample comprised 301 males and 185 females with an average age of 40.03 years (SD, 14.70 years). Regarding the diagnosis, there were 289 (59.5%) patients with AS, 79 (16.3%) patients with RA, 15 (3.1%) patients with SLE, 10 (2.1%) patients with osteoarthritis (OA), 10 (2.1%) patients with osteoporosis (OP), 33 (6.8%) patients with gout, 10 (2.1%) patients with Sjogren's syndrome (SS), 11 (2.3%) patients with psoriatic arthritis (PsA) and 33 (6.8%) with other rheumatic diseases. In terms of the classification of the course of their RD, 39 (8.0%) patients were diagnosed less than 1 year ago, 205 (42.2%) patients were diagnosed between 1 and 5 years ago, and 242 (49.8%) patients were diagnosed more than 5 years ago. A total of 292 (60.1%) patients had PGA-VAS scores between 1 and 5, and 194 (39.9%) patients had PGA-VAS scores between 6 and 10. The subjective perception of the COVID-19 epidemic scores (1-5) were as follows: Q1 (2.52±1.18), Q2 (3.26±1.10), and Q3 (4.38±0.81).

The difference of PTSD symptoms and sleep quality between RD patients and healthy controls

The PTSD symptoms and sleep quality of two groups were then analysed (Table 2). The mean PCL-5 score of the patients with RD (18.40 ± 11.47) was significantly higher than that of the healthy controls (11.07 ± 10.04) ($p<0.001$), with all four criteria rated significantly higher for RD patients than healthy respondents ($p<0.001$), indicating that all four types of symptoms (intrusion, avoidance, negative changes in cognition or mood, hyper-arousal) are more severe in rheumatic patients. A total of 12.1% (59/486) of RD patients and 4.1% (20/486) of healthy controls scored 33 or higher and met the diagnostic

criteria for PTSD. Compared with the number of healthy controls, there were significantly more RD patients who fulfilled the diagnostic criteria for PTSD ($p<0.001$). Logistic regression analysis showed that the unadjusted OR of experiencing PTSD symptoms among patients with RD compared to healthy people was 3.12 (95%CI 1.86-5.21), and the adjusted OR value was 3.26 (95%CI 1.94-5.48) after controlling for gender and age.

In terms of the diagnostic classification, although there were no significant differences between the subgroups, the Criterion B (intrusion symptoms) scores of the SLE patients were significantly higher than those of the RA patients ($p<0.05$) (see Figure 1).

Regarding sleep quality and disorders, the scores of the four items from the PSQI ("subjective sleep quality", "unable to fall asleep within 30 minutes", "easily waking up at night or in the early morning" and "sleep time") were significantly higher in the RD patients than the healthy control group. The results indicated that during the COVID-19 pandemic, the prevalence and severity of PTSD were significantly higher in RD patients than healthy controls, and the sleep quality of PD patients was also worse.

Factors related to PTSD in RD patients

With the PCL-5 score as the dependent variable and related variables as independent variables, the results of the hierarchical regression analysis were listed in Table 3.

In the first step, the demographic variables included accounted for 2.3% of the variance in PTSD symptoms. In the second step, the clinical characteristics of the RD patients were included in the model, and the subjective assessment of the disease had a significant effect on the PCL-5 scores. For the course of the RD, we defined "1-5 years" as a dummy variable and found that the PCL-5 scores in the "<1 year" group were significantly higher than those in the reference group ($p<0.05$) (see Figure 2). These features related to RD accounted for 5.8% of the unique variance. In the third step, two questions on the subjective

perception of the COVID-19 epidemic (Q2 and Q3) were also statistically significant ($p<0.001$), accounting for 7.9% of the difference in the results. The sleep quality score was added to the final step of the hierarchical regression, thereby increasing the variance by 5.8%.

In the final model, gender ($\beta=0.147$, $p=0.001$), subjective assessment of the disease ($\beta=0.112$, $p=0.014$), and Q2 regarding the subjective perception of the COVID-19 epidemic ($\beta=0.110$, $p=0.046$) were positively correlated with the severity of PTSD symptoms, whereas age ($\beta=-0.155$, $p=0.001$) and Q3 ($\beta=-0.194$, $p<0.001$) were negatively correlated with PTSD symptoms. In summary, the total variation contribution of these variables to the PCL-5 score was significant ($R^2=21.7\%$, $F=10.899$, $p<0.001$).

Discussion

Although the disease status and the treatment of RD patients have been widespread concerned,[23] almost nothing is known with certainty about the psychological impact of the COVID-19 pandemic on RD patients. In fact, RD patients were more susceptible to mental disorders during this COVID-19 outbreak. It was demonstrated that RD patients suffered more from PTSD and sleep disorders than healthy controls and had significantly higher PCL-5 scores and individual criteria scores. That is to say, RD patients have higher odds of developing PTSD in the context of the COVID-19 pandemic. Our findings confirm the importance of psychological assessment and care for RD patients during the pandemic.

Fears had risen in RD patients because of the higher risks of COVID-19 infection, as a result of high similarity in clinical symptoms between RDs and COVID-19.[13] A significant bidirectional relationship between autoimmune diseases and PTSD was observed.[24] That is, PTSD patients were prone to comorbidity with autoimmune disease,[25] and vice versa.[26] It was hypothesised that psychoneuroimmunity (PNI) imbalance was the behind reason. PTSD was characterized by abnormal activation of the

hypothalamus-pituitary-adrenal axis (HPA axis), which was thought to communicate with the immune system in a two-way manner.[27] On the one hand, it had been suggested that dysregulation of the HPA axis will exacerbate systemic inflammation, which may be involved in the pathogenesis of chronic inflammatory autoimmune diseases such as SLE and RA.[28] On the other hand, the chronic inflammatory state caused by RD will aggravate the dysregulation of the HPA axis, which will further disturb the physiological stress response of RD patients and make them more susceptible to PTSD.[11] Circulating cytokines may also be involved in making RD patients more susceptible to PTSD. Some recent reports demonstrated that serum interleukin-1 (IL-1), IL-6, tumour necrosis factor (TNF) and interferon (IFN)-γ levels were increased in patients with PTSD.[29] These factors were also involved in the pathogenesis of RDs, such as RA and SLE.[30]

As expected, the sleep of RD patients was disturbed, in accordance with the results of previous studies.[31] Psychosocial variables, steroid use, and chronic pain were possible psychobiological factors.[32] Sleep disorders also seemed to be a core feature of PTSD,[33] suggesting that PTSD symptoms may be worse in RD patients.

Although no significant difference was observed in the PCL-5 scores among different diagnosis subgroups, all standard scores of patients with SLE and OP tended to be higher. SLE patients may be more stressed due to severe systemic involvement and drug shortages. They were concerned that chloroquine will become a specific drug for COVID-19,[34] resulting in a higher Criterion B (intrusion symptom) score for SLE patients than for other RA patients. Consistent with previous findings, patients with OP may be more sensitive to PTSD due to age.[35] However, future studies with more samples should be carried out to verify and expand such results.

It is not lightweight to explore the psychological impact of COVID-19 in different groups of RD patients.

Consequently, female, old age, poor sleep quality, long duration of RD, poor subjective evaluation of the disease and a pessimistic subjective perception of the epidemic were identified as risk factors for PTSD in RD patients during the COVID-19 epidemic.

In the current study, females were at higher risk to develop PTSD, in line with previous studies that explored predictors of PTSD during the COVID-19 epidemic.[15 36] It has been shown that females usually tended to present depression, physical anxiety sensitivity, and helplessness which were all proven to be PTSD-related risk factors.[37] As expected, age and sleep quality were predictive factors of PTSD and have been widely explored in relevant studies.[38 39]

It is important to note that long duration and poor subjective assessment of RD determined the risk of PTSD to a certain extent. Patients with longer disease course were more likely to suffer from psychological problems caused by chronic stress.[40] Among people with different disease durations, those in "1-5 years" group had significantly higher PTSD levels than those in "<1 year" group. However, inconsistent with the hypothesis, the difference between the "1-5 years" and ">5 years" group was not significant. One possible reason is that patients who were diagnosed as more than 5 year ago have adapted to their disease and have even become more resilient to other health-related stressors. Chronic pain usually determined the subjective assessment of the disease in RD patients, which was usually complicated by PTSD.[41] Obviously, during the pandemic of a life-threatening infectious disease, patients with a long disease duration and chronic pain should be regarded as at risk of PTSD.

Regarding the subjective perception of the epidemic, the symptoms of PTSD caused by pessimism and fear were more severe, which was consistent with research on the psychological impact of SARS.[18] Media reports emphasized that COVID-19 was a unique threat, which further exacerbated the possibility of panic, stress hysteria and fear. Fear is an adaptive response that triggers defensive behaviours to protect

ourselves. If the fear is not managed properly, PTSD will develop.[42] Thus, applying psychological interventions to reduce pandemic fears and instilling emotional adaptability during the COVID-19 pandemic may help prevent the development of PTSD.

Currently, several limitations are worth considering. This study lacked evidences on the prevalence of PTSD before the epidemic in both RD patients and health individuals. As a result, it is difficult to determine whether the high prevalence of PTSD in the RD group is due to COVID-19. Furthermore, our findings rely on a self-reported survey which may question the authenticity of response as well as give consideration to social desirability bias, which refers to the tendency for survey respondents to over-endorse items that they perceive others judge favourably. If participants believe that it is socially desirable to have psychological problems during the COVID-19 pandemic in order to get more attention, some who do not follow guidance may be reluctant to respond truthfully. Thus, the results may be inflated. Lastly, to guarantee a reliable subgroup analysis, larger samples are warranted in the future.

Conclusion

In the context of COVID-19, the present study will provide references not only rheumatologically but also psychologically. It is suggested that, compared to healthy controls, RD patients present a higher prevalence and severity of PTSD and more sleep disturbances. Under such future life-threatening infectious epidemics, as regular clinical care, the importance of mental health in RD patients is nothing to sneeze at.

Contributorship statement

XW, XG, ZS contributed to the writing of this article and the statistical analysis of this article, who are co-first authors, HM, WL and HX leaded the whole study, including putting forward this study,

carrying out the study, and was the co-corresponding author. ZW and HL contributed to perform the investigation and collection of all data and part of the statistical analysis of this article.

Competing interests

The authors declare that they have no conflicts of interest.

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Data sharing statement

Data can be provided after the Article is published through the email address of the corresponding authors for communication. The corresponding authors have the right to decide whether to share the data or not based on the research objectives and plan provided. With the permission of the corresponding authors, we can provide participant data without names and identifiers.

Tables

	RD patients	
	N	%
Age		
18-34	223	45.9
35-60	203	41.8
>60	60	12.3
Gender		
Male	301	61.9
Female	185	38.1
Clinical diagnosis		
Rheumatoid arthritis, RA	79	16.3
Ankylosing spondylitis, AS	289	59.5
Systemic lupus erythematosus, SLE	15	3.1
Osteoarthritis, OA	10	2.1
Osteoporosis, OP	10	2.1
Gout	33	6.8
Sjogren's syndrome, SS	10	2.1
Psoriatic arthritis, PsA	11	2.3
Other	29	6.0
Duration of disease		
<1 year	39	8.0

1-5 years	205	42.2
>5 years	242	49.8
PGA-VAS scores		
1-5	292	60.1
6-10	194	39.9
Perception of the COVID-19 epidemic situation	MEAN	SD
Q1: How dangerous is COVID-19 to life and health?	2.52	1.18
Q2: How much does COVID-19 affect life, work or study?	3.26	1.10
Q3: How confident are you in defeating COVID-19?	4.38	0.81

Table 1: Demographic information and clinical information for all the RD patients

Note: RD=rheumatic diseases. PGA-VAS scores=Patient Global Assessment Visual Analogue Scale scores.

	RD patients		Control		Chi-square/t	p-value
	Mean/N	SD/%	Mean/N	SD/%		
Total	486	100.00	486	100.00		
Age						
18-34	223	45.90	213	43.80	3.418	0.181
35-60	203	41.80	227	46.70		
>60	60	12.30	46	9.50		
Gender						
Male	301	61.90	302	62.10	0.004	0.947
Female	185	38.10	184	37.90		
PCL-5 Scores						
Total scores	18.40	11.47	11.07	10.01	-10.601	<0.001

Criterion B	4.86	3.40	3.22	3.34	-7.577	<0.001
Criterion C	2.21	1.97	0.89	1.46	-11.978	<0.001
Criterion D	6.20	4.59	3.58	3.93	-7.617	<0.001
Criterion E	5.12	3.66	3.58	3.46	-10.601	<0.001
Sleep quality						
Subjective sleep quality	1.19	0.77	0.78	0.76	-8.424	<0.001
Difficulty falling asleep	1.07	1.09	0.51	0.88	-8.782	<0.001
Frequent nocturnal or early morning awakening	1.41	1.16	0.82	1.06	-8.269	<0.001
Sleep duration	0.95	0.85	0.77	0.85	-3.217	0.001

Table 2: Group differences in demographic information, PCL-5 scores and sleep quality between the RD patient group and the control group

Note: RD=rheumatic diseases. PCL-5=PTSD checklist for DSM-5.

Variables	PCL-5 score				R Square	R Square Change	F	p-value
	B	β	t	p-value				
Step 1								
Age	-0.064	-0.081	-1.762	0.079	0.023	0.023	5.576	0.004
Female vs. Male	3.452	0.146	3.166	0.002				
Step 2								
Age	-0.100	-0.127	-2.719	0.007	0.080	0.058	8.381	<0.001
Female vs. Male	4.253	0.180	3.940	0.000				
Duration of disease <1 year vs. 1-5 years	-4.339	-0.103	-2.243	0.025				
Duration of disease >5 years vs. 1-5 years	0.170	0.007	0.156	0.876				
PGA-VAS scores	1.055	0.210	4.612	<0.001				
Step 3								

	Age	-0.088	-0.112	-2.491	0.013	0.159	0.079	11.260	<0.001
	Female vs. Male	3.797	0.161	3.579	<0.001				
	Duration of disease <1 year vs. 1-5 years	-3.847	-0.091	-2.061	0.040				
	Duration of disease >5 years vs. 1-5 years	0.182	0.008	0.174	0.862				
	PGA-VAS scores	0.905	0.180	4.014	<0.001				
	Q1: How dangerous is COVID-19 to life and health?	0.457	0.047	0.964	0.336				
	Q2: How much does COVID-19 affect life, work or study?	1.816	0.175	3.544	<0.001				
	Q3: How confident are you in defeating COVID-19?	-3.086	-0.217	-4.970	<0.001				
Step 4									
	Age	-0.121	-0.155	-3.412	0.001	0.217	0.058	10.899	<0.001
	Female vs. Male	3.471	0.147	3.323	0.001				
	Duration of disease <1 year vs. 1-5 years	-2.351	-0.056	-1.286	0.199				

Duration of disease >5 years vs. 1-5 years	0.556	0.024	0.546	0.586
PGA-VAS scores	0.561	0.112	2.473	0.014
Q1: How dangerous is COVID-19 to life and health?	0.520	0.053	1.130	0.259
Q2: How much does COVID-19 affect life, work or study?	1.331	0.128	2.642	0.009
Q3: How confident are you in defeating COVID-19?	-2.754	-0.194	-4.545	<0.001
Subjective sleep quality	1.627	0.110	1.999	0.046
Difficulty falling asleep	0.954	0.090	1.678	0.094
Frequent nocturnal or early morning awakening	0.715	0.072	1.401	0.162
Sleep duration	0.878	0.065	1.371	0.171

Table 3: Regression analyses with the PCL-5 score as the dependent variable in all RD patients (n=486)

Note: B =unstandardized beta; β =standardized regression weight. The duration of disease was transformed into two dummy variables (<1 year vs. 1-5 years, >5 years vs. 1-5 years), with 1-5 years as the reference group.

Figure legends

Figure 1: Group differences in all the PCL-5 criteria between the different subgroups of RD

Note: * p-value<0.05. PCL-5=PTSD checklist for DSM-5. All 4 criteria (B, C, D, E) are components of the PCL-5.

Figure 2: Differences in the PCL-5 scores between different disease duration groups

Note: * p-value<0.05. The duration of disease was transformed into three groups (< 1 year, 1-5 years, > 5 years).

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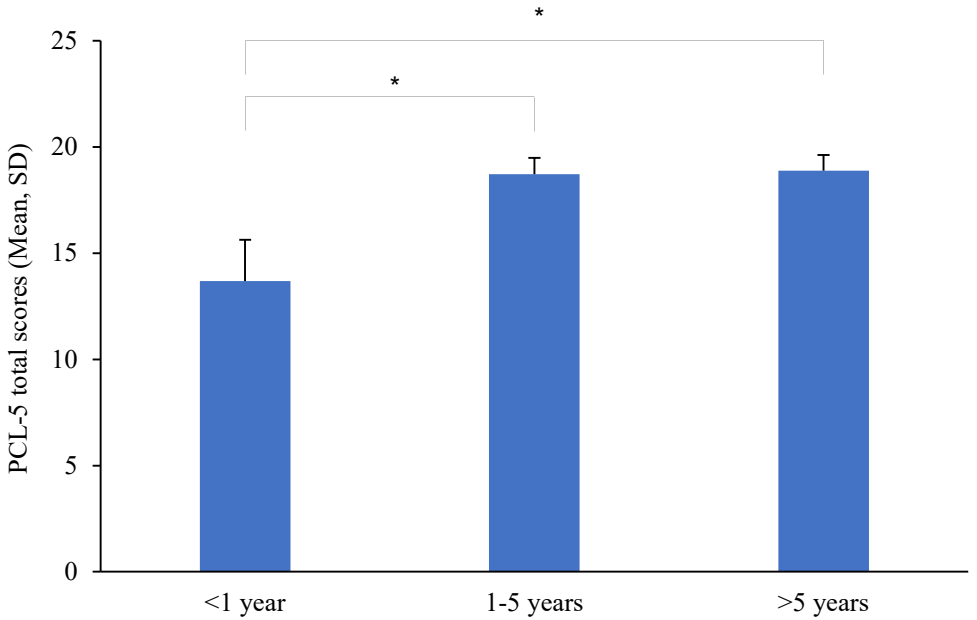

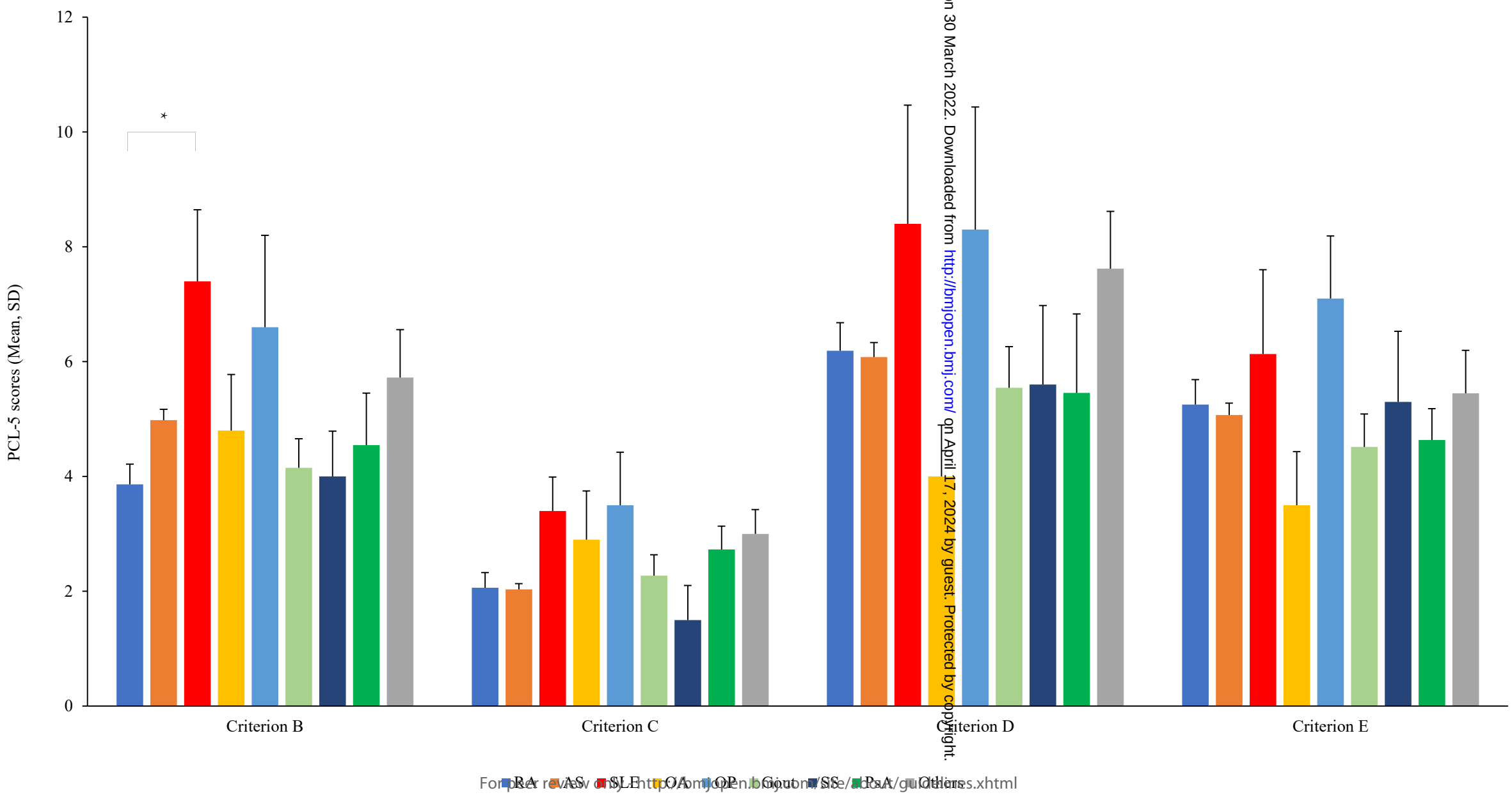

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Pg 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Pg 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Pg 5
Objectives	3	State specific objectives, including any prespecified hypotheses	Pg 6
Methods			
Study design	4	Present key elements of study design early in the paper	Pg 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Pg 6
Participants	6	(*a*) *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Pg 6
		(*b*) *Case-control study*—For matched studies, give matching criteria and the number of controls per case	Pg 6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Pg 7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Pg 7-8
Bias	9	Describe any efforts to address potential sources of bias	Pg 6
Study size	10	Explain how the study size was arrived at	Pg 6

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Pg 8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Pg 8
		(*b*) Describe any methods used to examine subgroups and interactions	Pg 8
		(*c*) Explain how missing data were addressed	
		(*d*) *Case-control study*—If applicable, explain how matching of cases and controls was addressed	Pg 8
		(*e*) Describe any sensitivity analyses	
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Pg 9
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Pg 9
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	Pg 9
		Cross-sectional study—Report numbers of outcome events or summary measures	
Results			
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Pg 10
		(*b*) Report category boundaries when continuous variables were categorized	Pg 10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Pg 10
Discussion			
Key results	18	Summarise key results with reference to study objectives	Pg 11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Pg 14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Pg 14
Generalisability	21	Discuss the generalisability (external validity) of the study results	Pg 14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Pg 15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.