# Anxiety impacts rheumatoid arthritis symptoms and health-related quality of life even at low levels

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## Abstract

### Objective

*We explored the burden of symptoms of anxiety and depression on health-related quality of life (HRQL) in patients with rheumatoid arthritis (RA).*

### Methods

*Adults with RA participating in an observational cohort completed PROMIS tests of depression, anxiety, fatigue, physical function (PF), pain interference (PI), sleep disturbance, and participation in social roles and activities at the baseline visit. Clinical measures of disease status were also obtained. We used ANOVA and partial correlation adjusting for the swollen joint count (SJC) to examine associations of anxiety and depression with other aspects of HRQL. Mild and moderate-severe anxiety were defined as T-scores ≥55.4 and ≥ 62.3 and mild and moderate-severe depression was defined as ≥52.5 and ≥58.6 based on previous validated clinical thresholds. Multivariable linear regression (MVR) was used to identify predictors of emotional distress with a subset analysis of those in remission/low disease activity.*

### Results

*Of 196 RA participants, 18% had mild anxiety, 9% had moderate-severe anxiety, 18% had mild depression, and 14% had moderate-severe depression symptoms. Anxiety and depression scores were associated with significantly worse mean scores across HRQL domains ($p < 0.05$). In MVR, depression ($\beta=0.75$, $p<0.001$), PF ($\beta=0.14$, $p=0.024$) and fatigue ($\beta=0.15$, $p=0.015$) predicted higher anxiety levels, whereas only anxiety predicted higher depression levels ($\beta=0.70$, $p=<0.001$). In subset analysis, PF no longer predicted higher anxiety levels.*

### Conclusion

*Emotional distress is common in RA, even when disease is well controlled, with considerable impacts on other aspects of HRQL even at mild levels.*

**Key words**

patient-reported outcomes, PROMIS, rheumatoid arthritis, anxiety, depression

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## Introduction

The primary goal of treatment for RA is to control inflammation and maintain health related quality of life (HRQL) and autonomy through symptom control and normalisation of function as well as to optimise participation in social and life activities. While current treatment regimens are powerful tools for delaying joint erosions and reducing pain and inflammation, they are not curative (1).

Emotional wellbeing is an important facet of HRQL. Patients with RA have higher levels of anxiety and depression compared to the general population (2-5). The increased emotional distress may be secondary to the unique stressors that RA patients may face including difficulty with physical limitations, interpersonal relationships, maintaining productivity in the workforce, adhering to multi-drug immunomodulatory regimens, and others that may not be defined (6, 7).

Emotional distress not only affects quality of life for patients with RA but also negatively impacts clinical outcomes, representing a large unmet clinical need and patient-care gap (8, 9). Depression, in particular, has been associated with increased symptoms, such as fatigue, diminished RA treatment response, and greater disability (10-14). Importantly, depressive symptoms do not appear to be associated with RA disease activity (15). Far fewer clinical trials have explored the impact of anxiety, independent of depression, on clinical outcomes and HRQL. In the limited studies that have examined the impact of anxiety at baseline, outcomes were similar to patients with depression including longer time to remission, or an inability to achieve remission, and worse physical function (8, 16-18). As most studies have examined the impact of anxiety and depression at moderate to severely high levels (19-21); the impact of mild levels of emotional distress remains unknown.

## Methods

*Participants*

We analysed the baseline visit of adults who were receiving treatment for RA at the Johns Hopkins Arthritis Center and participating in an observational study (described previously) (22). All participants received guideline-based treatment using a treat-to-target approach. Visits occurred between September 2012 and November 2014. The sample included all patients with complete baseline data.

*Outcomes*

The Patient Reported Measurement Information System® (PROMIS®) computer adaptive tests (CATs) were used to evaluate anxiety and depression which were previously determined to be an accurate and reliable method of assessing emotional distress (23). PROMIS HRQL CATs included fatigue, physical function, pain interference, sleep disturbance, and ability to participate in social participation. PROMIS has robust psychometric properties in RA (22, 24). PROMIS measures have been used to individualise treat-to-target approaches and contribute important information about the physical, emotional, and social health of the individual with RA (25, 26). Scores are normalised to the United States general population (mean of 50 and a standard deviation of 10); higher scores correlate to higher levels of the domain of interest.

Clinical markers of RA disease activity recorded included the CDAI, physician global assessment of health (EGA), patient global assessment of health (PGA), and pain (100 mm VAS). Remission was defined as a CDAI ≤2.8, low disease activity was defined as a CDAI >2.8 and ≤10, moderate disease activity was defined as a CDAI >10 and ≤22, and high disease activity was defined as a CDAI >22. ESR and CRP were also recorded if available within four weeks of the visit. PROMIS CATs were collected on tablet computers, and item response theory (IRT) determined scores were generated through the Assessment Center scoring service.(27) A comorbidity count was generated based on patient report and included chronic obstructive pulmonary disease (COPD), myocardial infarction, stroke/transient ischaemic attack, hypertension, osteoporosis, depression (formal diagnosis), diabetes, and peptic ulcer disease.

*Statistical analysis*

Descriptive statistics were calculated for sociodemographic and RA characteristics. We defined mild anxiety as PROMIS T-scores ≥55.4 and <62.3 based on a recent validation study by Hitchon *et al*. using a population of patients with generalised anxiety disorder confirmed by diagnostic interview using the Structured Clinical Interview for SDM-IV-TR Axis I Disorders-Research (SCID) (21). We defined moderate-severe levels of anxiety as PROMIS T-scores ≥62.3, determined by previously validated clinical thresholds based on the General Anxiety Disorder 7-item scale (GAD-7). Cross-walk cut-points for moderate and severe anxiety on the GAD-7 scale are 10 and 15, corresponding to PROMIS anxiety scores of 62.3–70 and >70 for moderate and severe anxiety (28). Mild and moderate-severe levels of depression were defined as PROMIS T-scores ≥52.5–58.6 and ≥58.6 based on clinical thresholds according to the Patient Health Questionnaire (PHQ-9) (29). We evaluated relationships among anxiety, depression and other RA symptoms and impacts using these cut-points.

We compared groups using *t*-tests and chi square if normally distributed and Wilcoxon rank-sum test if non-normally distributed. One-way ANOVA was utilised to explore differences in mean PROMIS domains within anxiety and depression categories. Associations among PROMIS scores and HRQL domains were examined using Pearson correlations with and without adjustment for 28-SJC (as a marker of inflammatory disease activity). We defined strong and moderate correlations as r ≥0.75 and r ≥0.3, respectively. Linear regression was used to evaluate predictors of high anxiety and depression including pain interference, physical function, sleep disturbance, fatigue, and social participation as well as anxiety for the depression model and depression for the anxiety model. Multivariable models were adjusted for age, sex, race, and education. Variance inflation factors were examined to evaluate collinearity among variables. Sensitivity analyses were performed by examining results for patients in remission or low disease activity. All analyses were performed using STATA 15 software (College Station, TX).

## Results

*Study participants*

Participants (n=196) were mostly female (81%) and white (83%) with mean (SD) age of 55 (13) years; 78% had completed some college (Table I). About half were employed full or part-time (56%). Most participants (93%) met ACR classification criteria for RA with a mean disease duration of 11 (10) years and had RF (60%) or anti-CCP antibodies (68%). Overall, their RA was well controlled with most participants in remission (n=62; 32%) or low disease activity (n=70; 36%) by CDAI; 46 (23%) had moderate disease activity, and 18 (9%) had high disease activity. The median (IQR) levels of ESR and CRP were within normal limits (ESR n=180, 14 (5, 29); CRP n=184, 0.3 (0.1, 0.7)).

Of 196 participants, 18% had mild anxiety, 9% had moderate-severe anxiety, 18% had mild depression and 14% had moderate-severe depression symptoms. Twenty four percent of participants (n=38) reported both anxiety and depression symptoms (mild symptoms or greater). Groups with and without anxiety and depression were similar by age

**Table I.** Participant characteristics (n=196) by level of anxiety and depressive symptoms.

| | *Anxiety* | | | | *Depression* | | | |
|---|---|---|---|---|---|---|---|---|
| *PROMIS Score* | Minimal <55.4 | Mild 55.4 - 62.2 | Moderate-Severe ≥62.3 | SIG | Minimal <52.5 | Mild 52.5-58.5 | Moderate-Severe ≥58.6 | SIG |
| n. | 142 (73%) | 36 (18%) | 18 (9%) | | 134 (68%) | 35 (18%) | 27 (14%) | |
| **Sociodemographic characteristics** | | | | | | | | |
| Age (years), mean (SD) | 54 (13) | 54 (13) | 56 (15) | 0.85 | 55 (13) | 55 (13) | 54 (14) | 0.88 |
| Male sex, n (%) | 30 (21%) | 6 (17%) | 2 (11%) | 0.54 | 28 (21%) | 4 (11%) | 6 (22%) | 0.42 |
| White race, n (%) | 118 (83%) | 30 (83%) | 14 (78%) | 0.85 | 108 (81%) | 31 (89%) | 23 (85%) | 0.50 |
| Education > high school, n (%) | 113 (80%) | 23 (64%) | 17 (94%) | 0.03 | 106 (79%) | 25 (71%) | 22 (82%) | 0.56 |
| Body Mass Index (kg/m$^2$), mean (SD) | 30 (7) | 29 (7) | 34 (8) | 0.07 | 30 (7) | 30 (7) | 33 (7) | 0.09 |
| RA Duration (years), mean (SD) | 11 (10) | 11 (10) | 11 (8) | 0.95 | 10 (9) | 11 (11) | 14 (11) | 0.30 |
| Number of comorbidities*, mean (SD) | 0.6 (0.7) | 0.9 (1.0) | 0.8 (0.8) | 0.16 | 0.5 (0.7) | 0.9 (0.8) | 0.9 (0.9) | **<0.01** |
| Fibromyalgia diagnosis, n (%) | 7 (5%) | 3 (9%) | 1 (6%) | 0.71 | 7 (5) | 3 (6) | 2 (7%) | 0.91 |
| Current Biologic, n (%) | 62 (44%) | 22 (61%) | 5 (28%) | **0.05** | 58 (43%) | 18 (51%) | 13 (48%) | 0.66 |
| Current DMARD, n (%) | 123 (87%) | 33 (92%) | 15 (83%) | 0.63 | 118 (88%) | 29 (83%) | 24 (89%) | 0.69 |
| **Disease characteristics** | | | | | | | | |
| Clinical Disease Activity Index, mean (SD) | 7 (8) | 9 (8) | 12 (10) | **0.05** | 7 (8) | 7 (6) | 14 (10) | **<0.01** |
| Swollen Joint Count-28 | 2 (3) | 3 (4) | 2 (3) | 0.81 | 2 (3) | 2 (3) | 4 (4) | **0.03** |
| Tender Joint Count-28 | 2 (3) | 1 (3) | 3 (5) | 0.15 | 1 (3) | 1 (1) | 3 (5) | **0.01** |
| Patient Global (0-100) | 24 (26) | 38 (27) | 50 (27) | **<0.01** | 24 (27) | 35 (21) | 48 (27) | **<0.01** |
| Evaluator Global (0-100) | 13 (15) | 15 (15) | 20 (20) | 0.18 | 13 (14) | 13 (14) | 23 (20) | **<0.01** |
| Remission, n (%) | 54 (38%) | 7 (19%) | 1 (6%) | **<0.01** | 54 (40%) | 5 (14%) | 3 (11%) | **<0.01** |
| Low Disease Activity, n (%) | 44 (31%) | 17 (47%) | 9 (50%) | **<0.01** | 41 (31%) | 21 (60%) | 8 (30%) | **<0.01** |
| Moderate Disease Activity, n (%) | 35 (25%) | 7 (19%) | 4 (22%) | **<0.01** | 29 (22) | 8 (23%) | 9 (33%) | **<0.01** |
| High Disease Activity, n (%) | 9 (6%) | 5 (14%) | 4 (22%) | **<0.01** | 10 (8%) | 1 (3%) | 7 (26%) | **<0.01** |

*Comorbidity count includes COPD, myocardial infarction, stroke/TIA, hypertension, osteoporosis, depression, diabetes, peptic ulcer disease.

sex, race and disease duration (Table I). As compared to those with minimal anxiety, participants with moderate-severe anxiety were more commonly negative for anti-CCP antibodies (40% positive in moderate-severe group *vs*. 73% positive in minimal group) and were less likely treated with biologics (28% moderate-severe group *vs*. 44% minimal group). Patients with moderate-severe anxiety had higher mean CDAI scores than those with minimal anxiety (mean difference (MD) 4.9, 95% CI (0.04–9.70)), although the patient global was the only component of the CDAI that differed between groups (MD 25.8, 95% CI 10.40–41.33). Patients with mild and moderate-severe anxiety also had significantly more pain than those with minimal anxiety (mild; MD 15.4, 95% CI 3.2–27.6, moderate-severe; MD 24.4, 95% CI 8.2–40.6).

Patients with minimal, mild and moderate-severe depression also shared similar clinical and demographic features except for slightly higher mean comorbidities in the moderate-severe group (Table I). There was not a difference in anti-CCP status or use of biologic agents among depression groups. As compared to those with minimal and mild depression symptoms, patients reporting moderate-severe depression symptoms also had significantly higher mean CDAI scores. However, the physician global assessment of health was also elevated in the moderate-severe depression group in addition to a higher patient global rating of health. As compared to those with minimal depression, those with mild and moderate-severe depression had more pain (mild, MD 14.9, 95% CI 2.9–27.2; moderate-severe, MD 26.0, 95% CI 12.6–39.5).

*HRQL by anxiety and depression status*

Compared to patients with minimal anxiety or depression, patients with anxiety and depression had significantly worse HRQL across all domains including pain interference, physical function, sleep disturbance, fatigue, and social participation (all $p$-values <0.05; Table II). In patients with moderate-severe anxiety, depression, fatigue, and social participation were at least one SD worse than the US population norm and pain interference, physical function, and sleep disturbance were at least one-half SD worse (26). Notably, compared to those with mild anxiety, patients with moderate-severe anxiety only had significantly worse depression. There was not a significant difference in levels of pain interference, physical function, sleep disturbance, fatigue, or social participation between mild and moderate-severe anxiety groups.

Similar patterns were evident for those with minimal *versus* moderate-severe depression scores. For those with moderate-severe depression, anxiety levels were one SD greater than the US population norm; pain interference, physical function, sleep disturbance, fatigue, and social participation were greater than one-half SD.

Anxiety was strongly and directly associated with depression even when adjusting for the SJC (Table III). Anxiety also had moderate, positive correlations with pain interference, sleep disturbance, and fatigue and moderate, negative correlations with physical function and social participation (all $p$-values <0.001). After controlling for the SJC, the associations were essentially unchanged. Similar patterns were noted between depression and HRQL domains (all $p$-values <0.001).

In univariate analysis, each HRQL domain (pain interference, physical function, sleep disturbance, sleep disturbance, fatigue, and social participation) significantly predicted higher levels of anxiety and depression (all $p$-values <0.001) (Table IV). In the full cohort, depression (β=0.65, $p$<0.001), physical function (β=0.14, $p$=0.024) and fatigue (β=0.13, $p$=0.010) predicted higher anxiety levels; only anxiety predicted higher depression levels (β=0.76, $p$=<0.001). Pain interference did not significantly predict anxiety or depression levels. These associations were similar in the subset analysis of patients in remission/low disease activity (n=132) except for the relationship between physical function and anxiety was no longer statistically significant.

**Table II.** Mean (SD) PROMIS scores by anxiety and depressive symptom status in people with RA (n=196).

| | Anxiety | | | Depression | | |
|---|---|---|---|---|---|---|
| | Minimal <55.4 | Mild ≥55.4–62.2 | Moderate-Severe ≥62.3 | Minimal <52.5 | Mild ≥52.5–<58.6 | Moderate-Severe ≥58.6 |
| n. | 142 (73%) | 36 (18%) | 18 (9%) | 134 (68%) | 35 (18%) | 27 (14%) |
| Anxiety | 46.8 (6.1)[a] | 58.4 (2.4)[b] | 65.0 (2.5)[c] | 47.2 (6.9)[a] | 55.8 (5.1)[b] | 60.0 (6.7)[c] |
| Depression | 45.5 (7.2)[a] | 55.0 (5.8)[b] | 62.0 (6.5)[c] | 44.2 (6.0)[a] | 55.0 (1.8)[b] | 63.6 (3.8)[c] |
| Pain interference | 51.3 (9.1)[a] | 58.8 (6.1)[b] | 60.2 (9.3)[b] | 51.1 (9.3)[a] | 57.7 (5.9)[b] | 60.0 (8.4)[b] |
| Physical function | 45.1 (8.9)[a] | 41.1 (6.6)[b] | 38.1 (9.9)[b] | 45.4 (9.1)[a] | 41.9 (5.2)[a,b] | 37.7 (8.7)[b] |
| Sleep disturbance | 49.9 (9.0)[a] | 55.0 (9.0)[b] | 56.2 (12.8)[b] | 49.5 (9.2)[a] | 55.1 (8.3)[b] | 56.2 (10.8)[b] |
| Fatigue | 51.2 (10.3)[a] | 58.1 (7.0)[b] | 62.5 (4.5)[b] | 51.1 (10.3)[a] | 57.1 (7.8)[b] | 61.1 (5.8)[b] |
| Social participation | 52.6 (8.4)[a] | 45.9 (7.5)[b] | 43.4 (8.9)[b] | 52.9 (8.8)[a] | 47.1 (5.2)[b] | 43.2 (8.3)[b] |

Values in the same row not sharing the same subscript are significantly different at $p$<0.05.

**Table III.** Correlations between anxiety, depression and health-related quality of life domains in people with RA.

| PROMIS Scale | Anxiety | | Depression | |
|---|---|---|---|---|
| | r | Adjusted r* | r | Adjusted r* |
| Depression | 0.81 | 0.81 | --- | --- |
| Anxiety | --- | --- | 0.81 | 0.81 |
| Pain interference | 0.49 | 0.48 | 0.51 | 0.50 |
| Physical function | -0.36 | -0.34 | -0.40 | -0.39 |
| Sleep disturbance | 0.38 | -0.37 | 0.37 | 0.36 |
| Fatigue | 0.54 | 0.53 | 0.51 | 0.50 |
| Social participation | -0.52 | -0.51 | -0.54 | -0.53 |

All $p$-values <0.000. *Adjusted for 28-swollen joint count.

## Discussion

This study evaluated the impact of anxiety and depression on RA symptoms,

**Table IV. A.** Predictors of anxiety and depression in RA with a **B**) subset analysis of participants in remission/low disease activity (LDA).

**A.** Full cohort (n=196).

| | Anxiety | | | | Depression | | | |
|---|---|---|---|---|---|---|---|---|
| | univariate | | adjusted* | | univariate | | adjusted* | |
| *PROMIS* | coef. | SIG | coef. | SIG | coef. | SIG | coef. | SIG |
| Depression | 0.76 | **0.000** | 0.65 | **0.000** | - | - | - | - |
| Anxiety | - | - | - | - | 0.87 | **0.000** | 0.76 | **0.000** |
| Pain interference | 0.44 | **0.000** | 0.06 | 0.351 | 0.48 | **0.000** | 0.11 | 0.110 |
| Physical function | -0.33 | **0.000** | 0.14 | **0.024** | -0.40 | **0.000** | -0.05 | 0.501 |
| Sleep disturbance | 0.33 | **0.000** | 0.03 | 0.400 | 0.34 | **0.000** | 0.01 | 0.777 |
| Fatigue | 0.44 | **0.000** | 0.13 | **0.010** | 0.44 | **0.000** | -0.2 | 0.651 |
| Social participation - ability | -0.49 | **0.000** | -0.09 | 0.125 | -0.54 | **0.000** | -0.12 | 0.067 |

*Adjusted for age, sex, race, and education.

**B.** Remission/Low Disease Activity (n=132).

| | Anxiety | | | | Depression | | | |
|---|---|---|---|---|---|---|---|---|
| | univariate | | adjusted* | | univariate | | adjusted* | |
| *PROMIS* | coef. | SIG | coef. | SIG | coef. | SIG | coef. | SIG |
| Depression | 0.83 | **0.000** | 0.75 | **0.000** | - | - | - | - |
| Anxiety | - | - | - | - | 0.86 | **0.000** | 0.70 | **0.000** |
| Pain interference | 0.49 | **0.000** | 0.02 | 0.812 | 0.55 | **0.000** | 0.11 | 0.095 |
| Physical function | -0.41 | **0.000** | 0.14 | 0.053 | -0.50 | **0.000** | -0.07 | 0.311 |
| Sleep disturbance | 0.36 | **0.000** | 0.05 | 0.259 | 0.35 | **0.000** | 0.01 | 0.855 |
| Fatigue | 0.52 | **0.000** | 0.15 | **0.015** | 0.52 | **0.000** | -0.01 | 0.715 |
| Social participation | -0.59 | **0.000** | -0.09 | 0.167 | -0.63 | **0.000** | -0.12 | 0.064 |

*Adjusted for age, sex, race, and education.

disease activity and physical and social function. We also evaluated predictors of high anxiety and depression levels in a usual care cohort of RA patients. We found that anxiety, especially at mild levels, was common and had significant impacts on pain, fatigue, sleep, physical function, and social participation. Across chronic diseases, minimally important differences in PROMIS scores range from 2–6 units for depression, anxiety, physical function, pain interference, and fatigue (30-32). We found differences greater than 4–10 units for all HRQL domains examined among mild or moderate emotional distress categories (Table II). Importantly, there was not a significant difference in T-scores for other HRQL domains between mild and moderate-severe anxiety groups, consistent with the recent validation study (21), emphasising the need to recognise and treat even mild anxiety symptoms.

Patients with moderate-severe anxiety and depression had significantly higher CDAI scores compared to those with low levels of anxiety and depression driven, in part, by higher patient global assessment ratings, consistent with previous literature (33, 34). Despite this, we found moderately strong, positive correlations between emotional distress and RA symptoms, physical function, and social function, even after adjusting for disease activity. These data possibly suggest that RA patients with high anxiety or depression symptoms have greater impairments of HRQL that may not resolve with better inflammatory control. When considering pharmacologic escalation or medication change, it is important for the treating physician to routinely evaluate for anxiety and depression when considering pharmacologic escalation or medication change if the objective is to improve HRQL. However, few clinical trials have explored whether treatment of anxiety or depression symptoms improves clinical outcomes in RA (12).

Interestingly, the physician global assessment of health was significantly higher among RA patients with moderate-severe depression symptoms but not with moderate-severe anxiety. This finding may suggest that symptoms of depression, but not anxiety, are more impactful on a physician's rating of global disease activity and perhaps better recognised than anxiety. We hypothesise that the lack of impact of anxiety on the physician's global rating of health is multifactorial but may stem from increased cultural acceptance of anxiety, especially at low levels. Increased assessment of emotional health using reliable and precise tools such as PROMIS or other validated screening tools may allow for better detection of emotional distress and prompt earlier management and engagement of mental health providers, if necessary.

We found that the most significant predictors of anxiety were depression, physical function and fatigue, and the most significant predictor for depression was anxiety. Contrary to our hypothesis, pain interference did not predict anxiety or depression. In a subset of our patients in remission/LDA (n=132, 67%), which eliminated the impact of RA disease activity, anxiety remained the largest predictor of depression. Untreated anxiety leading to higher levels of depression may have very serious clinical implications, including cardiovascular disease (35, 36), necessitating the importance of early detection and treatment.

This study has several strengths. This study analysed a sizeable, usual care RA cohort that had well-defined clinical markers as well as patient-reported outcome measures. There are also limitations of this study. Our RA cohort mostly represents well-educated white women with longstanding, well-controlled disease. The relationship between disease activity and anxiety and depression may be different with early disease, lower socioeconomic status, or higher levels of disease activity. Comorbidities, such as fibromyalgia, diabetes, or COPD may also have significant impacts on HRQL, and we did not adjust for these in our analyses. However, we did not find a significant difference in the comorbidity count amongst the different groups of emotional distress. Finally, this was a cross-sectional analysis of motivated individuals willing to participate in an observational study at a large, tertiary care

center. The prevalence of anxiety and depression in this cohort of individuals may differ from other practice settings or patient populations.

## Conclusions

In our RA cohort of participants with longstanding disease, anxiety and depression symptoms were associated with worse RA symptoms and impacts even when adjusting for disease activity. Anxiety and depressive symptoms were closely related, and even low levels of symptoms may have serious consequences, both on RA and HRQL, if left untreated. Comprehensive management strategies that include addressing worry and low mood may improve HRQL, positively impacting the ability to participate in meaningful social and life events and restoring a sense of normalcy for patients with RA.

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