Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Disease Activity and Mental Health Assessment in Rheumatoid Arthritis and Systemic Lupus Erythematosus with and Without Covid-19: Five-Year Multicenter Study

Marco Felipe Macêdo Alves

marcofma7@gmail.com

Universidade Federal do Cariri

Sally de França Lacerda Pinheiro

Universidade Federal do Cariri

Adriana Maria Kakehasi

Hospital das Clínicas da Universidade Federal de Minas Gerais

Gilda Aparecida Ferreira

Hospital das Clínicas da Universidade Federal de Minas Gerais

Isabela Paes de Sá Machado

Hospital Getúlio Vargas

João Pedro Belo Osório Salzano Lago

Hospital Getúlio Vargas

Lilian David de Azevedo Valadares

Hospital Getúlio Vargas

Gabriel Eduardo Grave

Hospital de Clínicas de Porto Alegre

Leonardo Peterson dos Santos

Hospital de Clínicas de Porto Alegre

Odirlei André Monticielo

Hospital de Clínicas de Porto Alegre

Ricardo Machado Xavier

Hospital de Clínicas de Porto Alegre

Rafael Nazaro Cassar Camargo

Hospital do Servidor Público Estadual

Nafice Costa Araújo

Hospital do Servidor Público Estadual

Sandra Lúcia Euzébio Ribeiro

Federal University of Amazonas

Viviane Angelina de Souza
Universidade Federal de Juiz de Fora
Angélica Vilela Rodrigues de Alvarenga
Universidade Federal de Juiz de Fora
Luiz Gustavo Chaves Gomes
Universidade Federal de Juiz de Fora
Licia Maria Henrique da Mota
University of Brasília
Ana Paula Monteiro Gomides Reis
University Center of Brasília
Edgard Torres dos Reis Neto
Federal University of São Paulo
Gecilmara Salviato Pilegii
Federal University of São Paulo
Marcelo de Medeiros Pinheiro
Federal University of São Paulo
Cláudia Diniz Lopes Marques
Federal University of Pernambuco

Research Article

Keywords: rheumatoid arthritis, COVID-19, symptom exacerbation, systemic lupus erythematosus, rheumatology

Posted Date: June 22nd, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9053192/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License

Additional Declarations: Competing interest reported. MMP is an Associate Editor, RMX is a Consulting Editor, and LMHM is a member of the Editorial Board of Advances in Rheumatology. These roles did not influence the review or editorial process of this manuscript.

Abstract

Background

COVID-19 is an infectious disease capable of causing dysregulation of the immune and inflammatory systems, mechanisms that are central to the pathophysiology of Systemic Lupus Erythematosus (SLE) and Rheumatoid Arthritis (RA). Psychaological symptoms following COVID-19 may act as confounding factors for disease activity indices in SLE and RA. There remains controversy in the literature regarding the potential activation or exacerbation of these diseases after COVID-19. This study aimed to compare disease activity and psychological outcomes in patients with RA and SLE, with and without a history of COVID-19, after five years of follow-up.

Method

This multicenter, cross-sectional study analyzed previously collected data from the Brazilian Registry of Patients with Chronic Inflammatory Diseases infected with SARS-CoV-2 (ReumaCoV) and additional data obtained five years later from the same individuals. Clinical and epidemiological characteristics, disease activity indices, and scores for depression, fatigue, stress, and anxiety were assessed. Patients were also asked whether they perceived a worsening of RA or SLE following COVID-19. Data were analyzed using descriptive statistics; normality by Shapiro–Wilk; group comparisons with chi-square/Fisher, t-test or Mann–Whitney; repeated measures by Friedman test ($p < 0.05$).

Results

The study included 168 patients: 81 with RA and 87 with SLE, distributed between the groups with COVID-19 (n = 107) and without COVID-19 (n = 61). After five years of follow-up, no significant differences were observed between groups in the Clinical Disease Activity Index (CDAI) or Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K) scores, as well as the fatigue, depression, or stress scores. However, patients with a history of COVID-19 had higher mean anxiety scores compared to controls (10.9 ± 11.0 vs. 7.6 ± 8.1; $p = 0.031$). Subjective worsening after COVID-19 was reported by 23.1% of patients with RA and 12.7% of those with SLE, and, in RA, it was associated with higher mean DASS-21 scores. Long COVID-19 was associated with higher mean anxiety scores (Long COVID-19: 18.7 ± 13.2 vs. without long COVID-19: 8.5 ± 9.7, $p = 0.007$).

Conclusions

Although no difference was observed in disease activity scores, higher anxiety levels were found among patients who had previous history of COVID-19, particularly those who met criteria for long COVID-19.

BACKGROUND

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune rheumatic disease characterized by progressive joint inflammation and extra-articular manifestations, that can lead to joint damage and

deformities[1]. This disease is mediated by several inflammatory cytokines, including tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6)[2]. Systemic lupus erythematosus (SLE) is also a chronic, systemic, autoimmune rheumatic disease; however, it presents with heterogeneous clinical and laboratory manifestations[3]. Clinical involvement may affect various systems, primarily the joints, skin, and serous membranes[4]. The signs and symptoms result from damage mediated by autoantibodies, immune complexes, and inflammatory cytokines such as interferon-alpha (IFN-α)[5].

Several viral infections have been implicated in the genesis and activation of these diseases, including infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[6]. Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, begins with viral replication in cells of the upper respiratory tract. Upon recognition of viral nucleic acids, these cells produce inflammatory cytokines such as IFN-α, which play a key role in the pathophysiology of SLE. In addition, there is evidence of systemic hyperinflammation in severe forms of COVID-19, with excessive release of IL-6 and TNF-α – key cytokines involved in RA activity[7,8].

Observational studies have demonstrated a higher frequency of SLE exacerbations in individuals who have had COVID-19[9,10]. RA patients who have experienced severe forms of COVID-19 showed a higher frequency of disease activation compared with those who had mild or moderate forms[11]. In a survey conducted in China involving 572 patients with immune-mediated rheumatic diseases (IMRDs), 29.1% reported worsening of symptoms following COVID-19[12].

COVID-19 survivors may experience psychological symptoms, such as depression and anxiety[13]. In individuals with SLE and RA, these symptoms should be considered when assessing disease activity, as they may worsen patient-reported components of disease activity indices[14].

In Brazil, research on COVID-19 in IMRDs has been mainly conducted through the Brazilian Registry of patients with Chronic Immune-Mediated Inflammatory Diseases Infected with SARS-CoV-2 (ReumaCoV)[15]. The first ReumaCoV study phase followed 601 individuals with IMRDs for six months. No significant differences were observed when comparing disease activity indices. However, some patients —particularly those with RA (32.2%) and SLE (23.3%)—reported worsening of their rheumatic disease after COVID-19[16]; therefore, based on reports of disease worsening following COVID-19 among individuals with SLE and RA during the first phase of the ReumaCoV study, these patients were reevaluated five years after the initial assessment using sociodemographic data, disease activity indices, and validated measures of fatigue, depression, anxiety, and stress.

METHODS

Design

This was a multicenter, analytical, observational, cross-sectional, quantitative study with a comparison group.

Location and period

The study was coordinated by Universidade Federal do Cariri (UFCA). Eight Brazilian centers previously registered in the ReumaCoV agreed to participate. Figure 1 illustrates the geographic locations of the study centers.

Figure 1. Geographic locations of the study centers across Brazil.

HUGV-UFAM: Hospital Universitário Getúlio Vargas - Universidade Federal do Amazonas; HGV-PE: Hospital Getúlio Vargas – Pernambuco; HCPA-UFRGS: Hospital de Clínicas de Porto Alegre - Universidade Federal do Rio Grande do Sul; HSPE-IAMSPE: Hospital do Servidor Público do Estado de São Paulo – Instituto de Assistência Médica ao Servidor Público Estadual; HU-UFJF: Hospital Universitário - Universidade Federal de Juiz de Fora; HC-UFMG: Hospital das Clínicas - Universidade Federal de Minas Gerais; EPM-UNIFESP: Escola Paulista de Medicina - Universidade Federal de São Paulo; HUB-UnB: Hospital Universitário de Brasília - Universidade de Brasília.

Database records were collected at the beginning of recruitment and six months later. Additional data corresponding to the five-year follow-up period were collected. Interviews were conducted between January and June 2025.

Sample of Participants

Planned sample included 198 patients with RA, of whom 94 had a history of COVID-19 and 104 did not, and 247 with SLE, of whom 135 had a history of COVID-19 and 112 did not. All participants had been previously registered in the ReumaCoV database. These numbers correspond to the total number of RA and SLE patients included during first phase of ReumaCoV study.

Inclusion Criteria

Participants were eligible for inclusion if they met the following criteria

1. Age ≥ 18 years;
2. Registration in the ReumaCoV database;

3. Case group: Confirmed diagnosis of COVID-19 according to the criteria of Brazilian Ministry of Health[17] and established diagnosis of RA and SLE by a rheumatologist and all of them fulfilled the classification criteria according to the 2010 ACR/EULAR classification criteria[18] and the 2019 ACR/EULAR classification criteria[19], respectively. Patients initially assigned to the control group were reclassified into the case group after receiving a diagnosis of COVID-19.
4. Control group: Patients with RA or SLE without diagnosis of COVID-19;
5. Provision of written informed consent.

Exclusion Criteria

Following exclusion criteria were applied to both Case and Control Groups:

1. Primary immunodeficiency;
2. Previous organ or bone marrow transplantation;
3. History of neoplasms within the last five years;
4. Current antineoplastic chemotherapy;
5. Diagnosis of human immunodeficiency virus (HIV) infection;
6. Thymic diseases.

Data collection

During first phase of ReumaCoV study, patients were evaluated at three time points: visit 1 (inclusion), visit 2 (three months), and visit 3 (six months), from May to December 2020. Data were stored in the Research Electronic Data Capture (REDCap) system.

In the present study, patients previously enrolled during the first phase, from both Case and Control groups, were contacted by telephone and invited to participate in a new assessment visit conducted five years after the initial study, which had not been originally planned. Participants were asked to provide new consent.

Study data were collected and managed using REDCap electronic data capture tools hosted by the Brazilian Society of Rheumatology. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing: 1) an intuitive interface for validated data capture; 2) audit trails to track data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with sources[20,21].

Methods for assessing disease activity

Previously validated assessment methods were used for RA and SLE. Disease activity in individuals with RA was measured using the Clinical Disease Activity Index (CDAI)[22,23]. In patients with SLE, disease

activity was assessed using the SLE Disease Activity Index 2000 (SLEDAI-2K)[24], based on data available in medical records.

Disease exacerbation was defined as follows:

- RA: worsening of symptoms compared with the period prior to COVID-19, associated with an increase in the CDAI score of at least 4.5 and/or the need for a change in treatment[25].
- SLE: worsening of symptoms compared with the period prior to COVID-19 associated with an increase in SLEDAI-2K score of at least 4 and/or the need for a change in treatment[26].

Patients were also asked whether they perceived a worsening of RA or SLE following COVID-19.

Assessment of fatigue, depression, stress and anxiety

Fatigue was assessed by Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-Fatigue). The Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-Fatigue) is a 13-item instrument that evaluates self-reported fatigue and its impact on daily activities and functioning. Although originally developed for patients with cancer-related anemia, it has been validated for use in patients with RA and SLE[27,28].

Each item is scored on a Likert scale ranging from 0 to 4, based on symptom intensity over the previous week. Scores are calculated by subtracting the item score from 4 (4 – item score), except for items 5 and 7, which are scored directly. Item scores are summed, with lower total scores indicating greater fatigue.

Depression, stress and anxiety were assessed by Depression, Anxiety, and Stress Scale-21 (DASS-21). DASS-21 is a short, 21-item assessment tool that measures self-reported depression, anxiety, and stress. Respondents rate the severity of symptoms experienced in the previous week on a Likert scale from 0 to 3, with higher scores indicating greater symptom severity. This instrument has been previously applied in patients with RA and SLE[29,30].

Ethical considerations

The study was approved by the Research Ethics Committee of UFCA under the Certificate of Presentation for Ethical Review (CAAE) number 82236724.7.1001.5698. Authorization to use the ReumaCoV database was obtained from the Brazilian Society of Rheumatology. All participants were contacted again to provide renewed written informed consent for the collection of additional data.

Data analysis and interpretation

The normality of variables was assessed using the Shapiro-Wilk test. A descriptive analysis of all study variables was performed. Qualitative variables were presented using absolute (n) and relative (%)

frequency distributions, while quantitative variables were described using measures of central tendency and dispersion, including mean, standard deviation, median, minimum, and maximum values.

Associations between groups and qualitative variables were assessed using Pearson's chi-square test or Fisher's exact test, when appropriate. Comparisons of quantitative variables between groups were conducted using Student's t-test for independent samples when the assumption of normality was met. When normality was not confirmed, the nonparametric Mann-Whitney U test was applied. The nonparametric Friedman test was used to compare repeated measures across different assessment time points.

A significance level of 5% ($p < 0.05$) was adopted for all analyses. Data were processed and analyzed using IBM SPSS Statistics software, version 28, and R software, version 4.3.1.

RESULTS

General

Of the 445 individuals invited to participate in the study, 168 completed the interview (37.8%). Most participants were female (94%), the mean age was 51.9 years, and 31.8% had completed higher education.

A total of 107 participants were allocated to the Case Group (COVID-19+) and 61 to the Control Group (COVID-19-), with no significant differences in age or sex. Twenty-eight participants originally from the Control Group were reallocated to the Case Group after acquiring COVID-19 between six months and five years of follow-up. Overall, 81 participants had RA and 87 had SLE (Fig. 2).

Figure 2. Distribution of study participants.

COVID-19+: patients with a confirmed diagnosis of COVID-19. COVID-19−: patients without a diagnosis of COVID-19. RA: Rheumatoid arthritis. SLE: Systemic lupus erythematosus.

*: reclassification occurred due to COVID-19 diagnosis between the six-month and five-year follow-up periods.

The most prevalent comorbidities were systemic arterial hypertension, kidney disease, and diabetes mellitus, without significant difference between groups. Most participants reported receiving at least three doses of a COVID-19 vaccine. In the Case Group, the most frequent method for COVID-19 confirmation was real-time polymerase chain reaction (RT-PCR) testing (55.1%), as observed in Table 1.

Table 1
Epidemiological and clinical features of individuals at the time of the current data collection.

Total	**Total**	**Case**	**Control**	**P - Value**
	168(100)	**107(63.7)**	**61(36.3)**	
Age (Mean ± SD)	51.9 ± 12.1	50.9 ± 10.9	53.6 ± 13.9	0.192
Gender – n (%)				
Male	10(6.0)	8(7.5)	2(3.3)	0.331
Female	158(94.0)	99(92.5)	59(96.7)	
BMI (Mean ± SD)	28.3 ± 5.5	28.4 ± 6.0	27.9 ± 4.4	0.531
Federative Unit – n (%)				
Amazonas	55(35.5)	36(35.3)	19(35.8)	0.855
Minas Gerais	16(10.3)	11(10.8)	5(9.4)	
Pará	1(0.6)	1(1.0)	0(0)	
Paraíba	1(0.6)	0(0)	1(1.9)	
Pernambuco	32(20.6)	20(19.6)	12(22.6)	
Rio Grande do Sul	27(17.4)	19(18.6)	8(15.1)	
São Paulo	18(11.6)	12(11.8)	6(11.3)	
Distrito Federal	4(2.6)	3(2.9)	1(1.9)	
Goiás	1(0.6)	0(0)	1(1.9)	
Education Level – n (%)				
Illiterate	2(1.3)	1(1.0)	1(1.8)	0.146
Incomplete elementary education	19(12.1)	9(8.8)	10(18.2)	
Completed elementary education	12(7.6)	8(7.8)	4(7.3)	
Incomplete high school	8(5.1)	3(2.9)	5(9.1)	
Completed high school	46(29.3)	29(28.4)	17(30.9)	
Incomplete higher education	8(5.1)	6(5.9)	2(3.6)	
Completed higher education	50(31.8)	35(34.3)	15(27.3)	
Graduate	12(7.6)	11(10.8)	1(1.8)	

SD: standard deviation; BMI: body mass index; RT-PCR: real-time polymerase chain reaction.

Total	Total	Case	Control	P - Value
	168(100)	**107(63.7)**	**61(36.3)**	
Diagnosis – n (%)				
Rheumatoid arthritis	81(48.2)	52(48.6)	29(47.5)	0.999
Systemic lupus erythematosus	87(51.8)	55(51.4)	32(52.5)	
Comorbidities – n (%)				
Smoking	6(3.8)	3(2.9)	3(5.6)	0.418
Alcoholism	3(1.9)	1(1.0)	2(3.7)	0.275
Heart disease	7(4.2)	2(1.9)	5(8.2)	0.100
Diabetes mellitus	23(13.7)	17(15.9)	6(9.8)	0.353
Lung disease	21(12.5)	14(13.1)	7(11.5)	0.814
Kidney disease	25(14.9)	13(12.1)	12(19.7)	0.259
Hypertension	83(49.4)	52(48.6)	31(50.8)	0.873
Doses of COVID-19 vaccines – n (%)				
1	1(0.7)	1(1.1)	0(0.0)	0.663
2	11(7.5)	6(6.3)	5(9.6)	
3	36(24.5)	26(27.4)	10(19.2)	
4	41(27.9)	25(26.3)	16(30.8)	
5	42(28.6)	25(26.3)	17(32.7)	
> 6	16(10.9)	12(12.6)	4(7.7)	
COVID-19 confirmatory criteria – n (%)				
RT-PCR		59 (55.1)		
Clinical-Epidemiological		19 (17.8)		
Rapid test (Antigen)		17 (15.9)		
Serology		12 (11.2)		
SD: standard deviation; BMI: body mass index; RT-PCR: real-time polymerase chain reaction.				

Table 1 **(placed at the end of the document)**

The most common symptoms during acute COVID-19 were myalgia, asthenia, fever, and headache, with a mean duration of 11.3 ± 10.2 days. Long COVID-19, defined as the persistence or development of new symptoms three months after the initial SARS-CoV-2 infection, lasting for at least two months, without any other plausible explanation[32], was identified in 35 patients (35.7%).

Rheumatoid arthritis

There were no significant differences in the mean CDAI scores between the Case and Control Groups. However, the Control Group exhibited higher levels of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).

Following COVID-19, 12 patients with RA reported subjective worsening of their underlying disease. This number was similar to that of participants who met objective criteria for disease exacerbation: five due to a change in treatment and seven due to an increase in CDAI score after COVID-19 (Table 2).

Table 2
Clinical features of patients with RA at the time of the current data collection.

Total	**Total**	**Case**	**Control**	**p-value**
	81(100)	**52(64.2)**	**29(35.8)**	
CDAI (Mean ± SD)	13.4 ± 12.0	13.6 ± 12.8	13.1 ± 12.1	0.889
CRP (Mean ± SD)	15.9 ± 43.5	6.4 ± 9.5	46.6 ± 84.7	**0.035**
ESR (Mean ± SD)	22.8 ± 21.5	18.2 ± 18.4	38.4 ± 24.9	**0.012**
Disease worsening after COVID-19 (reported by patients) – n (%)		12(23.1)		
CDAI worsened after COVID-19 – n (%)		7 (13.5)		
Treatment changes after COVID-19 – n (%)		5 (9.6)		

CDAI: *Clinical Disease Activity Index*. CRP: C-Reactive Protein. ESR: Erythrocyte sedimentation rate; SD: Standard deviation. Results with statistically significant p-values are shown in bold. Note: CRP and ESR data were not available for all patients.

Systemic lupus erythematosus

No significant differences were observed between cases and controls in mean SLEDAI-2K indices. The most common manifestations of disease activity were joint, renal, and skin involvement. There were no significant differences between groups regarding manifestations of disease activity, anti-dsDNA antibodies, or C3 and C4 complement levels.

After COVID-19, seven individuals with SLE described worsening of disease activity. Of these, six met objective criteria for post-infection activation, including an increase in SLEDAI-2K score in four participants and a change in treatment in two ones (Table 3).

Table 3
Clinical features of patients with SLE at the time of the current data collection.

Total	**Total**	**Case**	**Control**	**p-value**
	87(100)	**55(63.2)**	**32(36.8)**	
SLEDAI-2K (Mean ± SD)	2.2 ± 4.6	2.5 ± 5.2	1.5 ± 2.8	0.298
SLE Involvement – n (%)				
Joint	20(23.0)	12(21.8)	8(25.0)	0.734
Heart	3(3.4)	2(3.6)	1(3.1)	0.999
Skin	11(12.6)	7(12.7)	4(12.5)	0.999
Hematological	7(8.0)	4(7.3)	3(9.4)	0.999
Lung	4(4.6)	3(5.5)	1(3.1)	0.999
Kidney	15(17.2)	9(16.4)	6(18.8)	0.776
Central nervous system	2(2.3)	2(3.6)	0(0.0)	0.530
Vasculitis	1(1.1)	0(0.0)	1(3.1)	0.368
Serositis	2(2.3)	1(1.8)	1(3.1)	0.695
Anti-dsDNA – n (%)				
Negative	30(40.5)	17(34.7)	13(52.0)	0.364
Positive	10(13.5)	7(14.3)	3(12.0)	
Not available	51(45.9)	25(51.0)	9(36.0)	
Patient global assessment (Mean ± SD)	2.6 ± 2.9	2.8 ± 2.9	2.2 ± 2.8	0.298
Complement C3 (Mean ± SD)	119.5 ± 38.7	116.1 ± 39.4	124.5 ± 38.0	0.303
Complement C4 (Mean ± SD)	27.6 ± 17.9	28.7 ± 22.2	26.1 ± 8.5	0.898
Disease worsening after COVID-19 (reported by patients) – n (%)		7(12.7)		
SLEDAI-2K worsened after COVID-19 – n (%)		4 (7.3)		
Treatment changes after COVID-19 – n (%)		2 (3.6)		

Anti-dsDNA: Antibodies anti-double-stranded desoxyribonucleic acid; SD: Standard deviation; SLE: Systemic Lupus Erythematosus. SLEDAI-2K: *Systemic Lupus Erythematosus Disease Activity Index* –

2000.

Fatigue, depression, stress and anxiety

Figure 3 presents the mean scores obtained on the DASS-21 and FACIT-Fatigue scales.

Patients in the Case Group had a significantly higher mean anxiety score than those in the Control Group (10.9 ± 11.0 vs. 7.6 ± 8.1, p = 0,031). Mean depression and stress scores were similar between groups (Depression 10.4 ± 11.2 vs. 9.3 ± 9.9, p = 0.561; Stress 13.1 ± 10.9 vs. 10.1 ± 10.5, p = 0.093). The mean FACIT-Fatigue scores were also similar between groups (33.9 ± 13.3 vs. 36.5 ± 12.3, p = 0.262).

Figure 4 illustrates the mean anxiety scores differences between patients with or without long COVID-19.

Figure 4. Mean anxiety scores comparison between patients with RA or SLE with or without long COVID-19.

RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus

Data related to long COVID-19 was available in 49 RA patients. 12 (24%) met long COVID-19 criteria. Mean anxiety score was greater in those individuals (13.3 ± 9.5 vs. 7.4 ± 8.8, p = 0.047). Long COVID-19 was not associated with subjective disease worsening after COVID-19 (respectively, 36.4% vs. 23.5%, p = 0.448).

Regarding SLE, data related to long COVID-19 was available also in 49 patients. 23 (47%) met long COVID-19 criteria, and those patients also had greater mean anxiety scores (18.7 ± 13.2 vs. 8.5 ± 9.7, p = 0.007). Subjective disease worsening after COVID-19 was not associated with long COVID-19 (respectively, 22.7% vs. 8%, p = 0.228).

Tables 4 and 5 compare the mean DASS-21 and FACIT-Fatigue scores in patients with RA and SLE, respectively, with or without report of disease worsening after COVID-19. Patients with RA who reported disease worsening after COVID-19 had higher mean DASS-21 scores (depression, anxiety and stress), without difference in FACIT-Fatigue score. However, SLE patients that reported disease worsening after COVID-19 had similar DASS-21 and FACIT-Fatigue scores in comparison to those who did not report.

Table 4
Relationship between disease worsening after COVID-19 and DASS-21 and FACIT-Fatigue scores in RA patients

	With report of disease worsening after COVID-19	**Without report of disease worsening after COVID-19**		
	n (%)	**n (%)**		**p**
Total	12(18.7)	51(79.7)		
Depression (Mean ± SD)	14.0 ± 10.0	6.8 ± 8.0		**0.012**
Anxiety (Mean ± SD)	14.3 ± 10.7	7.2 ± 7.5		**0.022**
Stress (Mean ± SD)		16.5 ± 10.9	9.3 ± 8.0	**0.027**
FACIT – Fatigue (Mean ± SD)		27.8 ± 15.4	35.4 ± 12.1	0.110

Table 5
Relationship between disease worsening after COVID-19 and DASS-21 and FACIT-Fatigue scores in SLE patients

	With report of disease worsening after COVID-19	**Without report of disease worsening after COVID-19**		
	n (%)	**n (%)**		**p**
Total	7(9.9)	64(90.1)		
Depression (Mean ± SD)	20.9 ± 14.8	10.6 ± 11.5		0.069
Anxiety (Mean ± SD)	17.7 ± 16.9	10.1 ± 10.8		0.355
Stress (Mean ± SD)	19.1 ± 13.8	13.1 ± 12.4		0.265
FACIT – Fatigue (Mean ± SD)		27.4 ± 16.5	36.2 ± 11.9	0.131

Differences in disease activity between periods

34 SLE patients and 26 RA patients from Case Group had activity scores available from all periods (recruitment, 6 months and 5 years) and were included in this analysis. Regarding RA, there was no significant difference between CDAI means over five-year follow-up (Fig. 5A). (Case group: Recruitment 16.3 ± 15.9, 6 months 11.6 ± 9.6, 5 years 13.4 ± 11.3, p = 0.322; Control group: Recruitment 17.7 ± 14.4, 6

months 11.7 ± 11.9, 5 years 12.9 ± 12.3, p = 0.06). In contrast, among participants with SLE, there was a significant reduction in mean SLEDAI-2K scores over the five-year follow-up period in both groups (Fig. 5B) (Case group: Recruitment 3.91 ± 3.7, 6 months 6.2 ± 3.8, 5 years 2.5 ± 5.2, p = 0.001; Control group: Recruitment 4.2 ± 4.1, 6 months 4.2 ± 4.4, 5 years 1.5 ± 2.8, p = 0.045).

DISCUSSION

In this multicenter study, no significant differences in CDAI and SLEDAI-2K scores were observed after five years of follow-up. Similar results were reported in the first phase of the ReumaCoV study, which analyzed disease activity after six months of follow-up[16].

In contrast, a retrospective study of patients with RA hospitalized for COVID-19 demonstrated worsening of underlying disease activity, as assessed by the DAS-28-CRP, in 32 of 43 participants[32]. Likewise, another study involving individuals with RA also demonstrated increased disease activity after COVID-19, reflected by higher DAS-28 scores (4.82 *versus* 3.79, $p < 0.001$)[33].

Apart from the initial phase of the ReumaCoV study, no other investigations have compared CDAI scores between individuals with and without COVID-19. CDAI was selected for the present study due to the unavailability of laboratory tests for all participants, which would have compromised the use of the DAS-28, as it requires laboratory parameters for its application[34]. A systematic review published in 2012 reported a high level of agreement between CDAI and DAS-28, with concordance indices ranging from 0.89 to 0.93[35], allowing comparison between the findings of the afore mentioned studies and those of the present investigation.

With respect to SLE, a Brazilian study similarly found no differences in SLEDAI-2K scores between individuals with and without COVID-19[36]. However, a case-control study demonstrated a higher frequency of disease activity among patients with prior COVID-19, using the SELENA-SLEDAI index (17.6 *versus* 5.5%, p = 0.001)[9].

Differences between the findings of the present study and those of previous investigations may be attributed to methodological differences, such as follow-up duration, sample size, availability of laboratory tests, clinical and laboratorial profile of patients, and metrics used to assess disease activity. These conflicting results highlight the lack of consensus in the literature regarding the impact of COVID-19 on disease activity in IMRD. Moreover, most studies did not evaluate the burden of mental health and psychological disorders on the disease activity scores that may artificially inflate them, especially related to pain and fatigue, one of the key strengths of our study.

Some factors inherent to the present sample may have contributed to protection against worsening of rheumatic diseases after a viral infection. Most participants had received at least three doses of SARS-CoV-2 vaccines, which may have reduced infection severity and the risk of disease exacerbation in both SLE and RA. This finding was also seen in a Korean cohort, in which the incidence of SLE and RA

following SARS-CoV-2 infection was lower in the group that had received at least one dose of a COVID-19 vaccine (hazard ratio [HR] 0.59; 95% CI 0.49–0.71)[37].

In addition, the long follow-up period and ongoing treatment of patients in this cohort may have resulted in better disease control, thereby reducing the likelihood of post-infection worsening. This hypothesis is reinforced by a cross-sectional study of 306 individuals with RA in China, which found that poor disease control prior to SARS-CoV-2 infection was associated with disease reactivation (Odds Ratio [OR] 2.10; 95% CI 1.23–3.58)[38].

Although no significant differences in disease activity scores were observed at the five-year reassessment, 23.1% of participants with RA and 12.7% of those with SLE reported subjective worsening of their underlying disease following SARS-CoV-2 infection. These numbers were slightly lower than those found in the initial six-month analysis, in which 32.2% of participants with RA and 23.3% of those with SLE reported worsening after COVID-19[16].

Subjective disease worsening after COVID-19 was associated with higher mean depression, anxiety and stress scores in RA patients. This suggests that, at least in RA, psychological burden can be more important than increasing disease activity to explain the patients' perception of disease worsening after SARS-CoV-2 infection. Depression and anxiety were associated, in other study, with higher tender joint count and worse general health in RA; also, depression was associated with lower probability of achieving remission in RA[39].

A meta-analysis reported a prevalence of long COVID-19 of 43%, which is close to the 35.7% observed in the present sample[40]. A cohort study conducted in the United States involving individuals with SLE and RA reported a long COVID-19 prevalence of 29.8%, slightly lower than that found in the present study[41].

Symptoms of long COVID-19 should be interpreted with caution in patients with SLE and RA, as they may be confused with manifestations of the underlying diseases or with other comorbid conditions, such as fibromyalgia. They may overlap with symptoms of rheumatic diseases and erroneously induce higher disease activity scores[8]. For instance, arthralgia may be counted as tender joints in the CDAI, while fatigue and memory complaints may be interpreted as organic brain disease in the SLEDAI-2K.

Both RA and SLE patients who met the criteria for long COVID-19 exhibited higher mean anxiety scores. A systematic review reported an anxiety prevalence of up to 47.8% among individuals with long COVID-19[42]. Female sex and the presence of clinical comorbidities were identified as key predictors of mental health disorders—factors that were highly prevalent in our sample. However, we did not assess patients' prior history of mental health disorders, which limits our ability to determine whether COVID-19 acted as a trigger for new-onset anxiety or exacerbated pre-existing psychiatric conditions.

No significant differences in the CDAI scores were observed between the recruitment periods at six months and five years. SLEDAI-2K showed a nonsignificant increase in the Case Group at six months, likely reflecting early post-COVID 19 disease worsening. After five years, there was a significant reduction

in the index in both groups, which may have been a consequence of appropriate treatment of the underlying disease.

Furthermore, in the present sample, anxiety scores were significantly higher among individuals with a history of COVID-19, without differences in depression, fatigue and stress. During the initial six-month follow-up, higher levels of anxiety, depression, fatigue, and stress were also found in the Case Group[16]. This discrepance between studies may be likely due to the loss to follow-up of some individuals in the five-year analysis.

The present findings are consistent with studies conducted in other publications. A study from a tertiary hospital in Afghanistan using the DASS-21 found higher rates of moderate to extremely severe anxiety (69.7%) compared with depression (31.7%) or stress (42.9%) among individuals affected by COVID-19[43]. Similarly, an observational study in India involving hospitalized COVID-19 patients reported a higher prevalence of anxiety (85%) than depression (63.3%) or stress (26.7%)[44].

COVID-19 may be associated with the development or worsening of anxiety through several factors, including social isolation during the acute phase of infection, fear of unfavorable disease progression, physical symptoms caused by infection, and social stigma. In a large Chinese study involving 19,802 participants during the SARS-CoV-2 pandemic, the risk of anxiety was higher in people with chronic diseases and in individuals with COVID-19 symptoms[45]. The presence of comorbid conditions, such as SLE and RA, may be related to anxiety due to fear of worsening and death from COVID-19.

Assessment of psychological factors in patients with rheumatic diseases is therefore of great importance in clinical practice, as these symptoms may negatively affect quality of life and worsen pain perception, with increased disease activity indices. A study involving 76 individuals with RA demonstrated significant correlations between DASS-21 and arthritis activity metrics, such as CDAI, DAS-28-CRP, and tender joint count[14]. Similarly, a case-control study of 120 patients with SLE, half of whom had a history of COVID-19, showed higher depression and anxiety scores in the Case Group, with infection identified as a predictor of severe depression and moderate to severe anxiety. There was also a correlation between depression and anxiety rates and other SLE assessment metrics, such as SLEDAI and the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR)[46].

Patients with SLE and RA who have a history of COVID-19 may therefore benefit from more appropriate psychological monitoring, including screening questionnaires for depression, stress, and anxiety during rheumatology consultations, and access to psychological support services, such as group therapy and consultations with mental health specialists.

Among individuals with RA, ESR and CRP levels were higher in the Control Group, and no clinically relevant reason for this finding was identified. However, inflammatory markers are nonspecific and may be elevated in other inflammatory or noninflammatory conditions, such as obesity and aging[47].

Therefore, assessment of disease activity by metrics is more reliable than isolated complementary exams.

This study has several limitations. First, there was a substantial loss to follow-up, with only 37.8% of invited participants completing the interview, which could have resulted in selection bias. Second, there was a lack of laboratory test data, as it depends on follow-up, assisting team requests, patient performance, and access to and/or submission of these results by participants. If laboratory tests had been performed on all individuals in a systematic manner, results could have been more consistent with the other evaluation metrics. Finally, memory bias cannot be excluded, as participants were required to report events occurring over a five-year period.

CONCLUSIONS

After five years of follow-up, no significant differences in the CDAI and SLEDAI-2K indices were observed between individuals in the Case and Control Groups. Over time, while the CDAI remained stable, SLEDAI-2K scores decreased in both Case and Control Groups.

Individuals with a history of COVID-19 exhibited higher anxiety scores, whereas no significant differences were observed in depression, stress, or fatigue. This population, especially those who met criteria for long COVID-19, should undergo more frequent screening for mental health problems, particularly anxiety. In addition, the importance of multiprofessional psychological follow-up after COVID-19 is emphasized.

Given the methodological discrepancies of existing studies and the limited number of published investigations, further research using standardized methodologies, similar disease activity scores, and laboratory analysis of individuals is required to clarify the relationship between COVID-19 and disease activity in SLE and RA.

Abbreviations

ACR
American College of Rheumatology
BMI
Body mass index
CDAI
Clinical Disease Activity Index
CNS
Central nervous system
COVID
19–Coronavirus disease 2019
CRP
C–reactive protein
DAS

28–Disease Activity Score 28

DAS

28–**CRP**–Disease Activity Score 28–C–reactive protein

DASS

21–Depression, Anxiety and Stress Scale–21

ESR

Erythrocyte sedimentation rate

EULAR

European League Against Rheumatism

FACIT

Fatigue–Functional Assessment of Chronic Illness Therapy–Fatigue Scale

HIV

Human immunodeficiency virus

IFN

α–Interferon alpha

IL

6–Interleukin 6

IMRD

Immune–mediated rheumatic diseases

RA

Rheumatoid arthritis

ReumaCoV

Brazilian Registry of Patients with Chronic Inflammatory Diseases Infected with SARS–CoV–2

RF

Rheumatoid factor

RT

PCR–Real–time polymerase chain reaction

SARS

CoV–**2**–Severe acute respiratory syndrome coronavirus 2

SELENA

SLEDAI–Safety of Estrogens in Lupus Erythematosus–Systemic Lupus Erythematosus Disease Activity Index

SLE

Systemic lupus erythematosus

SLEDAI

2K–Systemic Lupus Erythematosus Disease Activity Index 2000

SLICC/ACR

Systemic Lupus International Collaborating Clinics/American College of Rheumatology

TNF

α–Tumor necrosis factor alpha

UFCA
Universidade Federal do Cariri

Declarations

Ethics approval and consent to participate:

This study was conducted in accordance with the Declaration of Helsinki and received approval from the Ethics Committee of the coordinating institution. The study was approved by the Research Ethics Committee of Universidade Federal do Cariri (UFCA) under the Certificate of Presentation for Ethical Review number 82236724.7.1001.5698. Informed consent was obtained from all participating centers and from all individual participants before inclusion in the study.

Consent for publication:

Not applicable

Competing interests:

MMP is an Associate Editor, RMX is a Consulting Editor, and LMHM is a member of the Editorial Board of Advances in Rheumatology. These roles did not influence the review or editorial process of this manuscript.

Competing Interests

MMP is an Associate Editor, RMX is a Consulting Editor, and LMHM is a member of the Editorial Board of Advances in Rheumatology. These roles did not influence the review or editorial process of this manuscript.

Funding:

The principal investigator received a Master’s degree scholarship from the Fundação Cearense de Apoio ao Desenvolvimento Científico e Tecnológico (FUNCAP), which supported this research.

Author Contribution

MFMA, SFLP, AMK, APMGR, ETRN, GSP, GAF, LMHM, MMP, OAM, RMX and CDLM conceived and designed the study. MFMA, AMK, GAF, IPSM, JPBOSL, LDAV, GEG, LPS, OAM, RMX, RNCC, NFC, SLER, VAS, AVRA, LGCC and LMHM collected the data. MFMA, SFLP and CDLM interpreted the data. MFMA drafted the manuscript.All authors critically revised the manuscript for important intellectual content and approved the final version.

Acknowledgement

We would like to thank the Brazilian Society of Rheumatology for providing access to REDCap platform.

Data Availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

References

1. Smolen JS, Aletaha D, Barton A, et al. Rheumatoid arthritis. Nat Rev Dis Primers. 2018;4:18001.
2. Kondo N, Kuroda T, Kobayashi D. Cytokine networks in the pathogenesis of rheumatoid arthritis. Int J Mol Sci. 2021;22:10922.
3. Elia A, Zucchi D, Silvagni E, et al. Systemic lupus erythematosus: one year in review 2025. Clin Exp Rheumatol. 2025;43:397–406.
4. Fanouriakis A, Tziolos N, Bertsias G, Boumpas DT. Update on the diagnosis and management of systemic lupus erythematosus. Ann Rheum Dis. 2021;80:14–25.
5. Shiozawa S. Pathogenesis of Autoimmunity/Systemic Lupus Erythematosus (SLE). Cells. 2025;14:1080.
6. Korzeniowska A, Bryl E. Infectious agents in the pathogenesis of autoimmune rheumatic diseases. Transl Res. 2024;276:39–45.
7. Lamers MM, Haagmans BL. SARS-CoV-2 pathogenesis. Nat Rev Microbiol. 2022;20:270–84.
8. Dewanjee S, Kandimalla R, Kalra RS, et al. COVID-19 and rheumatoid arthritis crosstalk: emerging association, therapeutic options and challenges. Cells. 2021;10:3291.
9. Cheung CL, To CH, Ho LY, Chan KL, Tse SM, Mok CC. Effect of COVID-19 infection on disease flares and herpes zoster reactivation in patients with systemic lupus erythematosus: a case–control study. Ann Rheum Dis. 2023;82(Suppl 1):15081.
10. Mageau A, Géradin C, Sallah K, Papo T, Sacre K, Timsit J-F. Risk of systemic lupus erythematosus flare after COVID-19 hospitalization: a matched cohort study. PLoS ONE. 2024;19:e0309316.
11. Embaby A, Maged L, Abdel-Hamid H, El Hadidi KT. Factors associated with severe infection in rheumatoid arthritis patients: lessons learned from the COVID-19 pandemic. Infection. 2024;52:1337–45.
12. Lai P, Chen H, Yan Y, et al. The effect of COVID-19 infection on patients with rheumatic diseases in China. Clin Rheumatol. 2024;43:1199–206.
13. Mazza MG, Palladini M, Poletti S, Benedetti F. Post-COVID-19 depressive symptoms: epidemiology, pathophysiology, and pharmacological treatment. CNS Drugs. 2022;36:681–702.

14. Giannotta M, Fornaro M, Morrone M, Anelli MG. Impact of mood disorders assessed with DASS-21 on disease activity in patients with rheumatoid arthritis and fibromyalgia. Ann Rheum Dis. 2024;83:1306–7.
15. Marques C, Kakehasi AM, Gomides AP, et al. A Brazilian cohort of patients with immuno-mediated chronic inflammatory diseases infected by SARS-CoV-2 (ReumaCoV-Brasil registry): protocol for a prospective, observational study. JMIR Res Protoc. 2020;9:e24357.
16. Marques C, Pinheiro MM, Lopes J, et al. COVID-19 on patients with immune-mediated rheumatic disease: a comparative study of disease activity, fatigue, and psychological distress over six months. Adv Rheumatol. 2025;65:4.
17. Brazil. Health Ministry. Guia de vigilância epidemiológica: emergência de saúde pública de importância nacional pela doença pelo coronavírus 2019 - COVID-19. [Article in Portuguese] Brasília. Ministério da Saúde; 2022.
18. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2010;69:1580–8.
19. Aringer M, Costenbader K, Daikh D, et al. 2019 EULAR/ACR classification criteria for systemic lupus erythematosus. Arthritis Rheumatol. 2019;71:1400–12.
20. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap) – a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inf. 2009;42:377–81.
21. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software partners. J Biomed Inf. 2019;95:103208.
22. Aletaha D, Nell VP, Stamm T, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. Arthritis Res Ther. 2005;7:R796–806.
23. Aletaha D, Smolen J. The Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI): a review of their usefulness and validity in rheumatoid arthritis. Clin Exp Rheumatol. 2005;23:S100–8.
24. Gladman DD, Ibañez D, Urowitz MB. Systemic Lupus Erythematosus Disease Activity Index 2000. J Rheumatol. 2002;29:288–91.
25. Yee CS, Farewell VT, Isenberg DA, et al. The use of Systemic Lupus Erythematosus Disease Activity Index-2000 to define active disease and minimal clinically meaningful change based on data from a large cohort of systemic lupus erythematosus patients. Rheumatol (Oxford). 2011;50:982–8.
26. Konzett V, Kerschbaumer A, Smolen JS, et al. Definition of rheumatoid arthritis flare based on SDAI and CDAI. Ann Rheum Dis. 2024;83:169–76.
27. Cella D, Yount S, Sorensen M, Chartash E, Sengupta N, Grober J. Validation of the Functional Assessment of Chronic Illness Therapy–Fatigue Scale relative to other instrumentation in patients with rheumatoid arthritis. J Rheumatol. 2005;32:811–9.

28. Goligher EC, Pouchot J, Brant R, et al. Minimal clinically important difference for 7 measures of fatigue in patients with systemic lupus erythematosus. J Rheumatol. 2008;35:635–42.
29. Khan A, Pooja V, Chaudhury S, Bhatt V, Saldanha D. Assessment of depression, anxiety, stress, and quality of life in rheumatoid arthritis patients and comparison with healthy individuals. Ind Psychiatry J. 2021;30:S195–200.
30. Tee CA, Salido EO, Reyes PW, Ho RC, Tee ML. Psychological state and associated factors during the 2019 coronavirus disease (COVID-19) pandemic among Filipinos with rheumatoid arthritis or systemic lupus erythematosus. Open Access Rheumatol. 2020;12:215–22.
31. Medicine Division; Board on Global Health; Board on Health Sciences Policy, Health M. Committee on Examining the Working Definition for Long COVID. A Long COVID Definition: a chronic, systemic disease state with profound consequences. Washington, DC: National Academies; 2024.
32. Vlădulescu-Trandafir AI, Onose G, Munteanu C, et al. Unraveling the impact of COVID-19 on rheumatoid arthritis: insights from two Romanian hospitals — preliminary results. Biomedicines. 2024;12:2145.
33. Aglan L, Fathi N, Haseib SS, Elnoby F. Clinical impact of COVID-19 infection on rheumatoid arthritis patients. Aswan Univ Med J. 2024;4:232–43.
34. Prevoo ML, Hof MA, Kuper HH, Leeuwen MA, de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight–joint counts: development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995;38:44–8.
35. Gaujoux-Viala C, Mouterde G, Baillet A, et al. Evaluating disease activity in rheumatoid arthritis: which composite index is best? A systematic literature analysis of studies comparing the psychometric properties of the DAS, DAS28, SDAI, and CDAI. Joint Bone Spine. 2012;79:149–55.
36. Carvalho JS, Neto ER, Kakehasi AM, et al. Factors associated with poor outcomes in SLE patients with COVID-19: data from ReumaCoV-Brazil register. Lupus. 2023;32:42–53.
37. Kim MS, Lee H, Lee SW, et al. Long-term autoimmune inflammatory rheumatic outcomes of COVID-19: a binational cohort study. Ann Intern Med. 2024;177:291–302.
38. Li R, Zhao J-K, Li Q, et al. Analysis of related factors for RA flares after SARS-CoV-2 infection: a retrospective study from patient survey. Sci Rep. 2024;14:4243.
39. Selinde VJSH, Marijn V, Gonul HK, et al. Association between depression and anxiety and inability to achieve remission in rheumatoid arthritis and psoriatic arthritis. Rheumatology. 2025;64(5):2411–21.
40. Chen C, Haupert SR, Zimmermann L, Shi X, Fritsche LG, Mukherjee B. Global prevalence of post–coronavirus disease 2019 (COVID-19) condition or long COVID: a meta-analysis and systematic review. J Infect Dis. 2022;226:1593–607.
41. Teles MS, Brundage J, Chiang T-P, et al. Prevalence and risk factors of postacute sequelae of COVID-19 in adults with systemic autoimmune rheumatic diseases. J Rheumatol. 2024;51:928–33.
42. Rocha DM, Pedroso AO, Menegueti MG, et al. Predictors of Anxiety, Depression, and Stress in Long COVID: Systematic Review of Prevalence. Int J Environ Res Public Health. 2025;22(6):867.

43. Niazi AU-R, Alekozay M, Najm AF. Prevalence and associated factors of depression, anxiety and stress among coronavirus disease 2019 (COVID-19) patients in Herat, Afghanistan. Glob Health J. 2022;6:85–90.
44. Kumar K, Srivastava S, Meena A, Avasthi RK, Kashyap B. The association of psychosocial manifestations and quality of life with inflammatory markers in SARS-CoV-2 patients: a study from a dedicated COVID-19 tertiary care hospital. Cureus. 2023;15:e42341.
45. Zhong J, Zhong C, Qiu L, et al. Risk and protective factors for anxiety during COVID-19 pandemic. BMC Public Health. 2021;21:1063.
46. Abd El-Khalik DM, Eltohamy M. Post-COVID-19 depression and anxiety in patients with systemic lupus erythematosus. Lupus. 2023;32:974–82.
47. Alende-Castro V, Alonso-Sampedro M, Fernández-Merino C, et al. C-reactive protein versus erythrocyte sedimentation rate: implications among patients with no known inflammatory conditions. J Am Board Fam Med. 2021;34:974–83.

Figures

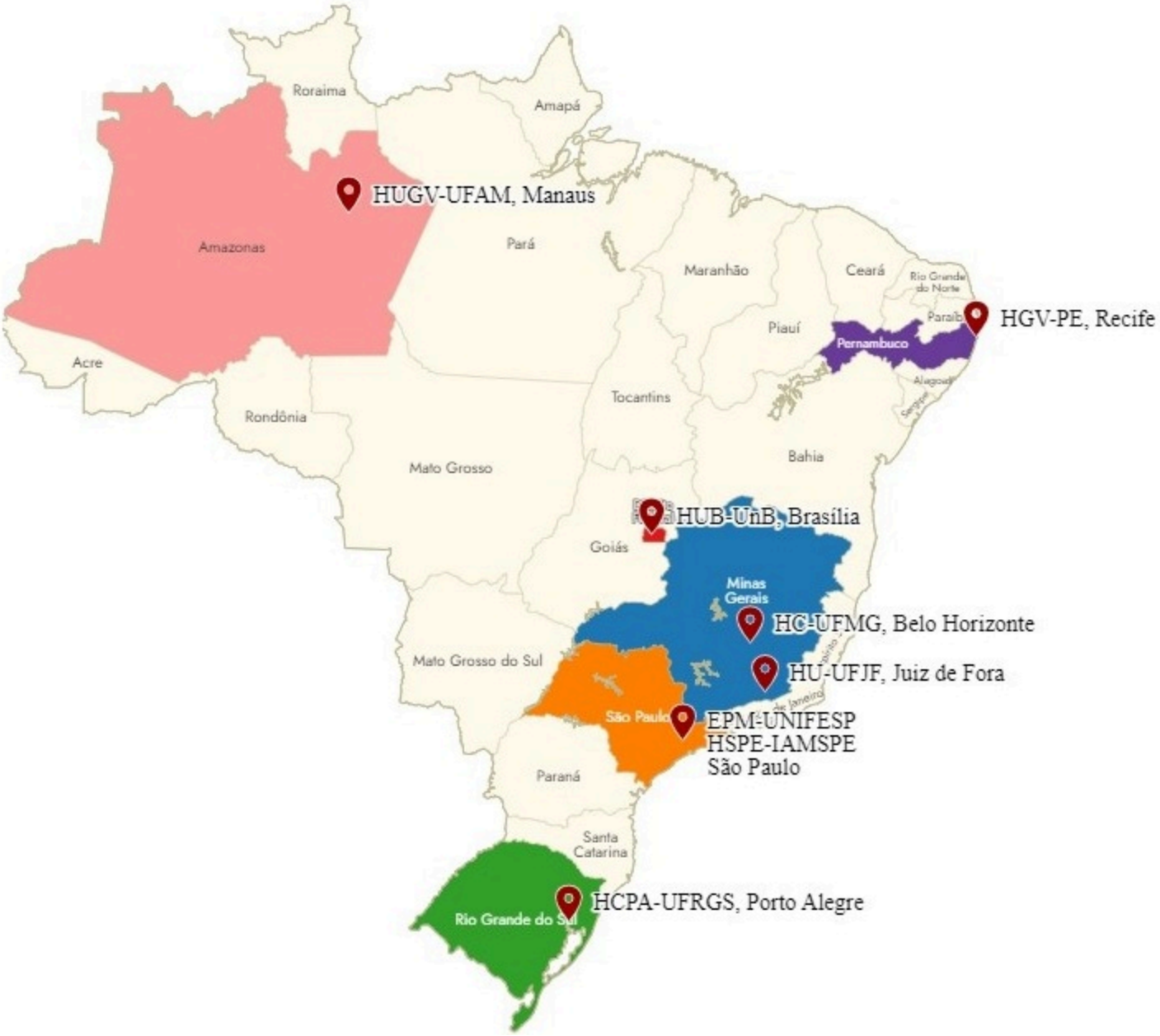


Figure 1

Geographic locations of the study centers across Brazil.

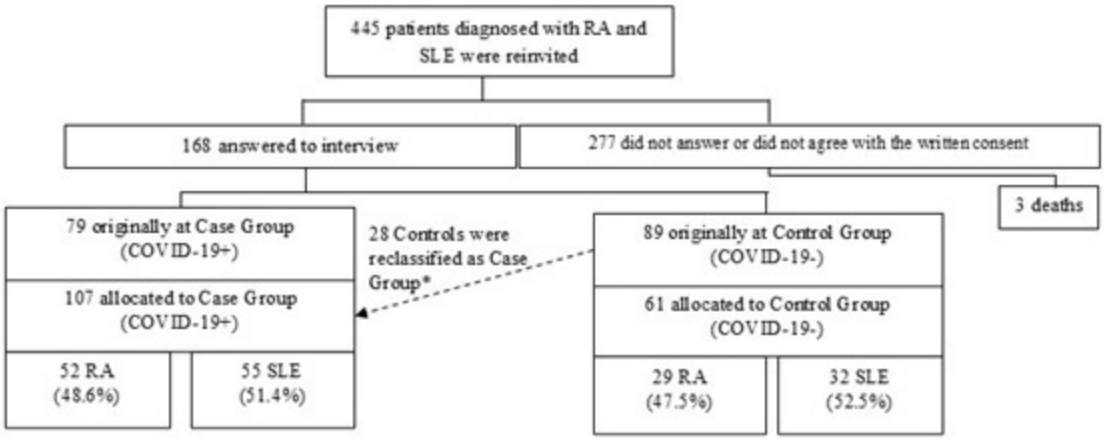


Figure 2

Distribution of study participants.

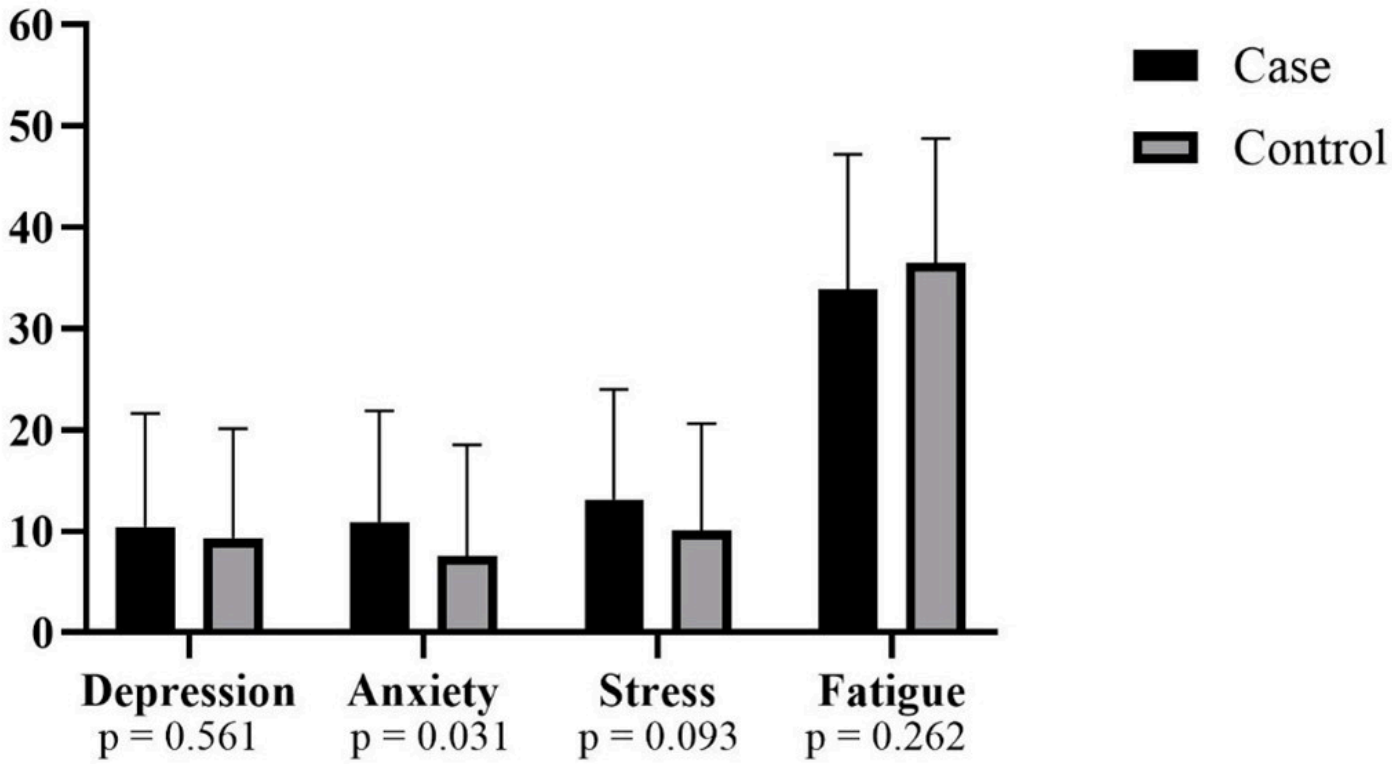


Figure 3

Mean scores for depression, anxiety, stress, and fatigue indices at the five-year time point.

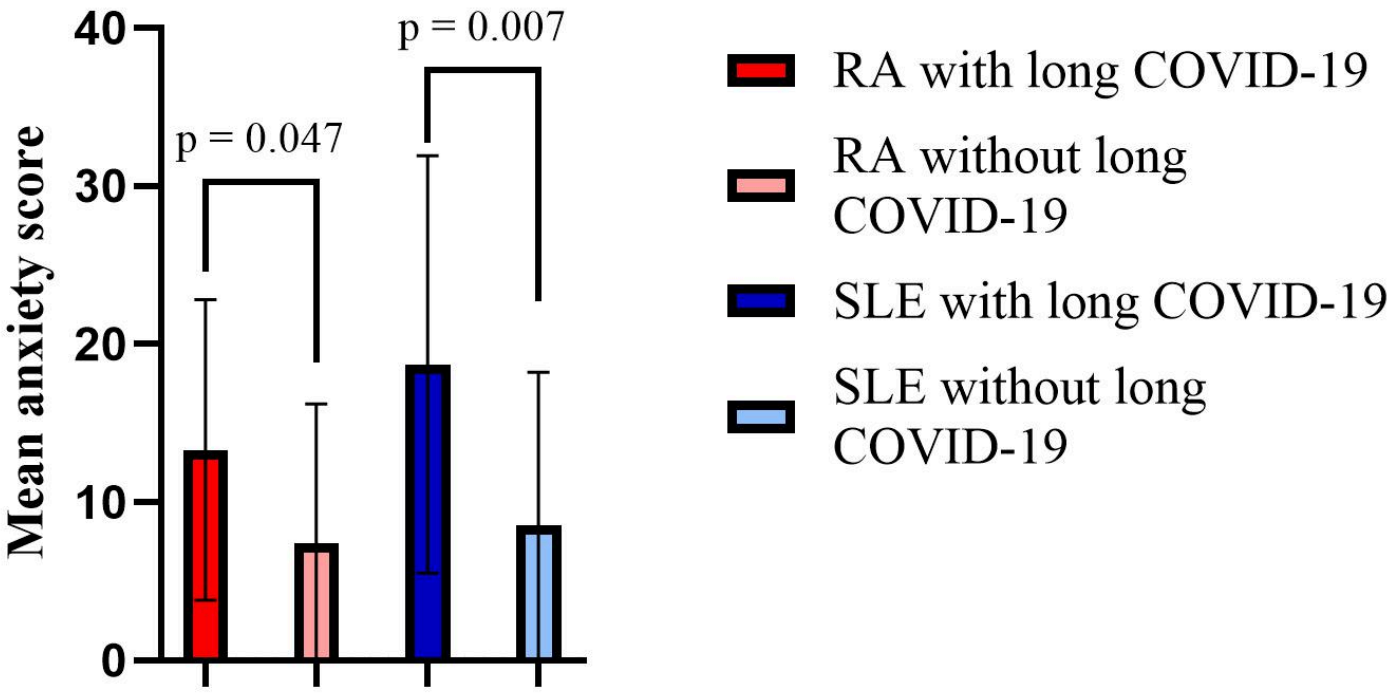


Figure 4

Mean anxiety scores comparison between patients with RA or SLE with or without long COVID-19.

RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus

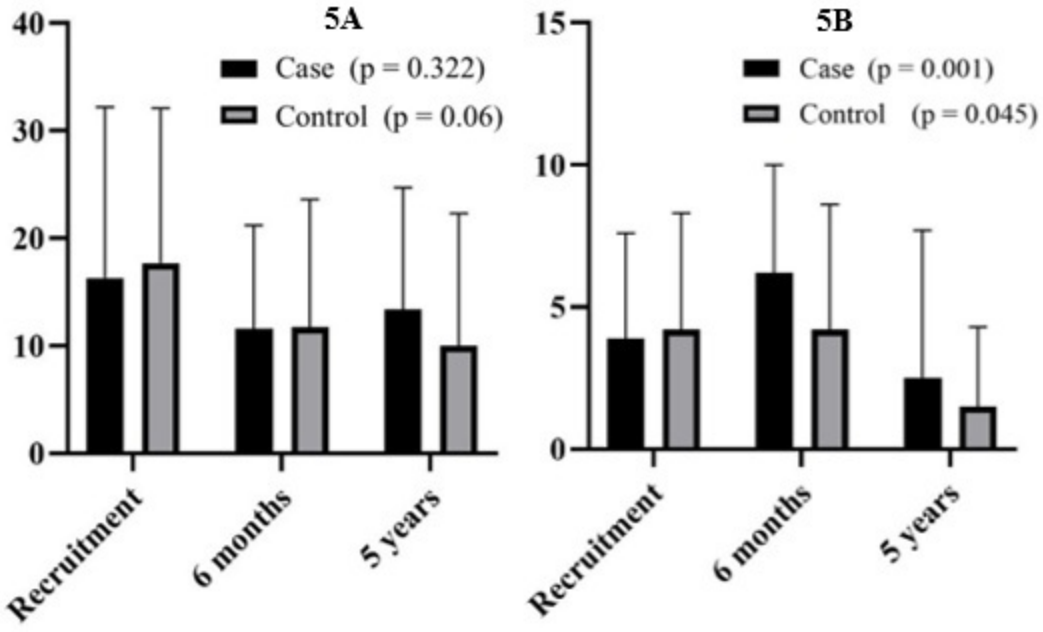


Figure 5

Mean CDAI (5A) and SLEDAI-2K (5B) scores over the study periods.