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**Research Article**

# Correlation Between Stress, Anxiety and Depression of Patients with Rheumatoid Arthritis During COVID-19 Pandemic and Their Non-compliance to Treatment: A Cross-sectional Study

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**Abstract**

**Background:** The prevalence of anxiety and depression is high in rheumatoid arthritis (RA) patients. As RA patients tend to be immunodeficient, they are at greater risk of coronavirus disease 2019 (COVID-19) infection due to their scheduled hospital appointments. Therefore, they have become more anxious and worried during COVID-19 pandemic, and some patients recently have canceled or postponed their treatment.

**Objectives:** This study aimed to assess the effect of stress, anxiety, and depression due to COVID-19 outbreak on non-compliance to treatment among RA patients.

**Methods:** In this cross-sectional study, we included 149 RA patients (male/female = 12: 137). Four questionnaires, including the 21-item Depression, Anxiety, and Stress Scale (DASS-21), 14-item Perceived Stress Scale (PSS-14), 18-item Health Anxiety Inventory (HAI-18), and 8-item Morisky Medication Adherence Scale (MMAS-8) were employed. The questionnaires were filled by the researchers on behalf of the participants using telephone interviews due to social distancing protocol.

**Results:** There was a significant negative correlation between stress ($P = 0.001$), anxiety ($P < 0.001$), health anxiety ($P = 0.014$), and depression ($P = 0.001$) and compliance to treatment among RA patients. However, anxiety was the only predictor for non-compliance to treatment.

**Conclusions:** Therapists should be aware of the symptoms of stress, anxiety, and depression among their RA patients, especially during stressful life events, and carefully monitor their compliance to treatment to prevent exacerbation of RA.

*Keywords:* Rheumatoid Arthritis, COVID-19, Non-compliance

## 1. Background

Rheumatoid arthritis (RA), an immune-mediated arthropathy, is a chronic disease (1) which can cause pain and limit the movements of patients (2). Therefore, it can be debilitating and negatively affect the sufferer's occupational functioning by disabling them in the climax of their career, especially in the fourth and fifth decades of life (1). Moreover, RA can increase the patient's medical costs (2) and affect the sufferer's educational functioning, social functioning, and received social support (2). As RA worsens the sufferer's quality of life, it is highly associated with anxiety and depression (1-4). Depression, anxiety, and mixed anxiety-depressive disorder make the patients' levels of pain perception, fatigue, disability, and disease activity increase, and their response to RA treatment worsens (1, 5, 6). Furthermore, depression leads to increased mortality in RA patients (7).

Certain cytokines [e.g., tumor necrosis factor $\alpha$ (TNF$\alpha$) and interferon $\gamma$ (IFN$\gamma$)] increase in the frontal cortex by serotonergic antidepressants. Some studies mentioned that anti-inflammatory drugs, the most commonly used RA medications, may attenuate the antidepressant effect of the serotonergic drugs by inhibiting this process (8). Some other studies showed that psychiatric medications may be associated with potentially adverse side effects or even lead to exacerbation of RA symptoms (1, 9, 10).

Based on a systematic analysis (11), RA prevalence and incidence rates are increasing by time, and this condition is challenging the public health globally. However, the early identification and treatment of RA, especially in females, can reduce its burden (11).

SARS-CoV-2 (severe acute respiratory coronavirus 2 syndrome) is a new viral infectious disease which originated from Wuhan in the Hubei province of China (12). Because of the rapid and global spread of the SARS-CoV-2, the World Health Organization (WHO) announced the disease as a public health emergency, calling it coronavirus disease 2019 (COVID-19) (13). COVID-19, in severe cases, may progress to interstitial pneumonia and alveolar damage, severe acute respiratory distress syndrome (ARDS), and even death (14).

Studies showed that patients suffering from rheumatoid disease may be at higher risk of infection under certain conditions (15-17). The higher risk in RA patients is due to the following reasons: (1) RA itself can lead to dysregulation and premature aging of the immune system; (2) RA is associated with a variety of chronic comorbidities, such as diabetes, which aggravate this immunocompromising condition; and (3) the immunosuppressive antirheumatic drugs which are used to treat RA can significantly increase the risk of infection (e.g., glucocorticoids (GCs) increase the risk by up to 4-fold and TNF-$\alpha$ inhibitors increase the risk by up to 2-fold) (17). Although there is no evidence showing that the mentioned factors make the RA patients susceptible to COVID-19 infection, these people might be at higher risk of complications if infected (18).

Shayganfard et al. (19) showed that higher health anxiety scores during the COVID-19 pandemic resulted in canceling or postponing routine medical health care in women in the perinatal stage. Michaud et al. (20) also showed that RA patients appeared more anxious and frightened during COVID-19 pandemic and they postponed or canceled their medical appointments, and some even stopped their medications.

## 2. Objectives

This study aimed to assess the effect of stress, anxiety, health anxiety, and depression on non-compliance to treatment in patients suffering from RA during the current SARS-CoV-2 pandemic.

## 3. Methods

### 3.1. Study Design

This cross-sectional study was carried out in Arak, Iran, from 20 March to 20 April 2020. This period was the flare-up of COVID-19 in Arak. Because of the social distancing measures during the COVID-19 outbreak, the questionnaires were filled by the researchers, who made telephone calls to the participants and asked them the questions of the questionnaires. During the phone calls, the aim of the study and the entire process, including the time the participants may take to answer the questions, were explained.

The study protocol was approved by the local institutional ethics committee of Arak University of Medical Sciences, and all human procedures were performed in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments. Also, informed consent was taken verbally before recording the participants' answers.

### 3.2. Patients

In this study, using the simple random sampling method, we included 149 patients who met the American College of Rheumatology (ACR) classification criteria for RA registered in the Iranian National Registry of rheumatic diseases (RHEUMATRY). These patients were registered by the Arak Rheumatology Registry Management Office (ARMO) in RHEUMATRY.

The inclusion criteria were patients over 18 years old suffering from RA for at least six months prior to the study, signing informed consent, being under immunosuppressive treatment such as prednisolone, and being treated as an outpatient. The exclusion criteria were request from the patient to leave the study at any stage of the study, RA exacerbation, change of patient status from outpatient to inpatient during the study, and infection with COVID-19.

### 3.3. Tools

In this study, the psychological effects of COVID-19 on RA patients (i.e., stress, anxiety, and depression) were assumed to be independent variables, and non-compliance to treatment was considered as the dependent variable. We collected the demographic information, including age, gender, education, marital status, and occupation, which could act as potential confounding factors or modifiers. Four questionnaires, including the 21-item Depression, Anxiety, and Stress Scale (DASS-21), 14-item Perceived Stress Scale (PSS-14), 18-item Health Anxiety Inventory (HAI-18), and 8-item Morisky Medication Adherence Scale (MMAS-8) were also employed.

#### 3.3.1. The Depression, Anxiety, and Stress Scale (DASS)

This is a reliable screening tool for depression, anxiety, and stress experienced over the subject's past week. The DASS has been designed based on the concept that depression, anxiety, and stress are all three dimensions of the same disorder which differ in severity (21). The scores obtained from each of the three subscales of DASS are categorized as 'normal, mild, moderate, severe, and extremely severe' based on their severity.

In this study, the short 21-item version of DASS was used, which has seven questions for each subscale. The longer version consists of 42 items. The DASS is a 4-point self-rated scale based on a Likert scale, which consists of the following items: 0 = did not apply to me at all; 1 = applied to me to some degree or sometimes; 2 = applied to me to a considerable degree; or a good part of time; 3 = applied to me very much, or most of the time (22). To acquire an equivalent score to the 42-item DASS, the results for each subscale were multiplied by 2. DASS is available in multiple languages, including Farsi (23). The Farsi version has been validated in several studies (24-26) and has an acceptable psychometrics and good internal consistency (Cronbach alpha for: total DASS-21 = 0.94; Depression = 0.85; Anxiety = 0.85; Stress = 0.87) (24).

#### 3.3.2. The Health Anxiety Inventory (HAI)

The HAI is a self-rated scale which measures concerns about health and hypochondriasis symptoms independently of physical health status (27, 28). The original version of the HAI has 64 items compared to the short version (HAI-SF), which has 18 items. In this study, the short version was used, which consisted of three subscales, including the perceived likelihood of having an illness (Illness Likelihood), anticipation and fear of the consequences of having an illness (Illness Severity), and awareness of bodily changes (Body Vigilance) (28). The psychometric properties of the Farsi version of HAI-SF were assessed, which showed moderate convergent validity in correlations with DOSS-21 (0.70; P = 0.0001), and acceptable internal consistency (Cronbach's coefficient alpha = 0.89) (29). Employing HAI-SF in this study introduced bias, as these patients suffer from a chronic disabling disease (RA). Therefore, it is not possible to make these patients ignore their current chronic disease completely while answering the HAI scale items. However, to increase the accuracy of the results, we asked the participants to focus only on COVID-19 while answering the questionnaire.

#### 3.3.3. The Perceived Stress Scale (PSS)

This scale is widely used to measure general stress of the participants in previous month and evaluate how stressful and/or controllable the respondents find a life situation or event. PSS is a self-rated scale which is scored based on a 5-point Likert scale comprising of: 0 = never; 1= almost never; 2 = sometimes; 3 = fairly often; 4 = very often (30, 31). There are three versions of PSS available, which differ in their number of items (4, 10, or 14 items) (30, 31). In this study, the Farsi version with 14 items (PSS-14) was used. The Farsi version has an acceptable psychometrics and good internal consistency (overall Cronbach's $\alpha$ coefficient of 0.76) (32).

#### 3.3.4. The Morisky Medication Adherence Scale (MMAS)

This is a fast and easy-to-use self-reported instrument to evaluate the compliance of the patient to treatment (33, 34). In this study, the 8-item version (MMAS-8) was applied, which has a better validity and reliability than the 4-item version (MMAS-4) (35). Seven items of MMAS-8 are scored based on dichotomous yes/no questions (for items 1 - 4 and 6 - 7: yes = 0, no = 1; for item 5: yes = 1, no = 0), and the last (8th) item uses a 5-item Likert scale comprising of: All the time = 0 to never/rarely = 4. The response (0 - 4) is divided by 4 to standardize the score of the last item (34). The total score of MMAS-8 ranges from 0 to 8 (35). A total score of 8 suggests high compliance; 5 or less, low compliance and between 5 and 8 (6 and 7), medium compliance (34). The MMAS-8 has been translated to the Farsi with an acceptable internal consistency (overall Cronbach's $\alpha$ coefficient of 0.697), sensitivity (92.8%), specificity (22.3%), positive predictive value (52.9%), negative predictive value (76.7%), and reliable test–retest reproducibility ($r = 0.940$; $P < 0.001$) (36).

### 3.4. Statistical Analysis

The data was analyzed using SPSS v.20. The descriptive statistics were analyzed as a whole and based on gender. Then, the difference between the descriptive statistics of the two gender groups were analyzed using the *t*-test, independent samples test, and Levene's test for equality of variances. To analyze the correlation between the variables, the Pearson and Spearman Rho's correlation tests were used. Assuming the compliance to treatment as a dependent variable, the linear relationship between the independent variables and the MMAS was assessed using the analysis of variances (ANOVA) and multiple linear regression model (enter method).

## 4. Results

### 4.1. Demographic Data of Participants

As mentioned above, 149 RA patients participated in this study. The age range of participants was 21 - 76 years (mean age: 46 years) and male to female ratio was 12:137. Also, 135 (90.6%) patients were married, and 14 (9.4%) were single (no divorced, widowed, or separated). Regarding job status, two (1.3%) patients were unemployed, 41 (27.5%) were employed, and 106 (71.1%) were housewives. In addition, 50 (33.6%) participants had high school or lower education, 55 (36.9%) had a diploma, and 44 (29.5%) had university education.

### *4.2. Descriptive Statistics*

In this study, four scales of PSS-14, DASS-21, HAI-18, and MMAS-8 were used. The mean and standard deviation of each scale are summarized in Table 1.

The severities (normal, mild, moderate, severe, and extremely severe) for each of the three subscales of DASS (stress, anxiety, and depression) are summarized in Table 2. The compliance to treatment was categorized as high, medium, and low. A summary of the frequencies of the compliance to treatment is illustrated in Table 2.

### *4.3. Correlations*

The correlation between compliance to treatment and stress, anxiety, depression, illness likelihood, illness severity and body vigilance is summarized in Table 3.

As illustrated in Table 3, there was a significant negative correlation between compliance to treatment and the scores of PSS scale (P = 0.006), DASS total scores (P = 0.001), stress subscale scores of DASS (P = 0.001), anxiety subscale scores of DASS ($P < 0.001$), depression subscale scores of DASS (P = 0.001), HAI total scores (P = 0.014), and illness likelihood subscale scores of HAI ($P < 0.001$).

No statistically significant correlation was found between compliance to treatment and illness severity subscale scores of HAI and body vigilance subscale scores of HAI.

### *4.4. Regression Models*

The linear relationship between the independent variables (age, gender, marital status, education, occupation, PSS total score, HAI total score, and DASS total score) and compliance to treatment was assessed using the multiple linear regression model (enter method). The ANOVA P-value for this regression model was 0.004 (F = 2.976, adjusted R square = 0.097). Among the independent variables, the only statistical significant P-value was for DASS total score (P = 0.005, $t$ = -0.875, Betta = -0.337). The P-values for the other independent variables were not statistically significant (age's P = 0.311, education's P = 0.167, occupation's P = 0.560, marital status' P = 0.219, PSS total P = 0.951, HAI total P = 0.980). Therefore, we used the regression model only for the DASS total score (as an independent variable) and the MMAS total score (as a dependent variable) by the Enter method. The ANOVA for this regression model was statistically significant ($P < 0.001$, F = 19.207, adjusted R square = 0.097, $t$ = -4.383, Betta = -0.340). To find a more precise relationship between DASS and MMAS results, the regression model was used again while considering the DASS subscales (stress, anxiety, and depression) as independent variables. The ANOVA for the model was statistically significant (P-value $< 0.001$, F = 7.417, adjusted R square = 0.115). Anxiety was the only subscale which had a statistically significant relationship with compliance to treatment (P = 0.006, $t$ = -2.796, Betta = -0.284). The P-values for the other two subscales were not significant (stress' P = 0.513, depression's P = 0.633). Finally, we performed the regression model for the anxiety subscale of DASS as the only predictor (independent variable) and compliance to treatment (MMAS result) as a dependent variable. The ANOVA for the regression model, using the Enter method, was statistically significant ($P < 0.001$, F = 21.214, adjusted R square = 0.120, $t$ = -4.606, Betta = -0.355).

## 5. Discussion

In this study, a negative significant correlation was found between stress, anxiety, and depression and compliance to treatment (Table 3). The higher stress, anxiety, and depression symptoms in RA patients are likely due to less compliance in treatment and vice versa. However, this does not necessarily mean that as the stress, anxiety, and depression of the patients increase, they adhere less to treatment. The multiple linear regression model showed that the only predictor for non-compliance to treatment was anxiety. In other words, as RA patients become more anxious, they become less likely to adhere to their treatment. Greater risk of COVID-19 infection in older people with multiple health comorbidities who receive immunosuppressive drugs (37, 38) in combination with increased risk of COVID-19 cross infection during hospital visits (16, 20) increase the patients' anxiety during the COVID-19 pandemic. This may negatively affect compliance to treatment in RA patients. Michaud et al. (20) found that during the COVID-19 pandemic, 42% of rheumatologic patients had a degree of change in their care, including cancellation or postponement of their appointments or even changes to their medications by their own decision. Shayganfard et al. (19) also showed that higher health anxiety scores during the COVID-19 pandemic resulted in cancelling or postponing the routine medical health care in women in the perinatal stage. As illustrated in Table 3, there was a negative correlation between compliance to treatment and health anxiety (HAI-18) and between compliance to treatment and illness likelihood scores in RA patients. Hence, the more anxious RA patients are as a result of their health being threatened and the possibility of having a serious illness, the less they adhere to their treatment.

Based on the existing literature, this is the first study conducted on health anxiety in RA patients. However, our study had some limitations. First, for more reliable results, we asked the participants to focus on COVID-19 while answering the HAI questionnaire. However, RA patients suf-

**Table 1.** The Mean and Standard Deviation for Stress, Anxiety, Health Anxiety, Depression, and Compliance to Treatment

| Variables | PSS-14 | DASS-21 | | | | HAI-18 | | | | MMAS-8 |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Total | Stress | Anxiety | Depression | Total | Illness Likelihood | Illness Severity | Body Vigilance | |
| **Mean (N = 149)** | 24.92 | 42.99 | 18.87 | 10.75 | 13.37 | 19.89 | 12.75 | 5.30 | 9.24 | 5.10 |
| **Std. Deviation** | 8.77 | 24.64 | 10.01 | 8.49 | 10.20 | 8.02 | 4.06 | 2.71 | 3.80 | 1.85 |

Abbreviations: PSS-14, the 14-item Perceived Stress Scale; DASS-21, the 21-item Depression, Anxiety and Stress Scale; HAI-18, the 18-item Health Anxiety Inventory; MMAS-8, the 8-item Morisky Medication Adherence Scale.

**Table 2.** The Frequency of the Severities

| Compliance to Treatment | | DASS Stress | | DASS Anxiety | | DASS Depression | |
|---|---|---|---|---|---|---|---|
| **Severity** | **No. (%)** | **Severity** | **No. (%)** | **Severity** | **No. (%)** | **Severity** | **No. (%)** |
| **Low** | 82 (55) | Normal | 52 (34.9) | Normal | 62 (41.6) | Normal | 59 (39.6) |
| | | Mild | 23 (15.4) | Mild | 12 (8.1) | Mild | 23 (15.4) |
| **Medium** | 54 (36.2) | Moderate | 34 (22.8) | Moderate | 30 (20.1) | Moderate | 33 (22.1) |
| | | Severe | 25 (16.8) | Severe | 22 (14.8) | Severe | 18 (12.1) |
| **High** | 13 (8.7) | Extremely Severe | 15 (10.1) | Extremely Severe | 23 (15.4) | Extremely Severe | 16 (10.7) |

Abbreviation: DASS, Depression, Anxiety and Stress Scale.

**Table 3.** The correlation Between Compliance to Treatment and Stress, Anxiety, Depression, Illness Likelihood, Illness Severity and Body Vigilance

| Compliance to Treatment | PSS-14 [a] | DASS-21 | | | | | | | HAI-18 | | | | Education [b] | Occupation [b] | Marital Status [b] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Total [a] | Stress [a] | Stress Severity [b] | Anxiety [a] | Anxiety Severity [b] | Depression [a] | Depression Severity [b] | Total [a] | Illness Likelihood [a] | Illness Severity [a] | Body Vigilance [a] | | | |
| **Correlation Coefficient** | -0.225 | -0.340 | -0.271 | -0.126 | -0.355 | -0.292 | -0.260 | -0.146 | -0.201 | -0.291 | -0.017 | -0.155 | -0.066 | 0.088 | -0.058 |
| **P (2-tailed)** | 0.006 | < 0.001 | 0.001 | 0.124 | < 0.001 | < 0.001 | 0.001 | 0.077 | 0.014 | < 0.001 | 0.838 | 0.058 | 0.420 | 0.288 | 0.485 |

Abbreviations: PSS-14, the 14-item Perceived Stress Scale; DASS-21, the 21-item Depression, Anxiety and Stress Scale; HAI-18, the 18-item Health Anxiety Inventory.
[a] Pearson.
[b] Spearman's Rho.

fer from a major chronic disease. Therefore, it is not possible to make these patients ignore their current disabling disease completely while answering the HAI scale items. Second, although the difference between the two gender groups in the DASS total score and DASS subscales was statistically significant, the male to female ratio (12: 137) prevented us from interpreting the results based on gender differences. Third, as Table 2 shows, 55% of RA patients had low compliance to treatment and only 8.7% of RA patients adhered highly to treatment during COVID-19 outbreak. COVID-19 makes rheumatologic patients more anxious (16, 20), which leads to less compliance to treatment. However, incidence of anxiety may not be limited to the COVID-19 pandemic and such non-compliance to treatment may also reoccur in rheumatologic patients during other stressful life events. For example, Heidari et al., in a study conducted before COVID-19 outbreak (39), reported that only 40.3% of RA patients in Iran adhere to oral treatment and the major concern of the patients was medication costs and affordability. Salt and Frazier showed that increased number of prescribed medications can predict non-compliance to treatment (40). Other studies reported that psychological factors (41), self-efficacy (42), and patient knowledge and education level (43) contribute in RA patients' compliance to treatment. Hence, COVID-19 might not be the single or main factor for anxiety and non-compliance to treatment of RA patients at the time of the study. Fourth, due to the cross-sectional design of the study, we were unable to prove the causality of anxiety as a single or major factor for non-compliance to treatment of RA patients. There may be many confounding factors. For example, non-compliance is more common in older ages (44) and the majority of RA patients are old. Furthermore, the majority of our participants (72.4%) were unemployed or housewives and had low income. This also predicts a lower compliance to treatment (44). Other factors which may negatively affect non-compliance to treatment are chronic pain (45, 46), which is a main symptom of RA, and insufficient support from the patient's family members (47).

### 5.1. Conclusions

Future cohort studies should focus on compliance to treatment of RA patients and compare the patients who are in stressful life events with those who are not. In conclusion, depression is a predictor of non-compliance to treatment (44) and therapists should be aware of the early signs and symptoms of depression in their rheumatologic patients. However, the therapists should also look for symptoms of stress and anxiety in their patients and monitor their compliance to treatment during stressful life events to prevent further exacerbation of RA.


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## Footnotes

**Authors' Contribution:** Study concept and design, M. S. and B. T.; Collecting the clinical data, B. T. and M. T.; Analysis and interpretation of data, M. S. and M. T.; Drafting of the manuscript, B. T. and M. S.; Critical revision of the manuscript for important intellectual content, M. S., B. T. and M. T.; Final approval of the published version, M. S., B. T., and M. T.; Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved, M. S., B. T., and M. T.

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