

# Impact of Perceived Stress During the SARS-CoV-2 Pandemic on Rheumatoid Arthritis Patients' Disease Activity

## An Online Survey

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**Introduction/Objectives:** Psychological stress worsens rheumatoid arthritis (RA) disease activity, and the COVID-19 pandemic has increased stress/anxiety in rheumatic patients. The purpose of this study was to determine if stress during the COVID-19 pandemic specifically impacts RA disease activity as reported by the patient.

**Method:** This was a cross-sectional COVID-19 RA survey study. University of California, Los Angeles rheumatology clinic patients were emailed a link to a survey in July and November 2020. The 30-question survey pertained to COVID-19–related stress, RA disease activity, and demographics. For the survey responders, anti-cyclic citrullinated antibody, rheumatoid factor, and age were extracted from the electronic health record. Analyses were performed to examine the association between the 4-item Perceived Stress Scale (PSS-4) and other COVID-19–related stress measures with the Routine Assessment of Patient Index Data 3 (RAPID3).

**Results:** A total of 1138/5037 subjects completed the emailed survey (22.6% response rate). When examining responses across RAPID3 categories (near remission, low, moderate, and high disease severity), there were significant increases in PSS-4 and other stress variables. Multiple linear regression models showed that PSS-4, financial stress, age, seropositivity, disease duration, and Black race were independently associated with worsened RAPID3 scores, when controlling for other confounding factors.

**Conclusions:** This study suggests that stress overall negatively impacts RAPID3, and Black RA patients had a higher RAPID3 score during the COVID-19 pandemic. Despite colossal efforts to combat the pandemic, RA patients currently suffer from stress/anxiety, and methods to mitigate these psychological effects are needed.

**Key Words:** COVID-19, disease activity, rheumatoid arthritis, stress

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Consent to participate was obtained from all patients with approval from UCLA institutional review board.

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Psychological stress is a known clinical phenomenon that adversely impacts rheumatoid arthritis (RA) patients. Stress and mood disturbances are linked to chronic inflammatory states and worsened RA symptoms.<sup>1</sup> Stress also increases circulating inflammatory cytokines in patients with RA and increases fatigue, swollen joint count, and pain.<sup>2,3</sup> Within the last year, increased and sustained stress has been pervasive throughout the world's population because of the COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Studies investigating the general public's mental health effects of this unprecedented outbreak and stay-at-home orders have shown increases in pandemic-induced stress, anxiety, and depression.<sup>4–9</sup>

RA patients have unique reasons that may predispose them to increased COVID-19–related stress. Rheumatoid arthritis increases risk for infections due to a dysregulated immune system and due to the use of immunosuppressive medications, including glucocorticoids, conventional synthetic disease-modifying antirheumatic drugs (DMARDs), biologic DMARDs, and targeted synthetic DMARDs.<sup>10</sup> In addition, early on in the pandemic, several RA medications were implicated as possible treatment of COVID-19, including hydroxychloroquine and interleukin 6 inhibitors (tocilizumab, sarilumab), which further complicated the picture of COVID-19's impact on RA patients' stress, and national drug shortages may have impacted their disease activity.<sup>11–15</sup> Although the association between stress and RA disease activity may appear obvious, few studies have examined this important presumed clinical association.<sup>16</sup> The COVID-19 pandemic provided us with an opportunity to gain insight into the effect of different types of stress on RA disease activity measures, which may provide insight into how patients have been affected during this pandemic and how stress influences RA disease activity.

The objective of this study was to investigate if stress associated with the COVID-19 pandemic has impacted RA patients' disease activity, using validated measures administered through an online survey.

## MATERIALS AND METHODS

### Study Population

A cross-sectional survey study was conducted among RA subjects between July 2020 and December 2020. This study was conducted at the University of California, Los Angeles (UCLA) after approval from the UCLA institutional review board (IRB #20-000930). Rheumatoid arthritis patients were seen at 1 of 10 UCLA rheumatology clinical sites that are throughout the greater Los Angeles area, including Westwood, Santa Monica, Santa Clarita, Porter Ranch, Burbank, Westlake Village, Torrance, Beverly Hills, Encino, and Downtown Los Angeles. The subjects were invited to fill out an online survey if they met the following criteria: at least 3 encounters with RA *International Classification of Diseases, Ninth and Tenth Revisions* codes and an active email address. Invited subjects were provided an online information

sheet explaining the study's purpose, and by clicking on the survey link, they provided their consent to participate in the study. The survey consisted of 50 items, using a secure web-based REDcap tool (REDCap, Nashville, TN). The survey was initially sent to 361 subjects in July 2020 and later to 4676 additional subjects in November 2020. Subjects were sent 2 email reminders, a week apart, if they did not fill out the survey online in response to the first email. An electronic informed consent was obtained at the beginning of the survey.

### Subject Characteristics

Data on gender, race/ethnicity, body mass index (BMI), employment status, and disease duration were collected using the survey. Age, anti-cyclic citrullinated peptide antibody, and rheumatoid factor laboratory values were collected by electronic medical chart extraction. Questions regarding alcohol usage and sleep quality were also assessed within the survey.

### Management of RA During COVID-19 Pandemic

The survey included questions relating to the COVID-19 pandemic, such as rheumatology appointment cancellations due to the pandemic and if the subject knew household members or other loved ones with COVID-19. They were additionally asked if they had ever had symptoms, testing, and/or diagnosis of COVID-19. Subjects also provided information on their RA medication usage, including current medications and medications stopped or started after the pandemic began, along with the reasons for any medication changes. Subjects were asked if they had considered changing their medications or contacted their physician regarding medication changes in response to the pandemic or if they had experienced any shortage in obtaining medications during the pandemic.

### RA Disease Activity Measures

Subjects completed the Routine Assessment of Patient Index Data 3 (RAPID3) score.<sup>17</sup> The RAPID3 measures disease severity by asking questions about functional activity, patient pain, and patient global assessment. The RAPID3 score cutoff points were utilized to categorize patients in near remission (score of  $\leq 3$ ), low severity (4–6), moderate severity (7–12), and high severity ( $\geq 13$ ).<sup>18</sup>

### Measures of Psychological Stress

The Perceived Stress Scale (PSS) is a well-validated, widely used instrument, developed in 1983 by Cohen and colleagues.<sup>19</sup> The PSS is a self-reported questionnaire designed to measure “the degree to which individuals appraise situations in their lives as stressful” over the last month. The subjects' stress levels were assessed by the modified and validated version, 4-item PSS (PSS-4).<sup>20,21</sup>

In addition, questions specifically related to the SARS-CoV-2 pandemic were adapted from 2 sources, Zhang and Ma<sup>9</sup> and Harris.<sup>22</sup> Subjects answered Likert-scale questions on overall stress, apprehension, panic, helplessness, stress from work, financial stress, stress from home, and stress from social distancing measures (e.g., “Please consider the following emotional states and indicate how you are currently feeling as compared with prior to the pandemic beginning (much decreased, decreased, unchanged/same as before, increased, much increased),” and the item was stated, for example, overall stress, apprehension, etc.). Although these questions have not yet been fully validated, they were found to have a Cronbach  $\alpha$  of 0.88 in the COVID-19 study published by Zhang and Ma<sup>9</sup> and were previously used in a 2006 SARS epidemic study.<sup>23</sup>

### Statistical Analysis

Quantitative variables were summarized as mean (SD), and categorical variables were summarized as the number and the percentage. Analysis of variance was used to compare quantitative measures between RAPID3 categories, and  $\chi^2$  tests were used to compare categorical measures. Two-sample *t* tests and  $\chi^2$  tests were used to compare demographic characteristics between those subjects who responded and those who did not respond to the survey. Pearson correlations were computed between PSS-4 and RAPID3 with the various clinical/demographic variables, patient-reported disease activity measures, and Likert stress measures. Multiple linear regression was used to evaluate the relationship between PSS-4 and other stress measures with RAPID3, adjusting for clinical/demographic characteristics. The clinical/demographics measures (age, race, gender, BMI, and disease duration) were forced into the multiple regression model, as they have been known to be associated with RA disease activity. Backward stepwise variable selection was then used to select the final set of stress measures (choosing from all the Likert stress measures described previously) for the multiple regression model. A significance level of  $p < 0.05$  was used as the significance level a priori.

### RESULTS

The survey was sent to 5037 RA subjects at UCLA. There were 1178 subjects who provided responses to the survey. Age, gender, and BMI values did not differ between responders and nonresponders to the survey. However, a higher proportion of Whites filled out the survey compared with the non-Whites who completed the survey (26.6% vs. 20.3%,  $p < 0.0001$ ). Forty subjects were excluded, as they indicated that they did not have RA. A final group 1138 RA subjects comprised the analysis population (22.6% response). The average age of respondents was 57.5 years, 79.4% were women, and 30% of the subjects indicated that they were of a non-White race (Supplementary Table 1, <http://links.lww.com/RHU/A465>). Approximately 62% of the subjects had seropositive RA (either rheumatoid factor and/or anti-cyclic citrullinated peptide antibody positivity), and 40% of the respondents self-reported being in remission at the time of filing out the survey.

### Association Between Disease and Stress Measures With RAPID3

Across the categories of RAPID3 (near remission, low, moderate, and high disease severity), demographic data for race/ethnicity, seropositivity, and BMI were significantly different ( $p < 0.01$ ) (Supplementary Table 2, <http://links.lww.com/RHU/A466>). The 4-item Perceived Stress Scale was found to increase across RAPID3 categories (near remission, mean, 3.8 [SD, 2.6]; and high, 7.5 [3.0];  $p < 0.0001$ ). For Likert-scale questions examining the impact of the pandemic on overall stress level, apprehension, panic, helplessness, financial stress, home stress, and work stress, there was a difference across the RAPID3 categories, where there was a larger percent of patients with increased stress at the higher disease severity category as compared with the near remission category (all  $p < 0.001$ ) (Supplementary Table 2, <http://links.lww.com/RHU/A466>). The greatest difference between groups was seen with financial stress due to the COVID-19 pandemic, with 22.4% of the subjects in the near remission group indicating they had increased financial stress compared with 54.6% in the high disease severity RAPID3 group. Social distancing stress was also higher in the high disease severity RAPID3 group, with 25.7% of this group experiencing a lot of stress compared with 6.6% of the near remission group. Subjects with high disease activity experienced decreased sleep quality

significantly more than did those with near remission ( $p < 0.0001$ ). Lastly, RA subjects' use of alcohol and cannabis increased across worsening RAPID3 categories ( $p \leq 0.05$ ).

### Correlations With RAPID3 and PSS-4

Demographics, patient-reported disease activity measures, and stress measures were correlated with RAPID3 and PSS-4. Overall, significant correlations ranged from low to high (0.08–0.8). As expected, RAPID3 and PSS-4 were moderately correlated ( $r = 0.48$ ;  $p < 0.0001$ ) (Table 1). Other Likert measures of stress relating to impact of the pandemic were significantly correlated with RAPID3, with financial stress having the largest correlation albeit weak in magnitude ( $r = 0.28$ ,  $p < 0.0001$ ). Social distancing stress was also mildly correlated with RAPID3 ( $r = 0.17$ ,  $p < 0.0001$ ).

### Multiple Regression Models for RAPID3

Multiple linear regression demonstrated that both PSS-4 and financial stress related to the pandemic were significantly associated with RAPID3 while controlling for age, gender, BMI, disease duration, race/ethnicity, and seropositivity (Table 2). All of the clinical/demographic variables were significant with the exception of gender. Asians had lower RAPID3 scores (adjusted mean difference of  $-1.7$ ,  $p = 0.002$ ) than White subjects, and Black subjects had higher RAPID3 scores (adjusted mean difference,  $1.4$ ;  $p = 0.044$ ) than White subjects.

### Direct COVID-19 Impact on RA Population

Approximately 54% of the subjects had been tested for COVID-19 at the time of survey collection, with 3.4% of the subjects (21 total) indicating that they had tested positive. In addition, 2.6% of the subjects indicated that they had a household member diagnosed with COVID-19, whereas 41.7% of the subjects had a loved one outside of their household (such as friend, family member, colleague, etc.) diagnosed with COVID-19. Most subjects experienced changes to their rheumatologic care as a result of the pandemic, where 62.4% of the subjects switched from in-person clinic visits to telehealth (video or telephone) appointments,

**TABLE 2.** Multiple Linear Regression of RAPID3

	Multivariate Regression	
	Estimate	p value
Age in years	0.052	<0.0001
Gender (male)	-0.397	0.08
BMI	0.159	<0.0001
Disease duration in years	0.037	0.02
Race/Ethnicity		
White	—	
Latinx	0.657	0.17
Asian	-1.684	0.002
Black	1.403	0.044
Other	0.606	0.420
Seropositivity		0.0007
No	—	
Yes	-0.599	0.016
PSS-4	0.874	<0.0001
Financial stress	0.823	0.0002

8.4% had their rheumatologist cancel a clinic visit, and 15.6% of the subjects themselves canceled the clinic appointment. Approximately 3% of the subjects reported that they stopped a rheumatologic medication due to COVID-19 as directed by their physician, whereas 3.0% of the subjects self-terminated a rheumatologic medication for reasons relating to COVID-19. Lastly, there were 11.5% survey respondents who reported difficulty obtaining their medications during the pandemic, as a result of shortages.

### DISCUSSION

Despite widespread COVID-19 vaccination plans and relaxation of stay-at-home mandates, it is clear that the pandemic is ongoing with ebbs and flows of SARS-COV-2 infection rates globally with different variants, and RA patients' recently acquired stress may persist for an uncertain stretch of time. In this large cross-sectional survey study, we report that both measurements of stress, the PSS-4 and the Likert-scale questions reflecting stress before/after the COVID-19 pandemic (i.e., panic, work/home stress, financial stress, and stress from social distancing), were associated with increased RAPID3. The PSS-4 and financial stress were independently associated with RAPID3 score after accounting for other covariates. Interestingly, Asians were associated with lower RAPID3 scores, and Blacks had higher RAPID3 scores when compared with the reference White group.

At the start of the pandemic, initial studies examined COVID-19 pandemic's impact on mortality/morbidity, lapse in clinic appointments, and stopping of rheumatic disease treatment, and later articles evaluated its impact on mental health. Few studies have examined autoimmune patients' perceived stress during the COVID-19 pandemic, and even fewer studies are exclusive to RA patients. A recent cross-sectional self-reported questionnaire study of 507 patients (74% inflammatory arthritis, 19% connective tissue diseases, and 6% fibromyalgia patients) suggested that the COVID-19 pandemic may have negative psychological consequences.<sup>24</sup> They showed that higher PSS-10 scores were significantly associated with younger age, being female, obese or overweight individuals, psychiatric pharmacotherapy, and anxiety from loss of income. Another study of 1800 patients with rheumatic diseases (spondyloarthritis, RA, osteoarthritis,

**TABLE 1.** RAPID3 and PSS-4 Correlation With Demographics, Stress, and RA Disease Activity

	RAPID3	PSS-4
PSS-4	0.48 <sup>a</sup>	—
RAPID3	—	0.48 <sup>a</sup>
Age	0.01	-0.19 <sup>a</sup>
BMI	0.22 <sup>a</sup>	0.08 <sup>b</sup>
Disease duration	0.06	-0.05 <sup>b</sup>
Overall stress level	0.24 <sup>a</sup>	0.44 <sup>a</sup>
Apprehension	0.23 <sup>a</sup>	0.40 <sup>a</sup>
Panic	0.23 <sup>a</sup>	0.41 <sup>a</sup>
Helplessness	0.25 <sup>a</sup>	0.49 <sup>a</sup>
Financial stress	0.28 <sup>a</sup>	0.37 <sup>a</sup>
Home stress	0.26 <sup>a</sup>	0.37 <sup>a</sup>
Work stress	0.19 <sup>a</sup>	0.31 <sup>a</sup>
Sleep quality	0.08 <sup>c</sup>	0.12 <sup>a</sup>
Social distancing stress	0.17 <sup>a</sup>	0.35 <sup>a</sup>

<sup>a</sup> $p < 0.0001$ .

<sup>b</sup> $p < 0.05$ .

<sup>c</sup> $p < 0.001$ .

etc.) suggested that the COVID-19 pandemic had negative effects on patient's overall health (self-reported disease activity and pain were elevated), well-being, and mental health.<sup>25</sup> A survey of 530 patients with rheumatic diseases including RA and systemic lupus erythematosus (7.5% survey response rate, and 61% RA patients) at the end of March 2020 suggested that subjects reported increased anxiety and feelings of uncertainty about their risk due to COVID-19 on free response.<sup>13</sup> Other published studies described similar findings: that rheumatic patients, with studies surveying populations in addition to RA patients such as patients with connective tissue disease, systemic lupus erythematosus, psoriatic arthritis, and fibromyalgia, described increased stress related to the COVID-19 pandemic, with increased rates of anxiety and depression.<sup>16,25–29</sup> Although our study focused only on RA patients, we provide data suggesting that RA patients' stress increased after the COVID-19 pandemic (based on the Likert stress questions). Moreover, our study results are consistent with these studies, showing that stress during the COVID-19 pandemic (general stress [PSS-4] and stress brought on specifically by the pandemic [Likert stress questions]) is associated with increased RA disease activity (RAPID3). Currently, no studies have examined financial stress in rheumatic patients during the pandemic.

Only 1 study, to our knowledge, has examined the relationship between COVID-19 pandemic stress and RA disease activity.<sup>16</sup> Approximately 80 RA patients, 80 ankylosing spondylitis patients, and 80 control subjects were recruited from a Turkish academic center. Patients were examined and completed multiple questionnaires in relation to stress, suicidality, depression/anxiety, ability to cope, and so on. Rheumatoid arthritis and ankylosing spondylitis patients were noted to have higher depression/anxiety compared with control subjects. In addition, the Disease Activity Score in 28 Joints (DAS28) scores correlated with the Ability to Cope With Trauma scores. Our COVID-19 RA study did not obtain DAS28 or the Clinical Disease Activity Index; however, it assessed disease activity by RAPID3. The RAPID3 is endorsed by the American College of Rheumatology as one of the preferred RA disease activity measures,<sup>18</sup> and during the pandemic, RAPID3 was one of the few disease activity measures that did not require modification when patients use telemedicine visits.<sup>30,31</sup> In addition, multiple studies across the world have found RAPID3 to correlate with DAS28 and Clinical Disease Activity Index, with correlations as high as 0.73.<sup>32–34</sup>

Our study has many strengths. Our email survey study of more than 1100 respondents is a large cohort and utilized the RAPID3, a validated metric. In addition, the large sample size allowed us to perform statistical tests to examine the independent association of multiple factors with RAPID3 scores, while accounting for covariates. Also, Likert stress measured stress specifically in relation to the COVID-19 pandemic. Further, our patient population was diverse.

Our study also has limitations. The study was conducted at an academic center within southern California (UCLA rheumatology) and may not accurately reflect RA patients globally. While the racial/ethnic makeup of the cohort is similar to that seen within the academic center, it does not represent the diverse population of Los Angeles County (White 28%, Black 8.7%, Asian 13.7%, and Latinx 47.7%; 2019 US Census Bureau estimates). In addition, our survey was emailed to patients in July 2020 and in November 2020, and this was prior to the January 2021 height of positive SARS-COV-2 rates in Los Angeles. This was a self-reported survey, although it was enhanced further with data from electronic health records. Our survey response rate was not 100%; however, we captured approximately 22% of the cohort, which is higher than some online COVID-19 survey studies.<sup>13</sup> Moreover, it is important to note that the PSS-4 is not a survey specific to the COVID-19

pandemic. It does, however, represent “the degree to which individuals appraise situations in their lives as stressful” over the last month. Although it is a popular tool for measuring psychological stress, it would not be able to ascertain the temporality prior to the COVID-19 pandemic and would represent their current stress level at the time the survey was filled out. On the other hand, the Likert stress questions did provide information on the impact of stress, specifically in relation to the COVID-19 pandemic. Only 21 RA patients had tested positive at the time of the survey, and we may have had higher intensity/frequency of stress seen in patients if the survey was sent in January 2021 during the height of the surge. Furthermore, this was a cross-sectional study, and biases could exist because of required fluency in utilization of digital technology, where they could easily access the social media and the news, possibly fueling stress. The survey was available only in English; therefore, language fluency in English with access to email, computer, smartphone, and/or tablet was required. Thus, it is understandable that multiple sources of survey response bias could have impacted the results of the study. Perhaps patients completed the study if they were interested/stressed about the COVID-19 or had higher RA disease activity, and we did see that a higher proportion of Whites completed the survey compared with non-Whites. In addition, cross-sectional studies cannot robustly evaluate temporality of the stress measures. It is still unclear if stress was causal to worsen RA disease activity or if higher RA disease activity led to the patients' increase in stress. Another wrinkle is present when inferring stress due to the COVID-19 pandemic. It is unclear if the stress was specifically due to the COVID-19 pandemic or general stress. However, the results of the Likert questions may provide some inferences due to the anchor used, “indicate how you are currently feeling as compared with prior to the pandemic beginning....” Finally, although an assumption can be made that all subjects equally experienced a decrease in mobility and physical activity as part of the general experience of being home during the pandemic, it is unclear if differences in physical activity may have had an impact on the differences in disease activity among subjects.

In conclusion, our large cross-sectional online survey study demonstrated that RA patients experienced increases in stress during the COVID-19 pandemic, which may have significantly impacted their patient-reported RA disease activity. Specifically, financial stress due to the pandemic and PSS-4 were associated with increased RAPID3 scores. Attention to race/ethnicity is important when assessing RA disease activity, as we demonstrated that Black RA patients have higher RAPID3 scores, whereas Asians have lower RAPID3 scores. Future research is warranted to confirm these findings. With the ongoing COVID-19 pandemic, clinicians will need to continue to assess and address the effects increased stress has on their RA patients' health. Further research is needed to investigate modalities to mitigate the stress and anxiety seen in RA patients.

## Key Messages

- (1) The PSS-4 and financial stress during the COVID-19 pandemic were found to be independently associated with higher RAPID3 scores.
- (2) Black Race/ethnicity was independently associated with higher RAPID3 scores, and Asian patients were associated with lower RAPID3 scores during the COVID-19 pandemic.

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