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Authors Jelena Ceranić¹, Branislava Glisić¹, Milan Petronijević¹, Darija Kisić Tepavčević², Gorica Ristić¹, Vojnosanitetski pregled (2021); Online First October, 2021.

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THE PREVALENCE OF DEPRESSION/ANXIETY IN PATIENTS WITH RHEUMATOID ARTHRITIS AND THE CORRELATION WITH QUALITY OF LIFE

UČESTALOST DEPRESIJE/ANKSIOZNOSTI KOD PACIJENATA SA REUMATOIDNIM ARTRITISOM I POVEZANOST SA KVALITETOM ŽIVOTA

Jelena Ćeranić¹, Branislava Glišić¹, Milan Petronijević¹, Darija Kisić Tepavčević², Gorica Ristić¹

¹ Department of Rheumatology and Clinical Immunology of the Military Medical Academy and Medical Faculty of the Military Medical Academy, University of Defense in Belgrade, Serbia
² Institute of Epidemiology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia

Correspondence to:
Jelena Ćeranić, Military Medical Academy, Rheumatology Clinic, Crnotravska 17, 11 000 Belgrade, Serbia. E-mail: drjceranic@gmail.com
ABSTRACT

Introduction. Rheumatoid arthritis (RA) is accompanied by numerous comorbidities, among which depression and anxiety (D/A) occupy a significant place. Objective. To assess the prevalence of D/A in RA patients and their correlation with quality of life. Methods. The study included RA patients treated at the Rheumatology Clinic of the Military Medical Academy in the period from May to November 2016. Disease activity was assessed by the Disease Activity Score 28-SE (DAS28-SE). Depression/anxiety was determined using the Hospital Anxiety and Depression Scale (HADS Questionnaire) and EuroQoL Five-Dimensional Questionnaire (EQ5D3L Questionnaire) Question 5. Three questionnaires were used to assess quality of life: the general RAND36 (The RAND 36-item Health Survey 1.0) and the specific RAQL and EQ5D3L. Results. On the basis of the HADS Questionnaire, the prevalence of depression was 52% with the average HADS score value of 7.6±3.2, while the prevalence of anxiety was 32% with the mean HADS score value of 5.8±3.8. Question 5 of the EQ5D Questionnaire showed that the prevalence of D/A was 77.4%, of which 71.7% of patients had moderate D/A, while 5.7% of patients had severe D/A. Impairment in all the domains of quality of life was found in some patients, as assessed by all the three questionnaires. The RAQL Questionnaire showed moderate quality of life impairment, with the value of 15.5±7.9. The EQ-VAS value was 58.6±16.0, while the EQ5D index was 0.6±0.3. Univariate linear regression produced a statistically significant negative predictive value of quality of life for the presence of anxiety/depression. Multivariate linear regression showed a statistically significant independent negative predictive value of quality of life, as assessed by the RAQL Questionnaire (p=0.010) and the mental quality of life component of the RAND 36 Questionnaire (p=0.030) for the degree of depression. Conclusion. In RA patients, there is significant prevalence of D/A as well as impairment of quality of life in all domains. The tests performed have shown that quality of life has a statistically significant negative predictive value for the presence of D/A.

Key words: depression/anxiety, rheumatoid arthritis, questionnaire, quality of life, comorbidities, prevalence.
APSTRAKT

Uvod. Reumatoidni artritis (RA) je praćen brojnim komorbiditetima medju kojima depresija i anksioznost (D/A) zauzimaju značajno mesto. Cilj. Proceniti učestalost D/A kod bolesnika sa RA i njihovu povezanost sa kvalitetom života. Metod. Ispitivanje je obuhvatio bolesnike sa RA koji su lečeni u Klinici za reumatologiju, Vojnomedicinske akademije, u periodu od maja do novembra 2016. g. Aktivnost bolesti je procenjivana pomoću Disease activity scor 28-SE (DAS28-SE). Depresija/anksioznost je određivana pomoću Hospital anxiety and depression scale (HADS upitnika) i petog pitanje EuroQoL five-dimensional questionnaire (EQ5D3L upitnika). Za procenu kvaliteta života korišćena su tri upitnika: opšti RAND36 (The RAND 36-item Health Survey 1.0) i specifični RAQL i EQ5D3L. Rezultati. Na osnovu HADS upitnika učestalost depresije je iznosila 52% sa prosečnom vrednošću HADS skora 7,6±3,2, dok je učestalost anksioznosti iznosila 32% sa srednjom vrednošću HADS skora 5,8±3,8. Pomoću petog pitanja EQ5D upitnika nadjeno je da je učestalost D/A 77,4% od čega je umerenu D/A imalo 71,7%, a izraženu 5,7% bolesnika. Kod naših pacijenata nadjena je narušenost u svim domenima kvaliteta života pomoću sva tri upitnika. RAQL upitnikom je dobijena umerena narušenost kvaliteta života sa vrednošću 15,5±7,9. Vrednost EQ-VAS je iznosila 58,6±16,0, dok je EQ5D index iznosio 0,6±0,3. Univariatnom linearnom regresijom dobijena je statistički značajna negativna prediktivna vrednost kvaliteta života za prisustvo anksioznosti/depresije. Multivariatnom linearnom regresijom pokazana je statistički značajna nezavisna negativna prediktivna vrednost kvaliteta života procenjena pomoću RAQL upitnika (p=0,010) i mentalne komponente kvaliteta života RAND 36 upitnika (p=0,030) za stepen depresije. Zaključak. Kod bolesnika sa RA postoji značajna učestalost D/A kao i narušenost kvaliteta života u svim domenima. Učinjenim ispitivanjima je pokazano da kvalitet života ima statistički značajnu negativnu prediktivnu vrednost za prisustvo D/A.

Ključne reči: depresija/anksioznost, reumatoidni artritis, upitnik, kvalitet života, komorbiditeti, prevalencija.
INTRODUCTION

Rheumatoid arthritis (RA) is a chronic disease characterized by persistent synovitis and systemic inflammation leading to joint destruction, functional disability and premature mortality. The disease is accompanied by numerous comorbidities that significantly impair quality of life. According to the results of the large multicenter COMORA (COMOrbidities in Rheumatoid Arthritis) study, which determined the prevalence of comorbidities in RA, depression was most common with 15%, followed by asthma with 6.6%, cardiovascular events (myocardial infarction, CVI) with 6%, solid tumors (except for basal cell carcinoma) with 4.5%, and COPD with 3.5% (1).

Despite the prevalence and significance, mental health has been rarely investigated in rheumatology studies and clinical practice. Reports show that mental health has been studied in less than 8% of published works dealing with rheumatoid arthritis, while quality of life is studied somewhat more frequently (in 19% of studies), mostly using the SF36 Questionnaire (2).

The prevalence of depression in RA ranges between 9.5% (3) and 41.5% (4), while the prevalence of anxiety ranges from 21% to 70% (5). Follow-up studies have indicated that the cumulative risk of the occurrence of depression after 9 years of RA is 40%. (6). Depression and anxiety in RA are associated with a higher degree of disease activity, reduced quality of life, increased use of healthcare services, as well as reduced adherence to therapy. The correlation between depression and RA is multifactorial: it may be a result of social and economic factors, functional disability and/or inflammation. There are various reasons for the large variation in the prevalence. It is very difficult to distinguish between patients with depressive disorder and those with a normal reaction to the fact that they live with a chronic, functionally limiting condition. Further, numerous symptoms of depression, such as fatigue, poor sleep and loss of appetite, can be part of the clinical picture of rheumatoid arthritis itself. In addition to the foregoing, the prevalence is also affected by different methods used for diagnosing depression. A gold standard is a psychiatric interview and diagnosis through the Diagnostic and Statistical Manual (DSM) or International Classification of Diseases (ICD) criteria. However, alternative self-report questionnaires can also be useful due to their practicality in everyday work. Previous research has indicated that the recognition and appropriate treatment of D/A improve the
response to treatment and considerably reduce symptoms associated with RA, improving the functional status and quality of life (7). That is why the objective of our study was to assess the prevalence of D/A in our patients and the correlation with quality of life.

METHODS

The study included RA patients who were treated at the Rheumatology Clinic of the Military Medical Academy in the period from May to November 2016. The enrolment criteria were the following: RA diagnosis based on the American College of Rheumatology (ACR) 1987 classification criteria and ACR/EULAR 2010, age ≥ 18 years. Patients with other systemic connective tissue diseases, fibromyalgia, previously verified cognitive disorder and psychiatric disease, and those who had used antidepressants in the previous month, were excluded from the study. Structured questionnaires compiled on the basis of literature data were used for the collection of information regarding subject and disease characteristics. The first part of the questionnaires included social and demographic characteristics of subjects: gender, age, place of residence (rural/urban environment), employment status, and level of education. The second part of the questionnaires pertained to the clinical characteristics of RA: disease duration, therapy (use of MTX, other DMARDs, corticosteroids, biological therapy).

To assess the activity of RA, the Disease Activity Score 28 (DAS 28-SE) was determined for all patients based on the total number of tender and swollen joints, the patient's assessment of disease activity on the VAS scale and erythrocyte sedimentation rate (ESR) (mm/h). The assessment of the patient's functional ability was performed using the HAQ DI (Health Assessment Questionnaire), which contains a total of 20 questions scored from 0 to 3 (0 = without difficulties, 3 = I cannot do it).

The following tests were performed when it comes to inflammation markers: erythrocyte sedimentation rate by Westergreenum (SE) and C-reactive protein (CRP) using the nephelometric method. Depression and/or anxiety were diagnosed using two questionnaires: Hospital Anxiety and Depression Scale (HADS) and Question 5 of the EuroQoL five-dimensional questionnaire (EQ-5D-3L). The HADS (8) questionnaire contains 14 questions (7 for depression and 7 for anxiety). The patient assesses the degree of agreement using the Likert scale, from 0 to 3. The total score for each scale is from 0 to
21. A score exceeding 11 indicates the presence of depression/anxiety; 8-10 indicates borderline cases, and 0-7 is a normal finding. The EQ-5D-3L (9) questionnaire contains five questions regarding various dimensions of health: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

Three questionnaires were used for the assessment of quality of life: general - the RAND 36-item Health Survey 1.0 (RAND36), specific - the Rheumatoid Arthritis Quality of Life (RAQL) and EQ5D3L. The RAND contains 36 questions scored in 8 domains (physical functioning, social functioning, limitations due to physical problems, limitations due to emotional problems, mental health, vitality, pain and general health perception). Each subscale is ranked from 0 to 100, where a higher score indicates better quality of life. The RAND can be converted into two composite scores: physical health composite score (PCS) and mental health composite score (MCS) (10). The RAQL contains 30 questions regarding the mental and physical domains, which are answered with yes and no (1/0). The total score is 30, and lower score indicates better quality of life (11). The EQ5D3L comprises two parts – a descriptive system and a visual analog scale (VAS). The EQ-5D-3L descriptive system measures five dimensions of health: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: without problems (1), there are some problems (2), severe problems (3). The EQ VAS represents a self-assessment of health on a vertical analog scale from the worst (0) to the best possible health (100). All five dimensions of the EQ5D-3L questionnaire are converted into a general health index using scores derived from a general population sample. The German time-trade-off (TTO) was used in this research as this European population is most similar to the studied population in Serbia.

The correlation analysis was assessed based on the Spearman's rank correlation coefficient. The investigation of the predictive value of inflammation parameters and main disease characteristics as the selected variables in the assessment of depression and quality of life was carried out using linear and logistic regression analysis methods. Values of p<0.05 were considered statistically significant differences. The obtained results were statistically processed using a statistical program for Windows, version 20.0 (Statistical Package for Social Science-SPSS Inc.).
RESULTS

The study included 53 patients with rheumatoid arthritis of an average age of 54.6±9.8 years. Women accounted for 86.8% (53/46). 35.8% of patients (53/19) were employed, while 42 patients (79.2%) had primary and secondary education. The main characteristics of subjects and rheumatoid arthritis are presented in Table 1. 79.2% of patients (53/42) were treated with methotrexate, while 64.2% (53/34) received glucocorticoids. 37.7% of patients (53/20) received biological therapy, mainly Tocilizumab (61%). The average DAS 28 was 4.0±1.8. About a third of patients (26.4%) were in remission, and slightly more of them had high disease activity (34%). The functional status of the investigated group (HAQ DI) was mildly impaired, and the average value was 0.77±0.77.

Table 1.

Clinical features and anti-rheumatic treatment in patients with RA

| The main characteristics of subjects and rheumatoid arthritis | N=53 |
|-------------------------------------------------------------|------|
| Disease duration (years)                                    | 8.0±7.2 |
| Presence of RF and/or anti CCP At n (%)                     | 46 (86.8) |
| Methotrexate use, n (%)                                     | 42 (79.2) |
| Therapy corticosteroids, n (%)                              | 34 (64.2) |
| Therapy another BMD, n (%)                                  | 11 (20.8) |
| Any biological therapy, n (%)                               | 20 (37.7) |
| Tender joint count TJC                                      | 5.8±5.7 |
| Swollen joint count SJC                                     | 2.2±3.3 |
| VAS*                                                        | 43.5±18.9 |
| DAS28-ESR‡                                                  | 4.04±1.79 |
| DAS 28 < 2.6, n (%)                                         | 14 (26.4) |
| DAS28 2.6-3.1, n (%)                                        | 3 (5.7) |
| DAS28 >3.1, n (%)                                           | 15 (28.3) |
| DAS28 >5.1, n (%)                                           | 18 (34) |
| HAQ DI**                                                    | 0.77±0.77 |

The values represent X±SD (mean value ± standard deviation)
The prevalence of depression assessed by the HADS questionnaire was 52%. The average value of the HADS score for depression was 7.6±3.2. As assessed by the same questionnaire, the prevalence of anxiety was 32% with the average HADS score value of 5.8±3.8.

The prevalence of D/A assessed by Question 5 of the EQ5D questionnaire was 77.4%, of which 38 patients (71.7%) had D/A and 3 patients (5.7%) had severe D/A.

**Table 2.**

| HADS - Hospital anxiety and depression scale |  |
|---------------------------------------------|--|
| **Depression score**                        | 7.6±3.2 |
| 0-7, n (%)                                  | 24 (48) |
| 8-10, n (%)                                 | 18 (36) |
| > 11, n (%)                                 | 8 (16)  |
| **Anxiety score**                           | 5.8±3.8 |
| 0-7, n (%)                                  | 34 (68) |
| 8-10, n (%)                                 | 11 (22) |
| >11, n (%)                                  | 5 (10)  |
| **EQ5D3L**                                  |        |
| Number of patients with anxiety/depression, n (%) | 41/53 (77.4) |
| Number of patients with moderate anxiety/depression, n (%) | 38/53 (71.7) |
| Number of patients with severe anxiety/depression, n (%) | 3/53 (5.7) |

The values represent X±SD (mean value ± standard deviation)

HADS - Hospital anxiety and depression scale

EQ5D3L - EuroQoL five-dimensional questionnaire

The RAQL questionnaire indicated moderately impaired quality of life with the average value of 15.5±7.9. A significant percentage of patients had difficulties in all the
five quality of life domains when the EQ5D questionnaire was used, mainly in the domain of the presence of pan/discomfort and everyday functioning. The same questionnaire was used to analyze the impact of emotional problem on quality of life. It was established that 77.4% of patients (53/41) had problems due to the presence of anxiety/depression. As part of the said questionnaire, based on the personal quality of life assessment by the patient, the average value on the VAS scale of 58.6±16.0 was obtained, while the average value of the general health index (EQ5D index) was 0.6±0.3.

Table 3.

**Quality of life assessment using RAQL and EQ5D3L questionnaires**

| RAQL | 15.5±7.9 |
|------|----------|
| Present state of health (EQ 5D3L), any problems | Mobility, n (%) | 41 (77.4) |
| | Self-care, n (%) | 34 (64.2) |
| | Usual activities, n (%) | 44 (83.0) |
| | Pain/Discomfort, n (%) | 51 (96.2) |
| | Anxiety/Depression, n (%) | 41 (77.4) |
| EQ VAS | 58.6±16.0 |
| EQ5D index value, mean (SD) | 0.6±0.3 |

The values represent X±SD (mean value ± standard deviation)

RAQL - The Rheumatoid Arthritis Quality of Life

EQ5D - EuroQoL five-dimensional questionnaire

EQ VAS – Visual Analog Scale for the assessment of general health as part of the EQ5D questionnaire

EQ5D index – general health index derived from all the five categories of the EQ5D questionnaire

The RAND36 questionnaire was used for an additional quality of life assessment, and the values are presented in Table 4.
Table 4.

Quality of life assessment using RAND36 questionnaires

|                                      |        |
|--------------------------------------|--------|
| Physical functioning (%)             | 45.12±19.20 |
| Role limitations due to physical health (%) | 21.63±30.13 |
| Role limitations due to emotional problems (%) | 38.44±37.63 |
| Energy/fatigue (%)                   | 39.71±22.83 |
| Emotional well-being (%)             | 59.62±20.06 |
| Social functioning (%)               | 53.04±24.82 |
| Pain (%)                             | 40.19±23.41 |
| General health (%)                   | 46.83±16.59 |
| Health change (%)                    | 49.04±29.69 |
| PCS (%)                              | 38.44±22.35 |
| MCS (%)                              | 47.70±26.33 |

PCS - the physical component summary (PCS) score RAND 36
MCS - the mental component summary (MCS) score RAND36

An analysis of the quality of life and anxiety/depression degree ratio has produced a statistically significant negative predictive value of quality of life, as assessed by the RAQL and RAND36 questionnaires with the presence of anxiety/depression.

Table 5.

Univariate linear regression of the impact of quality of life on the degree of depression/anxiety‡

|                                      | RAQL | EQ5D | PCS RAND36 | MCS RAND 36 |
|--------------------------------------|------|------|------------|-------------|
| D score (HADS)                       | 0.596| ns   | -0.442     | -0.594      |
|                                       | (p=0.000) |       | (p=0.001)  | (p=0.000)   |
| A score (HADS)                       | 0.379| ns   | -0.308     | -0.442      |
|                                       | (p=0.008) |       | (p=0.032)  | (p=0.001)   |
| EQ5D (A/D)                           | ns   | ns   | ns         |             |

‡ the given values represent the standardized regression coefficient β.
Multivariate linear regression has shown a statistically significant independent negative predictive value of quality of life, as assessed by the RAQL questionnaire and the mental quality of life component of the RAND 36 questionnaire for the degree of depression.

Table 6.

Multivariate linear regression of quality of life for the degree of depression‡

| Independent variables | Score D (HADS) | p    |
|-----------------------|----------------|------|
| RAQL                  | 0.502          | 0.010|
| PSC RAND36            | 0.278          | 0.173|
| MCS RAND36            | -0.426         | 0.030|

‡ the given values represent the standardized regression coefficient β.

DISCUSSION

Rheumatoid arthritis (RA) is a chronic inflammatory disease accompanied by numerous comorbidities, among which depression and anxiety occupy a significant place.

The results of our study based on the HADS questionnaire show that 52% of patients have some depression symptoms. This result is in compliance with the previous studies in which the same questionnaire was used and which showed that more than 50% of RA patients had depressive disorders (4). In other studies, the prevalence of depression in RA patients was 14-46% depending on measuring instruments (12, 13). In our study, it was found using Question 5 of the EQ5D3L questionnaire that even 77.4% of patients had D/A. With the same questionnaire, Arno M and associates obtained the prevalence of D/A in patients with rheumatoid arthritis of 48%. (14) A possible reason for the lower presence of D/A could be the fact that in the said study more patients (74.4%) had low disease activity in comparison with 32% of our subjects. Rathbun et al. (15) in their research found a correlation between depression and the patient's assessment on the VAS scale and pain. Patient global VAS correlated with anxiety levels, which could partially explain the association between anxiety and worse disease activity outcomes in RA.(16) Numerous authors have shown that the correlation of depression and disease activity is bidirectional –
active RA leads to the occurrence of depression, while depression impacts the activity of RA. In the work of Hider et al. (17), patients with depression had a higher DAS28 score, while patients with chronic depression had a slight decrease in the DAS28 score despite treatment with TNF-inhibitors.

When it comes to anxiety, our research using the HADS questionnaire (HADS score >8) showed that 32% of patients were anxious. Using the same questionnaire and HADS score >8, Yokogawa and associates found that 29.3% of patients were anxious (18). El-Miedany and El-Rasheed found that the prevalence of anxiety in RA was 70% (19), while Arnold et al. found the prevalence of 7.5%. Both studies were conducted based on a clinical interview as an instrument for anxiety disorder measurement. In any case, our results are in compliance with data from previous studies which have demonstrated the level of anxiety in RA of 21-70%, as assessed by various measuring instruments (5).

The reason for the high level of depression and/or anxiety is multifactorial. Investigating the impact of social and demographic characteristics of subjects, it was observed that women accounted for 86.8% of the studied group, and it is known that depression is more frequent in female than in male population.

Investigating the level of education, it was found that about 80% of patients had elementary and secondary education. Salaffi et al. (20) have established that a lower level of education represents a risk factor for chronic musculoskeletal pain and physical functioning, while Evers et al. have pointed at a correlation between a lower level of education and the degree of depression and anxiety in RA patients (21).

A large number of previous studies have demonstrated that a particular level of functional limitation determined using the HAQ is a strong predictor of depression in RA patients (22). Our study has not demonstrated a correlation between functional limitation and the degree of depression and/or anxiety as the average HAQ score value in our patients was 0.77±0.77, which is significantly lower than the average HAQ score in patients for whom a correlation with D/A has been found.

It is known that the quality of life of RA patients is considerably reduced, which we also obtained in our study using all the three questionnaires. The quality of life of our patients was reduced in all domains of the EQ5D3L questionnaire as well as all physical and mental health domains of the RAND36 questionnaire. These results are in compliance with the results of a study conducted by West and Jonsson (23), who have demonstrated an
adverse effect of RA itself on the patient's physical, emotional and social functioning. The study of Salaffi et al. (20) has demonstrated that the quality of life components relating to the patient's physical and functional condition are the most frequently affected domains of the SF36 questionnaire. Our results are in compliance with the said research as according to the EQ5D questionnaire the highest percentage of patients had difficulties in the domain of pain/discomfort (96.2%) and everyday functioning (83%), while according to the RAND 36 questionnaire the highest degree of impairment was in the domain of limitations in physical functioning (21.6±30.1). The presence of pain is actually the main characteristic of RA, which represents an important factor for determining quality of life in the early period of disease (24).

A meta analysis showed that patients with RA with depression tended to have lower quality of life than patients without depression. (25) Depressed patients with RA have more pain (26), high disease activity (27), and reduced quality of life. Our study has demonstrated a significant correlation between quality of life and the degree of depression and/or anxiety. Multivariate regression analysis has shown that the quality of life assessed using the RAQL questionnaire as well as the MCS score of the RAND 36 questionnaire is an independent predictor of the degree of depression. This is also in compliance with the studies of Covic and associates (28), who have discovered that physical limitations affect the patient's emotional condition, primarily depression. Numerous cross-sectional and longitudinal studies have demonstrated significant association of somatic symptoms with the occurrence of depression/anxiety. (29, 30).

CONCLUSION

In RA patients, there is a high prevalence of depression/anxiety as well as considerable impairment of quality of life. The degree of quality of life impairment is an independent negative predictor for the degree of depression. The correlation between psychological disorders and somatic symptoms is actually bidirectional, indicating the need for discovering and treating psychological disorders simultaneously with somatic symptoms. Routine detection and treatment of depression and anxiety should be part of a future strategy to improve the overall treatment of rheumatoid arthritis (31), which requires a multidisciplinary approach in RA treatment. (32).
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