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Socioeconomic and therapy factor influence on self-reported fatigue, anxiety and depression in rheumatoid arthritis patients

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ABSTRACT

Introduction: Fatigue, anxiety and depression are very frequent symptoms in patients with rheumatoid arthritis (RA).
Goals: In this study we evaluated the influence of socioeconomic characteristics, therapy and comorbidities on the self-reported high fatigue, anxiety and depression in patients with RA.
Method: Multicenter cross-sectional study was performed in 22 health institutions in Serbia during the period from April–August 2014 in population of older RA patients. Self-reported patients health status was measured by: Fatigue Assessment Scale, Patient Health Questionnaire-9 and Generalized Anxiety Disorder-7. Treatment modalities were defined as: (1) non-steroidal anti-inflammatory drugs (NSAIDs) and/or analgesics and/or corticosteroids; (2) synthetic disease-modifying antirheumatic drugs (DMARDs) alone or in combination with corticosteroids and/or NSAIDs and (3) any RA treatment which includes biologic DMARDs.
Results: There were significant predictors of high depression: synthetic DMARDs therapy in combination with corticosteroids and/or NSAIDs, physiotherapist self-payment, frequent taxi use, alternative treatment and employment status. The need for another person's assistance, supplemental calcium therapy and professional qualifications were the predictors of a high fatigue, whereas the age above 65 years had the protective effect on it. Anxiety was an independent high fatigue predictor. The predictors of a high anxiety were: gastroprotection with proton-pump inhibitors and patient occupation.

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Conclusion: Socioeconomic predictors of self-reported high depression, anxiety or fatigue are different for each of the mentioned outcomes, while accompanied with the basic RA treatment they exclusively explain a high depression. The anxiety, jointed with the socioeconomic variables and supplemental therapy, is a significant fatigue predictor in RA patients.

Influência de fatores socioeconômicos e de tratamento sobre a fadiga, ansiedade e depressão autorrelatadas em pacientes com artrite reumatoide

Palavras-chave:
Artrite reumatoide
Fadiga
Ansiedade
Depressão
Desfechos autorrelatados

RESUMO

Introdução: A fadiga, a ansiedade e a depressão são sintomas muito frequentes em pacientes com artrite reumatoide (AR).
Objetivos: Neste estudo, avaliou-se a influência de características socioeconômicas, características de tratamento e comorbidades na elevação na fadiga, ansiedade e depressão autorrelatadas em pacientes com AR.
Método: Este estudo transversal multicêntrico foi feito em 22 instituições de saúde na Sérvia de abril a agosto de 2014 na população de pacientes idosos com AR. O *status* de saúde autorrelatado dos pacientes foi medido pelos instrumentos *Fatigue Assessment Scale*, *Patient Health Questionnaire*-9 e *Generalized Anxiety Disorder*-7. As modalidades de tratamento foram definidas como: 1) anti-inflamatórios não esteroides (AINE) e/ou analgésicos e/ou corticosteroides; 2) fármacos antirreumáticos modificadores da doença sintéticos (DMARD) isoladamente ou em combinação com corticosteroides e/ou AINE e 3) qualquer tratamento para a AR que incluísse DMARD biológicos.
Resultados: Houve preditores significativos de depressão elevada: tratamento com DMARD sintéticos em combinação com corticosteroides e/ou AINE, pagamento particular de fisioterapia, uso frequente de serviços de táxi, terapias alternativas e *status* ocupacional. A necessidade de assistência de outra pessoa, o tratamento suplementar com cálcio e as qualificações profissionais foram os preditores de fadiga elevada. A idade acima de 65 anos teve um efeito protetor sobre a fadiga elevada. A ansiedade foi um preditor independente de fadiga elevada. Os preditores ansiedade elevada foram: gastroproteção com inibidores da bomba de prótons e ocupação do paciente.
Conclusão: Os preditores socioeconômicos de níveis elevados de depressão, ansiedade ou fadiga autorrelatadas são diferentes para cada um dos desfechos mencionados; quando acompanhados do tratamento básico para a AR, esses preditores socioeconômicos explicam exclusivamente uma depressão elevada. A ansiedade, associada às variáveis socioeconômicas e ao tratamento complementar, é um importante preditor da fadiga em pacientes com AR.

Introduction

Rheumatoid arthritis (RA) is a multifactorial systemic chronic inflammatory disease that primarily causes pain, swelling, joint stiffness and loss of joint function.[1] If not properly treated the RA can cause joint damage including their permanent destruction.[2] The RA causes joint damage during the first or second year of the disease. That is why an early diagnosis and an adequate treatment of RA are very important. The RA treatment goal is the achievement of clinical remission, i.e. discontinuation of the disease activity.[3] By including one synthetic Disease-Modifying Antirheumatic Drug (DMARD) or, if necessary, two of them in combination during six months it is expected to achieve the remission or at least the low RA activity. If not achieved with synthetic DMARDs the biologic DMARDs should also be included. Besides the aforementioned therapy, non-steroidal anti-inflammatory drugs (NSAIDs) should be included, together with corticosteroids if needed, in order to control the pain and the inflammation and improve RA patient's general health condition. During the administration of the above mentioned therapy, it is necessary to protect the digestive tract bleeding with proton-pump inhibitors (PPI), especially in patients with high gastrointestinal bleeding risk. In addition, regular hematological and biochemical laboratory results follow ups are needed in order to monitor a possible marrow bone damage and hepatotoxicity during the DMARDs administration.[4,5]

Fatigue is a subjective symptom that appears within the wide range of diseases including the RA. Even though the international consensus about the definition of the fatigue still hasn't been achieved, a big number of authors define it as: "an overwhelming, sustained sense of exhaustion and decreased

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capacity for physical and mental work".[6] The RA patients define their fatigue as persistent, multidimensional symptom with severe, long term consequences to their daily life[7–9] or as a symptom that disrupts their daily activities and causes a non-refreshing sleep.[10] Several studies have shown that the high fatigue in RA patients was related to the pain, depression symptoms, sleep disorder, high physical effort, gender and psychosocial factors.[11,12] Other reports found that depression is related to the pain, fatigue, inability to work and lower therapy compliance.[13,14] Some studies report a high incidence of a common depression and anxiety appearance in RA patients.[15] However, there is a lack of reports in the literature about common influences of the basic, adjuvant and supplemental RA therapy and socioeconomic factors to the anxiety, depression and fatigue in RA patients.

Study goals

The primary goal of the study was to evaluate the influence of the basic RA therapy, the adjuvant and supplemental therapy, the demographic and socioeconomic characteristics, the RA complications and comorbidities to the anxiety, depression and fatigue in RA patients. The secondary objective was to evaluate the relationship between the depression and the fatigue and anxiety of RA patients.

Methodology

Study location and time period

The study was conducted during the time period from April–August 2014 and included the RA patients from 20 Serbian primary healthcare institutions, one tertiary healthcare institution – Institute of Rheumatology, Clinical Centre of Serbia, Belgrade, Serbia, and also two specialized health spa institutions – Niška Banja, Niš, Serbia and Jodna Banja, Novi Sad, Serbia.

Study design

A multicenter epidemiologic cross-sectional study in the population of older RA patients was conducted. The cross section was made according to the obtained self-reported outcome categories of high fatigue absence/presence, high depression absence/presence and high anxiety absence/presence.

Patients and procedures

The patients of both genders suffering from RA older than 18 years were included. The criterion for excluding patients from the study was at least one missing answer in the fatigue, depression or anxiety questionnaires.

During one visit to the doctor the patients filled in the survey that contained questions grouped into three sections. First section contained questions related to demographic and socioeconomic characteristics of the patients. The second one referred to the duration of the disease, type and duration of the current RA therapy, as well as the RA treatment complications. In the third section there were three measuring instruments of self-reported health condition of the patient: "Fatigue Assessment Scale" (FAS) with 10 items; "Patient Health Questionnaire" (PHQ-9) with 9 items, and "Generalized Anxiety Disorder" (GAD-7) with 7 items. Patients needed approximately 30 min to fill out all the questionnaires.

Variables in the study

The resulting variables in the study were PHQ-9 score, FAS score and GAD-7 score. The values of FAS score ≥22 were considered as a high fatigue.[16] High anxiety was defined as GAD-7 score ≥10,[17,18] while the high depression was defined by the values of PHQ-9 score ≥10.[19] The GAD-7 and PHQ-9 surveys contain the questions with provided answers about the presence of the problem that caused dificulties to the patients during the previous two weeks, and which were numbered by ascending Likert ordinal scale from 0 to 3 (0 – not at all; 1 – few days; 2 – more than a half of the time and 3 – almost every day). The PHQ-9 survey is used to evaluate the level of depression,[20,21] while the GAD-7 was primarly developed to evaluate the generalized anxiety disorder.[17] The FAS contains ten questions that describe the presence of possible conditions with five provided ordinal answer modalities from 1 to 5 (1 – never; 2 – sometimes; 3 – ordinarily; 4 – often; 5 – always). The resulting FAS score ranges from 10 to 50. The FAS survey was primarly designed as an instrument to evaluate and monitor the fatigue in the general patient population,[22] and it has also been validated as a reliable masuring fatigue instrument in the sarcoidosis patients.[23]

The examined demographic and socioeconomic variables were: age, gender, marriage status, professional qualifications, employment status, occupation, the need for another person's assistance, the need for frequent taxi use, physioterapist payment, assisitance device use due to RA, the presence of other diseases, osteoporosis presence, orthopedic surgical intervention and fractured limbs caused by the RA. The included treatment predictors were: current RA therapy status, current RA therapy duration (months), period from the beginning of the first RA symptoms until the start of the current therapy (months), proton-pump inhibitor and H_2 receptor antagonist use in order to protect the stomach, the use of supplements that contain glucosamine sulfat, chondroitin sulfat, hyaluronic acid, antirheumatic cream use, vitamin D_3 and calcium consummation, self-initiative therapy cessation, stomach or duodenum bleeding during RA therapy, surgery performed because of the stomach or duodenum bleeding, as well as the use of alternative ways of treatments. The current RA therapy is defined by three modalities such as: (1) NSAIDs and/or analgesics and/or corticosteroids; (2) synthetic DMARDs alone or combined with corticosteroids and/or NSAID and (3) any RA treatment which includes biologic DMARDs. There were also data recorded about the duration of the RA (months) as well as disease symptoms duration (months).

Statistical data processing

Before the data description, for each continous numerical variable the Kolmogorov–Smirnov's approval test of data set with

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normal distribution was performed. In the data with a normal distribution, the continous variables are described by a mean and a standard deviation, while the data that deviate from normal distribiution are described by a median and an interquartile range. The nominal variables are descibed by frequency and percentage according to the appropriate categories. In the methods of inferential statistics, the correlation of individual category predictors with each of the monitored self-reported outcomes (absence/presence of the high fatigue, anxiety or depression level) was evaluated by Phi or Carmer's V correlation coefficient. Difference evaluation in the continous numerical variables between the group with the presence and the group with the absence of the tested self-reported outcomes, was done by Mann–Whitney method. The risk factor analysis for each of the self-reported outcomes was done by the binary logistic regression method. The assessment of the relationship between the level of depression with the fatigue and anxiety levels was performed by the multiple linear regression (stepwise method). The diagnosis of collinearity between the predictors in the linear regression model was done by the arbitrary assesment of the conditional index and the variance inflation factor (VIF).[24,25] The absence of a doubt in the existance of the collinearity was defined by a conditional index less than 15 and VIF value less than 3. The accepted level of significance was 0.05. The statistical analysis was conducted using IBM SPSS Statistics 20. This study was approved by the institution's institutional review board and obtained patients' consent.

Results

Out of 494 patients, 409 of them have fulfilled the inclusion study criteria. The mean age of the patients was 58.03 ± 12.16 years. The RA duration median was 144 months with the interquartile range from 84 to 288 months, while the symptoms duration median (pain, limited mobility) caused by the RA was 159.5 months with the interquartile range from 107 to 240 months. Duration median of the current RA therapy was 60 months with the interquartile range from 24 to 108 months. The median of the time passed from the beginning of the symptoms caused by the RA until all current RA therapies start was 68.5 months with the interquartile range from 24 to 164 months, namely: (1) until the therapy with NSAIDs and/or analgesics and/or corticosteroids (median = 48 months; interquartile range from 13 to 201 months); (2) until the therapy with synthetic DMARDs alone or in combination with corticosteroids and/or NSAIDs (median = 49 months; interquartile range from 12 to 151 months); (3) any RA treatment which includes biologic DMARDs (median = 99 months; interquartile range from 46 to 166 months). The average value of the FAS score was 27.31 ± 8.81. The mean value of the PHQ-9 score was 10.13 ± 7.00 and of the GAD-7 score was 8.21 ± 6.11.

Description of demographic and socioeconomic variables is presented in Table 1. In Table 2 the categories of the therapy variables were described.

One hundred and ninety seven (48.14%) patients had the PHQ-9 score ≥10. The same number also had the FAS score ≥22, while 148 (36.19%) patients had the GAD-7 score ≥10. The descriptive statistics for the duration of the disease, difficulties duration, current therapy and the period from the beginning of the symptoms until the current RA therapy start with the level of difference significance between the groups of patients with the absence and the group of patients with the presence of high depression, anxiety and the high fatigue are presented in Table 3.

Table 1 – Description of demographic and socioeconomic variables in study population of patients with rheumatoid arthritis (*n* = 409).

Variables	*f* (%)
Gender	
Female	356 (87.0)
Male	53 (13.0)
Occupation	
Worker	46 (11.3)
Farmer	5 (1.2)
Housewife	53 (13.0)
Official	41 (11.7)
Pensioner	227 (53.7)
Unemployed	37 (9.0)
Formal education level	
Without school	7 (1.6)
Elementary school	89 (21.9)
Secondary school	146 (35.8)
College	98 (23.9)
Faculty	69 (16.8)
Maritial status	
Married	274 (67.0)
Unmarried	32 (7.9)
Divorced	28 (6.9)
Widow/widower	67 (16.4)
Extramarital communities	8 (1.8)
Employment status	
Employed – able to work	82 (20.1)
Employed – disable due to RA	13 (3.2)
Unemployed – working capable	61 (15.0)
Unemployed – disable due to RA	26 (6.3)
Retired	227 (55.4)
Need of another person's assistance	
Yes	178 (43.5)
No	231 (56.5)
Frequent taxi use	
Yes	182 (44.6)
No	227 (55.4)
Self-payment of physiotherapist	
Yes	106 (25.9)
No	303 (74.1)
The use of assistive devices	
Yes	96 (23.5)
No	313 (76.5)
Other diseases	
Without other diseases	174 (42.5)
With other rheumatic disease	22 (5.5)
With other non-rheumatic disease	213 (52.0)
Osteoporosis	
Yes	139 (34.0)
No	270 (66.0)
Orthopedic surgery for RA	
Yes	105 (25.7)
No	304 (74.3)
Fractures due to RA	
Yes	65 (15.8)
No	344 (84.2)

RA, rheumatoid arthritis; *f*, frequency.

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Table 2 – Therapy variables description in study population of patients with rheumatoid arthritis ($n = 409$).

Variables	*f* (%)
The current RA therapy	
NSAIDs and/or analgesics and/or corticosteroids	51 (12.5)
Synthetic DMARDs alone or in combination with corticosteroids and/or NSAIDs	198 (48.4)
Any RA treatment which includes biologic DMARDs	160 (39.1)
Proton-pump inhibitors	
Yes	273 (66.8)
No	136 (33.2)
Histamine H_2 receptor antagonist	
Yes	117 (28.5)
No	292 (71.5)
Supplement of glucosamine sulphate, chondroitin sulphate, hyaluronic acid	
Yes	56 (13.6)
No	353 (86.4)
Antirheumatic creams	
Yes	239 (58.5)
No	170 (41.5)
Vitamin D_3	
Yes	279 (68.2)
No	130 (31.8)
Calcium supplements	
Yes	175 (42.9)
No	234 (57.1)
Patients discontinuation of RA therapy	
Yes	75 (18.4)
No	334 (81.6)
Bleeding from the stomach or duodenum or the appearance of "black stool" during RA therapy	
Yes	45 (10.9)
No	364 (89.1)
Operations due to bleeding from the stomach or duodenum or the appearance of "black stools"	
Yes	18 (4.4)
No	391 (95.6)
Use of alternative methods of RA treatment	
Yes	52 (12.7)
No	357 (87.3)

RA, rheumatoid arthritis; NSAIDs, non-steroidal anti-inflammatory drugs; DMARDs, disease-modifying antirheumatic drugs; *f*, frequency.

It was estimated that the PHQ-9 score, the FAS score and the GAD-7 score category variables statistically significantly correlate with the majority of socioeconomic variables and comorbidity, except for gender, marital status and orthopedic intervention (Table 4). In addition, the GAD-7 score category variable has not shown a correlation with bone fracture. Also, it was noticed that the PHQ-9 score, the FAS score and the GAD score statistically significantly correlate with most of the therapy variables, except for the self-initiative discontinuation of the RA therapy and the alternative therapy use (Table 5). Aditionally, the PHQ-9 score and the FAS score have not shown a significant correlation with the vitamine D_3 therapy, while the FAS score has not correlated with the antirheumatic cream use and with the operation in gastrointestinal tract caused by bleeding. The GAD-7 score category variable also has not shown a significant correlation with the antirheumatic cream use, as well as the calcium therapy.

By the logistic regression model it was demonstrated that the high depression was related to five independent predictors (Table 6). The significant predictor of the high depression was the synthetic DMARDs therapy alone or combined with the corticosteroids and/or NSAIDs. The sociodemographic predictors of the PHQ-9 score $\geq$10 were physiotherapist self-payment, frequent taxi use, alternative treatment and employment status. Two categories of the employment status have shown to be significant predictors of the PHQ-9 score $\geq$10. Those are the category of unemployed but capable to work, and the category of unemployed as a disabled person due to the RA. Thanks to the mentioned predictors the 70.2% of the total variability of the dependent variable was explained, so the variability of the presence of the high depression is explained by 75.5%, while the variability of the absence of the high depression is explained by 65.3%.

The logistic regression model has shown that the high fatigue was related to five independent predictors (Table 6). The significant predictors of the high fatigue were the need for another person's assistance and the calcium use as a suplemental therapy as well as the professional qualifications. The age above 65 years had a protective result on the appearance od the high fatigue. The GAD-7 score as a covariate was independent predictor of the high fatigue. This logistic model explained the 84.4% of total variability of the dependent variable. The high fatigue presence variability is explained by 90.2%, while the absence of the high fatigue variability is explained with 68.2%.

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Table 3 – Descriptive statistics for the duration of the disease and symptoms and current therapy duration from the appearance of symptoms to the start of current therapy of rheumatoid arthritis according to the absence/presence of high depression, high fatigue and high anxiety in study population of patients with rheumatoid arthritis.

Variables	Outcome	Percentiles			p
		25	50	75	
The duration of the current RA therapy (months)	PHQ ≥ 10 absence	18.00	53.00	84.00	0.001
	PHQ ≥ 10 presence	36.00	72.00	120.00	
RA duration (months)	PHQ ≥ 10 absence	84.00	120.00	204.00	0.008
	PHQ ≥ 10 presence	96.00	168.00	240.00	
The period from the first appearance of RA symptoms to the start of the current RA therapy (months)	PHQ ≥ 10 absence	25.50	66.00	151.50	0.645
	PHQ ≥ 10 presence	24.00	73.00	183.50	
Duration of symptoms due to RA (months)	PHQ ≥ 10 absence	90.00	145.00	221.00	0.006
	PHQ ≥ 10 presence	112.50	180.00	263.50	
The duration of the current RA therapy (months)	FAS ≥ 22 absence	18.00	48.00	77.00	0.000
	FAS ≥ 22 presence	24.50	61.50	120.00	
RA duration (months)	FAS ≥ 22 absence	84.00	120.00	186.00	0.012
	FAS ≥ 22 presence	96.00	156.00	240.00	
The period from the first appearance of RA symptoms to the start of the current RA therapy (months)	FAS ≥ 22 absence	27.00	60.00	144.00	0.749
	FAS ≥ 22 presence	24.00	73.00	181.00	
Duration of symptoms due to RA (months)	FAS ≥ 22 absence	88.00	144.00	210.00	0.013
	FAS ≥ 22 presence	108.00	177.00	263.50	
The duration of the current RA therapy (months)	GAD ≥ 10 absence	20.00	60.00	84.00	0.002
	GAD ≥ 10 presence	36.00	72.00	120.00	
RA duration (months)	GAD ≥ 10 absence	84.00	144.00	204.00	0.015
	GAD ≥ 10 presence	96.00	168.00	240.00	
The period from the first appearance of RA symptoms to the start of the current RA therapy (months)	GAD ≥ 10 absence	25.00	72.00	161.00	0.018
	GAD ≥ 10 presence	24.00	66.00	189.00	
Duration of symptoms due to RA (months)	GAD ≥ 10 absence	93.00	152.00	228.00	0.790
	GAD ≥ 10 presence	122.00	180.00	274.50	

PHQ-9, Patient Health Questionnaire; FAS, Fatigue Assessment Scale; GAD-7, Generalized Anxiety Disorder; RA, rheumatoid arhtritis.

The significant predictor of the high anxiety in the logistic regression model were proton pump inhibitor gastroprotection and two occupation categories – housewife and pensioner (Table 6) and these predictors explained 64.8% of total pensioner of the dependent variable. The variability of the presence of the high anxiety was explained with 13.5%, while the explained pensioner of absence of the severe anxiety was 93.9%.

The linear regression model resulted in the statistically significant correlation of the PHQ-9 score with the GAD-7 and the FAS scores. That was presented by the equation: PHQ-9 score = −3.47 + 0.634 × GAD-7 score + 0.323 × FAS score. The multiple linear regression model statistics for the predictors were: (1) for the constant ($t = -0.784$; $p = 0.000$); (2) for the GAD-7 score ($t = 0.548$; $p = 0.000$) and (3) for the FAS score ($t = 0.402$; $p = 0.000$). The determination coefficient (R^2) for the mentioned linear model was 0.788. There was a statistically significant change of the R^2 for the mentioned linear regression model with the FAS score and GAD-7 score predictors for PHQ-9 score in comparisson with model that contains only the GAD-7 score (F changes = 124.979; df1 = 1; df2 = 408; $p = 0.000$). The R^2 of the model that contained the GAD-7 score, as the only predictor of the PHQ-9 was 0.716. The biggest conditional index in the linear regression model with two predictors was 10.021. The VIF values in both predictors were identical and were 2.221.

Discussion

According to the social signal transduction theory of depression, the low socioeconomic status implies the high risk of social conflicts, social isolation, excluding or rejecting a person, and also represents one of the most important provoking factors or big stressful life events that cause the major depression and stimulation of inflammation.[26] In RA patients the interpersonal loss and the social isolation are the key factors that can lead to the disease exacerbation caused by the inflammation or to the additional depression symptoms exacerbation and the appearance of the major depression.[27] Our results have shown that the experience of the unemployement due to a disability in RA patients, among all other resulting significant predictors, represents the strongest provoking factor of the high depression that includes the major depression too (Table 6). This RA patient's experience, besides that it clearly defines a bad socioeconomic status of the patient (unemployment), also has a strong component of the experience of the

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Table 4 – Correlations between categories of demographic and socioeconomic variables and variables of comorbidity with absence/presence of high depression, fatigue and anxiety in patients with rheumatoid arthritis.

Variables	PHQ-9 score ≥10 Correlation (*p*)		FAS score ≥22 Correlation (*p*)		GAD-7 score ≥10 Correlation (*p*)	
	Absence *n*1 = 212	Presence *n*2 = 197	Absence *n*1 = 212	Presence *n*2 = 197	Absence *n*1 = 212	Presence *n*2 = 197
Gender						
Female	−0.082 (0.101)		−0.072 (0.136)		−0.067 (0.165)	
Male						
Occupation						
Worker						
Farmer						
Housewife						
Official	0.341[a] (0.000)		0.273[a] (0.000)		0.229[a] (0.000)	
Pensioner						
Unemployed						
Formal education level						
Without school						
Elementary school						
Secondary school	0.329[a] (0.000)		0.323[a] (0.000)		0.259[a] (0.000)	
College						
Faculty						
Maritial status						
Married						
Unmarried						
Divorced	0.130 (0.148)		0.138 (0.083)		0.141 (0.077)	
Widow/widower						
Extramarital communities						
Employment status						
Employed – able to work						
Employed – disable due to RA						
Unemployed – working capable	0.302[a] (0.000)		0.267[a] (0.000)		0.209[a] (0.003)	
Unemployed – disable due to RA						
Retired						
Need of another person's assistance						
Yes	−0.368[a] (0.000)		−0.369[a] (0.000)		−0.271[a] (0.000)	
No						
Frequent taxi use						
Yes	−0.346[a] (0.000)		−0.282[a] (0.000)		−0.246[a] (0.000)	
No						
Self-payment of physiotherapist						
Yes	−0.312[a] (0.000)		−0.224[a] (0.000)		−0.229[a] (0.000)	
No						
The use of assistive devices						
Yes	−0.290[a] (0.000)		−0.199[a] (0.000)		−0.186[a] (0.000)	
No						
Other diseases						
Without other diseases						
With other rheumatic disease	0.190[a] (0.001)		0.214[a] (0.000)		0.152[a] (0.007)	
With other non-rheumatic disease						
Osteoporosis						
Yes	−.173[a] (0.001)		−0.156[a] (0.002)		−0.182[a] (0.000)	
No						
Orthopedic surgery for RA						
Yes	0.117 (0.083)		0.049 (0.632)		0.113 (0.088)	
No						
Fractures due to RA						
Yes	−0.110[b] (0.031)		−0.134[a] (0.007)		−0.078 (0.116)	
No						

PHQ-9, Patient Health Questionnaire; FAS, Fatigue Assessment Scale; GAD-7, Generalized Anxiety Disorder; RA, rheumatoid arthritis.

[a] Level of statistical significance for $p \leq 0.01$.

[b] Level of statistical significance for $p \leq 0.05$.

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Table 5 – Correlations between categories of therapy with absence/presence of high depression, fatigue and anxiety in patients with rheumatoid arthritis.

Variable	PHQ-9 score ≥10 Correlation (*p*)		FAS score ≥22 Correlation (*p*)		GAD-7 score ≥10 Correlation (*p*)	
	Absent *n*1 = 212	Present *n*2 = 197	Absent *n*1 = 254	Present *n*2 = 155	Absent *n*1 = 212	Present *n*2 = 197
The current RA therapy						
NSAIDs and/or analgesics and/or corticosteroids						
Synthetic DMARDs alone or in combination with corticosteroids and/or NSAIDs	0.228[a] (0.000)		0.223[a] (0.000)		0.193[a] (0.000)	
Any RA treatment which includes biologic DMARDs						
Proton-pump inhibitors						
Yes	−0.137[a] (0.007)		−0.145[a] (0.003)		−0.116[b] (0.019)	
No						
Histamine H_2 receptor antagonist						
Yes	−0.157[b] (0.011)		−0.131[b] (0.037)		−0.165[a] (0.005)	
No						
Supplement of glucosamine sulphate, chondroitin sulphate, hyaluronic acid						
Yes	0.161[a] (0.008)		0.111 (0.090)		0.122 (0.055)	
No						
Antirheumatic creams						
Yes	−0.191[a] (0.000)		0.131[b] (0.027)		0.137[b] (0.021)	
No						
Vitamin D_3						
Yes	0.023 (0.644)		0.031 (0.523)		−0.104[b] (0.039)	
No						
Calcium supplements						
Yes	−0.140[a] (0.004)		−0.110[b] (0.025)		−0.065 (0.230)	
No						
Patients discontinuation of RA therapy						
Yes	−0.065 (0.230)		−0.045 (0.395)		−0.082 (0.116)	
No						
Bleeding from the stomach or duodenum or the appearance of "black stool" during RA therapy						
Yes	−0.243[a] (0.000)		0.120[b] (0.014)		0.139[a] (0.005)	
No						
Operations due to bleeding from the stomach or duodenum or the appearance of "black stools"						
Yes	−0.154[a] (0.003)		−0.057 (0.246)		−0.113[b] (0.024)	
No						
Use of alternative methods of RA treatment						
Yes	0.079 (0.122)		−0.055 (0.271)		0.043 (0.385)	
No						

PHQ-9, Patient Health Questionnaire; FAS, Fatigue Assessment Scale; GAD-7, Generalized Anxiety Disorder; RA, rheumatoid arthritis; NSAIDs, non-steroidal anti-inflammatory drugs; DMARDs, disease-modifying antirheumatic drugs.

[a] Level of statistical significance for $p \leq 0.01$.

[b] Level of statistical significance for $p \leq 0.05$.

social rejection, isolation and interpersonal loss due to the disability. Other authors also found that the bad socioeconomic status increases the depression symptoms measured by PHQ-9 survey in RA patients.[28] Löwe et al. demonstrated that the depression is a significant predictor of the working incapability of the RA patients.[29] In our study, other significant socioeconomic predictors of the high depression were: pensioner status, unemployment of the working capable patients, frequent taxi use, self-payment of physiotherapist and self-payment of alternative treatment. The last mentioned factors also imply a bad socioeconomic RA patients' status due to the lack of the income or insufficient personal income, as well as their additional financial exhaustion by the expenses they have on their own during the daily activities, implementation of physiotherapy measurements or the alternative treatment or some other activities required at the rehabilitaion, pain relief and the improvement of the social functioning in general.

We also showed that, in general, the RA therapy has no influence on the appearance of the high depression in RA patients, but there is a significant influence of the synthetic DMARD therapy category alone or combined with corticosteroids or/and NSAID. In our study population patients with the aforementioned treatment modality were 80% more likely to have a high depression, which potentially indicates a higher RA activity in these patients. It was demonstrated in some longitudinal studies that persistent depression/anxiety symptoms predict poor treatment response which corresponds with increased RA activity over time.[30] In a univariate analysis of socioeconomic and clinical characteristics of the RA patients baseline, Margaretten et al. demonstrated that synthetic and/or biologic DMARDs therapy increases major depression

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Table 6 – Logistic regression models parameters according to sociodemographic, socioeconomic and therapeutic predictors of high depression, fatigue and anxiety in patients with rheumatoid arthritis.

Predictors	B	SE	Wald	df	p	Odds ratio	95.0% Confidence interval	
							Lower	Upper
Examined outcome – PHQ-9 score ≥ 10								
The current RA therapy			4.982	2	0.083			
NSAIDs and/or analgesics and/or corticosteroids	0.324	0.447	0.525	1	0.469	1.383	0.575	3.323
Synthetic DMARDs alone or in combination with corticosteroids and/or NSAIDs	0.630	0.283	4.972	1	0.026	1.878	1.079	3.269
Self-payment of physiotherapist	1.250	0.349	12.841	1	0.000	3.490	1.762	6.914
Employment status			18.117	4	0.001			
Employed – disable due to RA	0.404	0.864	.218	1	0.640	1.498	0.275	8.151
Unemployed – working capable	1.357	0.435	9.731	1	0.002	3.884	1.656	9.111
Unemployed – disable due to RA	1.900	0.697	7.423	1	0.006	6.687	1.704	26.238
Retired	1.384	0.354	15.252	1	0.000	3.989	1.992	7.989
Frequent taxi use	0.785	0.275	8.179	1	0.004	2.193	1.280	3.755
Use of alternative methods of RA treatment	0.772	0.385	4.024	1	0.045	2.164	1.018	4.600
Constant	−2.756	0.493	31.274	1	0.000	0.064		
Examined outcome – FAS score ≥ 22								
Need of another person's assistance	1.102	0.384	8.220	1	0.004	3.009	1.417	6.389
GAD-7 score	0.320	0.048	43.986	1	0.000	1.377	1.253	1.514
Calcium supplements	0.855	0.357	5.738	1	0.017	2.352	1.168	4.736
Age > 65 godina	−1.031	0.478	4.653	1	0.031	0.357	0.140	0.910
Formal education level			13.994	4	0.007			
Without school	17.112	18,629.741	0.000	1	0.999	27,004.818	0.000	
Elementary school	0.270	0.530	0.259	1	0.611	1.310	0.463	3.702
Secondary school	1.589	0.452	12.389	1	0.000	4.901	2.023	11.876
College	0.693	0.474	2.142	1	0.143	2.000	0.790	5.062
Constant	−1.532	0.586	6.837	1	0.009	0.216		
Examined outcome – GAD score ≥ 10								
Occupation			17.908	5	0.003			
Farmer	−0.024	1.207	0.000	1	0.984	0.976	0.092	10.400
Housewife	1.245	0.448	7.717	1	0.005	3.474	1.443	8.366
Official	−0.719	0.590	1.486	1	0.223	0.487	0.153	1.548
Pensioner	0.837	0.370	5.121	1	0.024	2.309	1.119	4.766
Unemployed	0.675	0.489	1.901	1	0.168	1.963	0.752	5.123
Proton-pump inhibitors	0.491	0.238	4.248	1	0.039	1.634	1.024	2.608
Constant	−1.566	0.382	16.822	1	0.000	0.209		

PHQ-9, Patient Health Questionnaire; FAS, Fatigue Assessment Scale; GAD-7, Generalized Anxiety Disorder; RA, rheumatoid arthritis; NSAIDs, non-steroidal anti-inflammatory drugs; DMARDs, disease-modifying antirheumatic drugs.

frequency.[31] However, in other reports there was no RA therapy influence on the self-reported high depression frequency in the RA patients.[32] Both before and during the study period the current biologic drugs provided by the health insurance of Republic of Serbia, that were available to the RA patients are human protein drugs that neutralize pro-inflammatory effects of tumor necrosis factor and interleukin-6. The above mentioned biologic drug combined with methotrexate is prescribed to the RA patients whose disease is still clinically active (i.e. whose Disease Activity Score is above 5.1) despite the implementation of methotrexate (at least 15 mg once a week) or despite the implementation of the combined two synthetic DMARDs during at least three months. Also, our results showed that median of RA patients time of "expectation" of biologic DMARDs therapy was almost twice longer compared to the other modalities of therapy. So, the RA patient that uses one or two synthetic DMARDs can have an experience that can be interpreted as: "my health condition caused by RA is a long time serious... I know that one of the drugs that I use can treat a cancer too... I can't understand that, even so, there is no hope for me... I am not worth to be given such an expensive biologic drug." Such an individual, longstanding patient experience of disforia, hopelessness and uselessness, can also be one of the contextual, psychosocial triggers for the appearence of major depression and poor RA treatment response.

We also found that the RA therapy (Table 6) does not increase the risk of the high fatigue or depression, as well as that the high fatigue and anxiety, completely independent one from another, lead to the high level of the self-reported depression symptoms. On the other hand, the results imply that the increase of the anxiety level also increases the risk of the high fatigue appearance. These are important facts since there is no specific pharmacotherapy of the high fatigue. With all the above mentioned, we highlight that the specific medicamentous therapy should be implemented with antidepressants that have a strong anxiolytic effect (for

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example with selective serotonin reuptake inhibitors), both in order to reduce the depression symptoms and to potentially decrease the high fatigue of the RA patients.

In our study the age above 65 years had a protective effect on the appearance of the high fatigue in RA patients. This kind of finding coexists with the findings of Watt et al., who showed that, depending on the age, fatigue in the general population has a non-linear trend.[33] In the general population a global fatigue evaluation after the age of 65 was decreasing because of the mental and cognitive fatigue component decrease. However, the studies in the RA patients populations did not show any changes in the fatigue level with the change of age.[34]

We also demonstrated that calcium suplementation therapy for prophylaxis or therapy of osteoporosis in the RA patients can significantly increase the risk of the high fatigue appearance. This potentially suggests that calcium supplements therapy in our patients was administered without adequate monitoring of serum ionized calcium. Fatigue is very common symptom of hypercalcemia.[35] Oelzner et al. reported that about 30% of the RA patients have hypercalcemia (high levels of serum ionized calcium) that occurs in association with the high disease activity, suppressed parathyroid hormone secretion, suppressed vitamin D hormone synthesis and bone mineral density reduction.[36]

From socioeconomic factors the important predictors of the high fatigue in the RA patients were the need for other people's help and care, as well as the level of the formal education that is defined as finished college education. In Serbia formal education to obtain a college degree lasts for 12 years. Castrejon et al. found that the RA patients with a formal education lasting less than or exactly 12 years had the bigger fatigue compared to the patients with formal education that lasted more than 12 years.[37] The need for other people's help and care implies some severe setback and these RA patients' problem in performing daily activities. In other studies it was shown that the restriction of daily activities correlates positively with the fatigue, and that the increase of the daily activities correlates negatively with the fatigue.[38,39]

When it comes to the socioeconomic predictors of the high anxiety in our study population, the significant risk factors were two categories of occupation – pensioner and housewife (Table 6). It is described in the literature that the housewives with the milder RA were more anxious even though they had their spouse's understanding for their disease.[40] Patients with the specific occupation categories whose social life is mostly spent in the house or mostly related to the house and family surroundings can possibly experience more anxiety that is inversely related to the RA severity and the experienced understanding by the persons with whom they live.

Additionally, the risk factor of the high anxiety appearance was also a stomach bleeding prevention by the PPI. In Serbia, unlike the drugs from the H_2 antagonist group which are cheap, the RA patients have to pay for the PPI gastroprotecive therapy by themselvess which is very expensive for them. The fear whether and how long they will be able to pay for the PPI, for the gastroprotection can also be a risk factor of the high RA patients' anxiety. The rest of the socioeconomic and therapy predictors in this study (Tables 4 and 5) have shown, in spite of the achieved statistical significance, a weak correlation with the self-reported outcomes of the patients. These predictors share a small mutual variance of all three outcomes (depression, fatigue and anxiety), which implies that they are not specific for any of them.

The limitations of our study primarily originate from its design. A cross sectional study design does not evaluate the specifics of the questioned predictors' influences on the appearance of the fatigue, depression and anxety in RA patients, compared to the patient population with another inflammatory or non-inflammatory disease. In our study, the RA activity was not monitored and therefore we cannot exclude certain bias in our explanations of the relationship between the appearance of the high depression and treatment responses. Since we have not monitored the status of calcemia and/or RA activity, there also may be some bias in our explanation of the link between the high fatigue and calcium therapy. Even though we had a large patients population in the study, the male population response number was unusually small. Consequently, compared to the female population, observed risk factors of the appearance of the questioned self-reported outcomes that come from the male population are potentially less analyzed. Also, in our RA patient population we haven't recorded any data about the use of antidepressant, sedative and/or anxiolytic drugs.

Conclusion

Demographic, socioeconomic and psychosocial factors, along with contextual and treatment factors, can largely explain the appearance of the high level of depression and fatigue and high anxiety in rheumatoid arthritis patients. The evaluation of the psychosocial, socioeconomic and therapy impacts, along with the rheumatoid arthritis activity and inflammation on the appearance of the high depression, high fatigue and high anxiety can be of great importance in future studies in rheumatoid arthritis patients.

Conflicts of interest

Author Mirjana Lapčević declares that she has no conflict of interest. Author Mira Vuković declares that she has no conflict of interest. Author Branislav S. Gvozdenović declares that he has no conflict of interest. Author Vesna Mioljević declares that she has no conflict of interest. Author Snežana Marjanović declares that she has no conflict of interest.

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