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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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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 patients with RD and 486 age-matched 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 four 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), patients with RD (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≤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 patients with RD during the COVID-19 epidemic.

Conclusion During the COVID-19 outbreak, patients with RD presented a higher prevalence and severity of PTSD and showed more sleep disturbances. Our findings confirm the importance of psychological assessment and mental healthcare out of regular clinical care for patients with RD 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 patients with RD and healthy controls.
- This study is a cross-sectional study, which limited to indicate whether the high prevalence and severity of PTSD in patients with RD due to the different reactions to the epidemic of COVID-19 or the RD.
- 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.

INTRODUCTION

COVID-19, caused by severe acute respiratory SARS-CoV-2, has spread throughout the world, causing a pandemic. By January 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 levels.[14] As a result, the psychological problems of patients with RD 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 patients with RD 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 AS and 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 patients with RD 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 standardised questionnaire under the guidance of physicians, which took about 10–15 min and included demographic and clinical characteristics, measurements of PTSD and sleep quality. The exclusion criteria for the patients with RD 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 min or less than 2 min 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-matched and sex-matched healthy individuals entered the analysis as controls.

Patient and public involvement

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

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

	Patients with RD	
	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	79	16.3
Ankylosing spondylitis	289	59.5
Systemic lupus erythematosus	15	3.1
Osteoarthritis	10	2.1
Osteoporosis	10	2.1
Gout	33	6.8
Sjogren's syndrome	10	2.1
Psoriatic arthritis	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

PGA-VAS, Patient Global Assessment Visual Analogue Scale; RD, rheumatic diseases.

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

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

	Patients with RD		Control			
	Mean/N	SD/%	Mean/N	SD/%	χ^2/t	P value
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	10.04	−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	1.43	−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	3.48	−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

PCL-5, PTSD checklist for DSM-5; RD, rheumatic diseases.

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 Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (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 hyperarousal 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,[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 four questions extracted from the Pittsburgh Sleep Quality Index (PSQI),[22] including 'subjective sleep quality', 'unable to fall asleep within 30 min', 'easily waking up at night or in the early morning' and 'sleep time lasting for 1 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 V.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 with healthy people. Last, hierarchical regression analysis was used to determine the independent variables related to PTSD in the RD group.

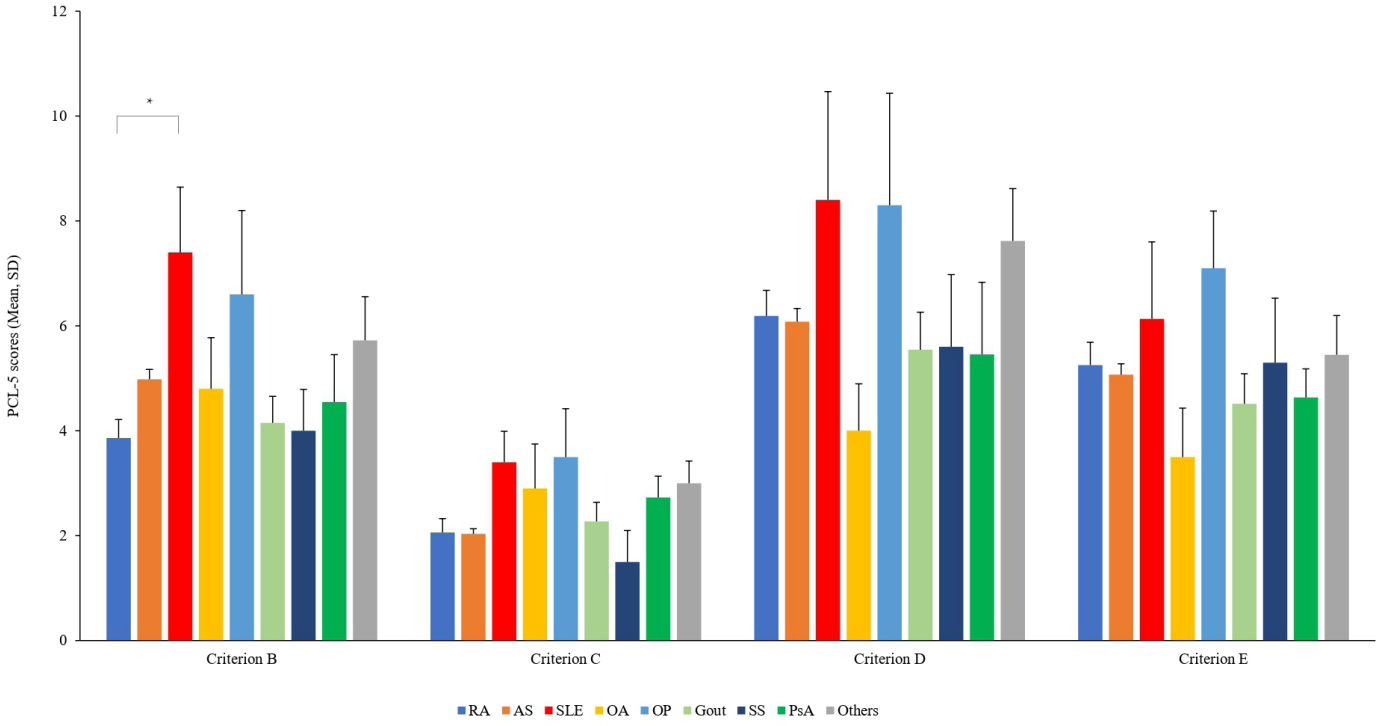

Figure 1 Group differences in all the PCL-5 criteria between the different subgroups of RD. All four criteria (B–E) are components of the PCL-5. *P<0.05. AS, ankylosing spondylitis; A, Osteoarthritis; OP, osteoporosis; PCL-5, PTSD checklist for DSM-5; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RD, rheumatic disease; SLE, systemic lupus erythematosus; SS, Sjogren's syndrome.

RESULTS

Demographic and clinical information of the patients with RD

A total of 490 patients with RD were recruited to complete the survey. Of the 490 respondents, 4 participants were removed due to illogical answers (eg, 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, 11 (2.3%) patients with psoriatic arthritis and 33 (6.8%) with other RDs. 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 patients with RD 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 patients with RD than healthy respondents (p<0. 001), indicating that all four types of symptoms (intrusion, avoidance, negative changes in cognition or mood, hyperarousal) are more severe in rheumatic patients. A total of 12.1% (59/486) of patients with RD 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 patients with RD 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 with healthy people was 3.12 (95% CI 1.86 to 5.21), and the adjusted OR value was 3.26 (95% CI 1.94 to 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 patients with SLE were significantly higher than those of the patients with RA (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 min', 'easily waking up at night or in the early morning' and 'sleep time') were significantly higher in the patients with RD than the healthy control group. The results indicated that during the COVID-19 pandemic, the prevalence and severity of

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

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				

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.
B, unstandardised beta; PCL-5, PTSD Checklist for DSM-5; PGA-VAS, Patient Global Assessment Visual Analogue Scale; RD, rheumatic disease; β, standardised regression weight.

PTSD were significantly higher in patients with RD than healthy controls, and the sleep quality of patients with PD was also worse.

Factors related to PTSD in patients with RD

With the PCL-5 score as the dependent variable and related variables as independent variables, the results of

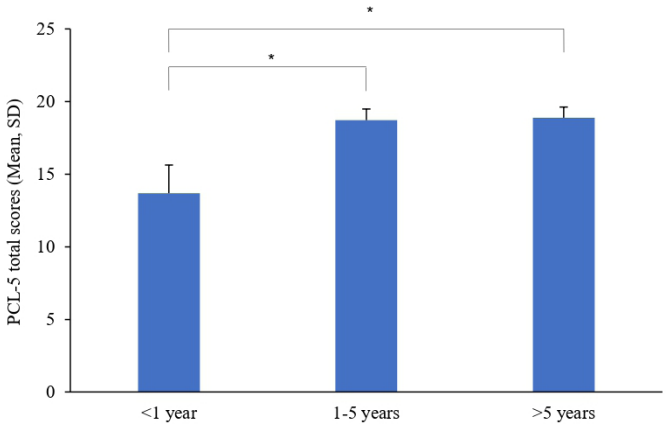

Figure 2 Differences in the PCL-5 scores between different disease duration groups. The duration of disease was transformed into three groups (<1 year, 1–5 years, >5 years). *P<0.05. PCL-5, PTSD Checklist for DSM-5.

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 patients with RD 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 (β=0.147, p=0.001), subjective assessment of the disease (β=0.112, p=0.014), and Q2 regarding the subjective perception of the COVID-19 epidemic (β=0.110, p=0.046) were positively correlated with the severity of PTSD symptoms, whereas age (β=−0.155, p=0.001) and Q3 (β=−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 patients with RD have been widespread concerned,[23] almost nothing is known with certainty about the psychological impact of the COVID-19 pandemic on patients with RD. In fact, patients with RD were more susceptible to mental disorders during this COVID-19 outbreak. It was demonstrated that patients with RD 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, patients with RD 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 patients with RD during the pandemic.

Fears had risen in patients with RD 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 imbalance was the behind reason. PTSD was characterised 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 patients with RD and make them more susceptible to PTSD.[11] Circulating cytokines may also be involved in making patients with RD 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 patients with RD 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 patients with RD.

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 patients with RD. 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 patients with RD 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 patients with RD, 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 emphasised 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 patients with RD 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 overendorse 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 with healthy controls, patients with RD 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 patients with RD is nothing to sneeze at.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study was approved by the Human Research Ethics Committee of Changzheng Hospital (2017SL046), and informed consent was obtained from all participants. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. 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, but not the study protocol,statistical analysis plan, or informed consent form. Data can be provided after the Article is published through the email address of the corresponding authors for communication.

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