Factors associated with anxiety and depression in rheumatoid arthritis patients: a cross-sectional study

Miyabi Uda

Kyoto Daigaku Daigakuin

Motomu Hashimoto

Kyoto Daigaku Daigakuin

Ryuji Uozumi

Kyoto Daigaku Daigakuin

Mie Torii

Kyoto Daigaku Daigakuin

Takao Fujii

Wakayama Kenritsu Ika Daigaku

Masao Tanaka

Kyoto Daigaku Daigakuin

Moritoshi Furu

Kyoto Daigaku Daigakuin

Hiromu Ito

Kyoto Daigaku Daigakuin

Chikashi Terao

Kyoto Daigaku Daigakuin

Wataru Yamamoto

Okayama Sweet Hospital

Genichi Sugihara

Kyoto Daigaku Daigakuin

Yukako Nakagami

Kyoto Daigaku Daigakuin

Tsuneyo Mimori

Kyoto Daigaku Daigakuin

Kazuko Nin (✉ nin@kuhp.kyoto-u.ac.jp)

Kyoto University <https://orcid.org/0000-0003-4720-6420>

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Abstract

Introduction / objectives Management of anxiety and depression in rheumatoid arthritis (RA) patients is vital. Previous studies investigating this topic are conflicting, and this topic still has not been thoroughly investigated. This study aimed to clarify the association of disease activity with anxiety and depression after controlling for physical disability, pain, and treatment.

Method We conducted a cross-sectional study of RA patients from the Kyoto University Rheumatoid Arthritis Management Alliance cohort. For assessments, we used the Disease Activity Score (DAS28), Health Assessment Questionnaire Disability Index (HAQ-DI), and Hospital Anxiety Depression Scale. Depression and anxiety were defined by a Hospital Anxiety Depression Scale score ≥ 8 . We then performed multivariable logistic regression analyses.

Results Of 517 participants, 17.9% had anxiety, and 28.2% had depression. The multivariable logistic regression analyses showed patients with DAS28-based non-remission had low association with anxiety (odds ratio [OR] [95% confidence interval {CI}], 0.93 [0.48–1.78]; $p = 0.82$) but slight association with depression (OR [95% CI], 1.45 [0.81–2.61]; $p = 0.22$). However, severity of the patient's global assessment (PtGA) on DAS28 was associated with anxiety (OR [95% CI], 1.15 [1.02–1.29]; $p = 0.03$) and depression (OR [95% CI], 1.21 [1.09–1.35]; $p < 0.01$). Additionally, HAQ-DI-based non-remission was associated with anxiety (OR [95% CI], 3.51 [1.85–6.64]; $p < 0.01$) and depression (OR [95% CI], 2.65 [1.56–4.50]; $p < 0.01$). Younger patients (OR [95% CI], 0.83 [0.68–1.01]; $p = 0.07$) and patients not treated with methotrexate (OR [95% CI], 0.67 [0.40–1.13]; $p = 0.13$) tended to suffer from anxiety. Patients using steroids had a closer association with depression than those not using them (OR [95% CI], 1.66 [1.03–2.67]; $p = 0.04$).

Conclusions Assessment of disease activity, PtGA, and HAQ-DI are important for assessing anxiety and depression in RA patients. Attention should be paid to improving PtGA and physical function.

Background

Anxiety and depression have higher prevalence in rheumatoid arthritis (RA) patients than in the general population [1–2]. Studies have found 26–46% of RA patients have anxiety, and 14.8–34.2% have depression [1]. RA patients with these conditions have worse outcomes, including poor medication adherence [3], worse therapeutic effects [3], increased medical costs [4–6], high mortality [7–8], and decreased quality of life [6, 9–10]. It is therefore important to examine risk factors for anxiety and depression in RA patients and enhance their treatment to include management of psychological factors.

Research has been conducted in this area to advance prevention and relief.

RA is an autoimmune inflammatory disease that causes joint deformation and physical dysfunction [11]; physical disability [12–14] and pain [15, 16–17] are known risk factors for anxiety and depression in RA patients. Recent studies have shown these conditions are associated with systemic inflammation caused by pro-inflammatory cytokines such as tumor necrosis factor (TNF) α , interleukin (IL) -1β , and IL-6 [18–19]. Cytokines are also suggested to cause depression by hyperactivation of the HPA axis [24]. Other studies have reported that C-reactive protein (CRP) levels are associated with anxiety and depression in RA patients [21].

Disease activity reflecting the above factors may be associated with anxiety and depression in RA patients; however, the results of studies on the correlation between such disease activity and these conditions remain inconsistent. Some studies have suggested a positive association between RA disease activity and anxiety and depression [22, 23], while others have not found this association [24]. The causal association thus warrants further investigation. A key reason is that physical disability, pain, and medication associated with anxiety and depression have not been adjusted for [22–24] in previous studies. Standard disease activity scores also have not been used [23]. The present study aimed to determine the factors associated with anxiety and depression in RA patients, including disease activity, pain, physical activity, and medications, using a robust cohort study.

Methods

Patients and setting

We performed a cross-sectional analysis of patients who visited the outpatient RA center of Kyoto University Hospital between May 1 and December 31, 2014 and whose data were collected in the 2014 Kyoto University Rheumatoid Arthritis Management Alliance (KURAMA) cohort [25]. All patients fulfilled the 1987 or 2010 American College of Rheumatology and European League Against Rheumatism RA classification criteria [26]. We excluded patients with psychiatric disorders, those receiving psychiatric treatment, and those who did not complete a Hospital Anxiety and Depression Scale (HADS) questionnaire [27]. The study protocol was approved by the Kyoto University Graduate School and Faculty of Medicine, Ethics Committee, and all procedures were performed in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. All patients gave written informed consent prior to participating in any study procedures.

Clinical assessments and outcomes

RA disease activity was assessed using the Disease Activity Score - CRP (DAS28-CRP), which is based on a 28-joint assessment; 28 tender joint count (TJC) and 28 swollen joint count (SJC); CRP; and the patient's global assessment (PtGA) [28–29] to determine each patient's total score. DAS28-CRP-based clinical remission/non-remission and DAS 4 variables (DAS4; comprising TJC, SJC, CRP, and PtGA) were used. Clinical remission of disease activity was defined as a DAS28-CRP score <2.6 [28–29].

The Health Assessment Questionnaire Disability Index (HAQ-DI) [30] was used to assess physical disability. This is an eight-category questionnaire with 20 subscales measuring functional disability. Each item is scored at 0–3 points (0 – without any difficulty, 1 – with some difficulty, 2 – with much difficulty, and 3 – unable to do), and the average value of the eight categories is calculated. Functional remission is defined as HAQ-DI ≤ 0.5 . Pain was evaluated using either the Visual Analogue Scale (VAS), with items scored at 0 (no pain) to 100 (maximum pain) points, or the TJC. Other data, such as age, sex, duration of disease, treatment (biological disease-modifying anti-rheumatic drugs [bDMARDs], methotrexate, and steroids), were collected from the KURAMA cohort [25]. Confounding factors include age, sex, pain, HAQ, and treatment. Age and duration of disease are measured as a total score. Sex and treatment were used for analysis with binary data.

The primary outcomes were anxiety and depression in this study. Outcomes were evaluated using the HADS [27], a 14-item questionnaire with seven subscales for both anxiety and depression. Each item is scored at 0–3 points, with total scores ranging 0–21 points for each condition. Scores of 0–7 are considered normal, 8–10 indicate mild anxiety or depression, and ≥ 11 indicate severe anxiety or depression. This study defines anxiety and depression as a HADS anxiety score ≥ 8 and HADS depression score ≥ 8 [27].

Statistical analysis

Unless otherwise stated, data are presented as mean $\pm$ standard deviation or number (%). First, we examined the associations between the RA patients' characteristics and both anxiety and depression. We did so using univariable logistic regression, and calculated the odds ratio (OR) and 95% confidence interval (CI). We then conducted multivariable logistic regression with clinical remission/non-remission as shown by DAS28-CRP score as an independent variable to investigate associations with both anxiety and depression. Based on clinicians' judgment and the univariable analysis results, explanatory variables were selected and adjusted for age, HAQ-DI, pain, treatment (bDMARDs, methotrexate, and steroids). We also conducted multivariable logistic regression with DAS 4 variables instead of DAS28-CRP-based remission to determine factors that may separately contribute to anxiety and depression in RA patients. All analyses were performed using JMP 14.0 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

We assessed a total of 542 RA patients and excluded 25 because they had received psychiatric treatment. Of the remaining 517, another nine were excluded from the anxiety analyses because of incomplete HADS anxiety questionnaires, for a total of 508 patients, while 10 were excluded from the depression analyses because of incomplete HADS depression questionnaires, for a total of 507 patients (Figure 1). Table 1 shows the patients' characteristics. The mean DAS28-CRP was 1.91 ± 0.82 ; 358 (78.9%) patients achieved DAS28-CRP-based remission. The mean HAQ-DI was 0.74 ± 0.77 ; 252 (51.3%) patients achieved HAQ-DI-based remission. The mean disease duration was 159.7 ± 138.7 months. Among all patients, 91 (17.9%) had anxiety, and 143 (28.2%) had depression, as measured by the HADS (Table 1).

Association between clinical variables and anxiety

First, we performed univariable logistic regression. DAS28-CRP-based non-remission, TJC severity, SJC, CRP, PtGA, HAQ-DI-based non-remission, severity of pain, and use of steroids were selected as candidates for factors associated with anxiety. We then conducted multivariable logistic regression (Table 2). In Model 1, patients with DAS28-CRP-based non-remission tended to suffer from anxiety (OR [95% CI], 0.93 [0.48–1.78]; $p = 0.82$). Patients with HAQ-DI-based non-remission had a closer association with anxiety than those in remission (OR

[95% CI], 3.51 [1.85–6.64]; $p < 0.01$). Additionally, younger patients tended to suffer from anxiety (OR [95% CI], 0.83 [0.68–1.01]; $p = 0.07$). Patients who were not treated with methotrexate tended to suffer from anxiety (OR [95% CI], 0.67 [0.40–1.13]; $p = 0.13$). In Model 2, pain was excluded from the explanatory variables because of collinearity between pain and PtGA (correlation coefficient, $r = 0.78$). As a result, patients with severe PtGA had notably closer association with anxiety (OR [95% CI], 1.15 [1.02–1.29]; $p = 0.03$). Similar to in Model 1, patients with HAQ-DI-based non-remission had closer association with anxiety than those with HAQ-DI-based remission (OR [95% CI], 3.21 [1.69–6.08]; $p < 0.01$).

Association between clinical variables and depression

Similar analyses were conducted for depression. First, we performed univariable logistic regression. DAS28-CRP-based non-remission, severity of PtGA, HAQ-DI-based non-remission, severity of pain, and use of methotrexate and steroids were the candidate factors associated with anxiety. We then conducted multivariable logistic regression (Table 3). In Model 1, patients with DAS28-CRP-based non-remission were slightly associated with depression (OR [95% CI], 1.45 [0.81–2.61]; $p = 0.22$). Patients with HAQ-DI-based non-remission were even more strongly associated with depression than those with HAQ-DI-based remission (OR [95% CI], 2.65 [1.56–4.50]; $p < 0.01$). Additionally, patients taking steroids were more closely associated with depression than patients not taking steroids (OR [95% CI], 1.48 [0.93–2.34]; $p = 0.09$). In Model 2, pain was excluded from the explanatory variables for collinearity. As a result, patients with severe PtGA were more notably associated with depression (OR [95% CI], 1.21 [1.09–1.35]; $p < 0.01$). Similar to in Model 1, patients with HAQ-DI-based non-remission had a closer association with depression than those with HAQ-DI-based remission (OR [95% CI], 1.95 [1.15–3.31]; $p = 0.01$). Patients taking steroids had a higher association with depression than those not taking steroids (OR [95% CI], 1.66 [1.03–2.67]; $p = 0.04$).

Discussion

This was a large cohort study using the KURAMA cohort [25]. We investigated the association of disease activity with anxiety and depression, after adjusting for physical disability, pain, and treatment of RA patients. Patients with DAS28-based non-remission had low association with anxiety but were slightly associated with depression. However, severity of PtGA, a component of the DAS28 composite measure, was strongly associated with anxiety and depression. Additionally, younger patients and patients who were not treated with methotrexate tended to suffer from anxiety. Patients taking steroids had a higher association with depression than those not taking steroids.

Previous studies investigating the association between disease activity and anxiety and depression have not been consistent. Disease activity [22–23], physical disability [12–14], and severity of pain [15–17] are among factors associated with anxiety and depression in RA patients. There are two key issues here: (1) DAS28 and pain were simultaneously introduced, but HAQ-DI and drug use were not included as covariates [22]; and (2) pain, HAQ-DI, and drug use were not included as covariates [23–24]. Therefore, the association between DAS28 and anxiety and depression has mainly been evaluated independently, and the effects of other factors may not have been properly evaluated. In the present study, we found that when disease activity, disability, pain, and

treatment of RA patients were adjusted for, patients with DAS28-based non-remission had low association with anxiety but slight association with depression.

We also found that PtGA—a component of the DAS28-CRP composite measure—was notably associated with anxiety and depression. Factors suggesting inflammation—e.g., CRP, TJC, and SJC—were not associated with anxiety and depression based on the multivariable analysis results. Previous studies have reported systemic inflammation as a potential cause of depression [18–20] and inflammatory markers as correlated with depression [21], suggesting an association between inflammation and depression. PtGA, however, employs the VAS for overall patient self-assessment and is the main tool for patient-reported outcomes [31]. The present results suggest that patients' self-assessment, but not inflammation, is associated with anxiety and depression in RA patients. Physical disability [32–33], pain [17, 32], and catastrophizing pain [34] are among factors that exacerbate PtGA. Therefore, to reduce anxiety and depression in RA patients, it is important to reduce such factors, and to improve patients' self-assessment and well-being. Cognitive behavioral therapy (CBT) and mindfulness [35–37] relieve the tendency to catastrophize and subsequently reduce pain and distress; therefore, these approaches may be effective interventions in this case. Additionally, there is a gap between doctor and patient PtGA assessments [38]. The treat-to-target strategy aims to achieve remission using the composite measure DAS28 [39]; however, in considering patients' anxiety and depression, it is better to focus on PtGA in the composite measure DAS28.

The present study found the HAQ-DI score, which identifies physical disability, was associated with anxiety and depression in multivariable analysis. Previous studies found the HAQ-DI score [12–14] was reported as a factor related to anxiety and depression. Our results suggest physical disability due to bone and joint damage affects anxiety and depression in RA patients. Physical disability also reportedly leads to decreased housework and activities by RA patients [40] and increased loss of work [40]. Impaired ability to perform activities of daily life is thought to affect anxiety and depression [13, 40]. With persistent disability, the possibility of concurrent anxiety and depression increases, irrespective of disease activity remission. To reduce anxiety and depression, it is important to evaluate HAQ-DI scores and increase quality of life by improving patients' abilities to perform daily activities.

Finally, in Model 1, younger RA patients and patients not treated with methotrexate tended to suffer from anxiety. Younger RA patients may be more anxious about the future with regard to factors such as disease-related concerns, treatment, and work. Additionally, because methotrexate is an anchor drug [41], inability to use it in the future may also create concern. In Model 2, patients taking steroids were associated with depression. Side effects of depression may owe to the pharmacological actions of steroids [42]. Appropriate treatment is needed in consideration of this risk of side effects.

A strength of this study is its use of a large cohort study to investigate the association between disease activity and anxiety and depression under adjusted factors affecting the anxiety and depression. Various scales are used to evaluate depression in RA patients. The HADS was used herein because it is unaffected by the physical symptoms associated with development of RA, such as fatigue and insomnia. Furthermore, the HADS can avoid overestimation in the evaluation of depression. Using the HADS allows the prevalence of anxiety and depression to be assessed more accurately than with other scales.

Despite our findings, this study also has some limitations. First, rather than a formal psychiatric diagnosis, we used self-reported symptoms to rate anxiety and depression levels. Additionally, we only considered currently taken medications and were unable to exclude the effects of prior treatment and drug amounts. There may also be selection bias because this study was conducted at a single university hospital and most patients had long disease duration and were in remission or had low disease activity. Considering the above, care must be taken in generalizing our findings.

Conclusions

RA patients with DAS28-based non-remission in this study had low association with anxiety but slight association with depression. Patients with high PtGA or HAQ-DI-based non-remission were associated with anxiety and depression. Assessment of disease activity, PtGA, and HAQ-DI are important for assessing anxiety and depression in RA patients. Additionally, rather than focusing solely on controlling disease activity, attention should be paid to improving or preserving patients' self-assessment, well-being, and physical function. Finally, younger RA patients and patients using methotrexate are more likely to experience anxiety, and patients using steroids should take particular care with regard to depression.

Declarations

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Ethical Standards

The patient protocols were approved by Kyoto University Graduate School and Faculty of Medicine, Ethics Committee. Approved and informed consent was obtained from study participants.

Conflict of Interest

The Department of Advanced Medicine for Rheumatic Diseases is supported by two local governments in Japan (Nagahama City, Shiga and Toyooka City, Hyogo) and five pharmaceutical companies (Mitsubishi Tanabe Pharma Co., Chugai Pharmaceutical Co., Ltd., AYUMI Pharmaceutical Corporation, Asahi Kasei Corporation, and UCB Japan Co., Ltd.).

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Tables

Characteristics of rheumatoid arthritis patients in this study

Characteristic	Overall
	N = 517
Age (years)	429 (83.0)
	62.5 ± 13.1
Disease duration, months	159.7 ± 139.7
	114 (22.1)
	125 (24.3)
	96 (18.6)
	180 (35.0)
Activity	
DAS28-CRP	1.91 ± 0.82
DAS28-CRP remission	358 (78.9)
	0.8 ± 1.5
	0.8 ± 1.5
HAQ-DI	29.1 ± 24.4
	0.4 ± 0.8
	0.74 ± 0.77
Remission	252 (51.3)
	27.6 ± 25.7
Biological DMARDs	187 (36.2)
Methotrexate	345 (66.7)
Corticoid	159 (30.8)
Depression	
Anxiety	91 (17.9)
Depression	143 (28.2)

Presented as mean ± standard deviation or number (%). DAS28-CRP: Disease Activity Score 28 joints C-reactive protein; DAS28-CRP <2.6); TJC: tender joint count; SJC: swollen joint count; PtGA: patient global assessment; CRP: C-reactive protein; HAQ-DI: Health Assessment Questionnaire Disability Index; Pain VAS: Visual Analogue Scale (range, 0 [no pain] to 100 [worst imaginable pain]); Biological DMARDs: biological disease-modifying anti-rheumatic drugs. Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS), Anxiety/Depression: HADS ≥8.

Multiple analyses of association between clinical factors and anxiety in rheumatoid arthritis patients (N = 508)

	Univariable analysis			Multivariable analysis			
				Model 1		Model 2	
	Odds ratio (95% CI)		p value	Odds ratio (95% CI)		Odds ratio (95% CI)	p value
non-	0.99	(0.55, 1.89)	0.98	0.88 (0.45, 1.71)	0.71	0.83 (0.43, 1.63)	0.59
	1.01	(0.84, 1.29)	0.98	0.83 (0.68, 1.01)	0.07	0.83 (0.68, 1.01)	0.06
	1.99	(1.12, 3.36)	0.01	0.93 (0.48, 1.78)	0.82		
	1.18	(1.03, 1.35)	0.02			1.02 (0.85, 1.22)	0.85
	1.14	(0.98, 1.34)	0.08			0.97 (0.79, 1.19)	0.76
	1.23	(0.90, 1.65)	0.17			1.01 (0.70, 1.43)	0.98
	1.29	(1.18, 1.42)	<0.01			1.15 (1.02, 1.29)	0.03
	4.32	(2.59, 7.48)	<0.01	3.51 (1.85, 6.64)	<0.01	3.21 (1.69, 6.08)	<0.01
	1.24	(1.14, 1.35)	<0.01	1.10 (0.98, 1.23)	0.12		
	1.12	(0.69, 1.77)	0.65	1.07 (0.63, 1.80)	0.81	1.05 (0.62, 1.77)	0.85
s	0.64	(0.40, 1.03)	0.06	0.67 (0.40, 1.13)	0.13	0.71 (0.42, 1.20)	0.20
	1.63	(1.01, 2.60)	0.04	1.12 (0.66, 1.92)	0.67	1.14 (0.66, 1.96)	0.64

age (stratified in 10 decades), Pain-VAS, HAQ-DI-based remission and treatment type. 95% CI: 95% confidence interval; DAS28-activity Score 28 joints C-reactive protein; TJC: tender joint count; SJC: swollen joint count; PtGA: patient global assessment; CRP: C-reactive protein; HAQ-DI: Health Assessment Questionnaire Disability Index, Pain VAS: Visual Analogue Scale (range, 0 [no pain] to 10 [maximum pain]); MARDs: biological disease-modifying anti-rheumatic drugs. DAS28 was used for gauging clinical remission (score <2.6); DAS 4 comprising TJC, SJC, CRP, and PGA).

able analyses of association between clinical factors and depression in rheumatoid arthritis patients (N = 507)

	Univariable analysis			Multivariable analysis			
				Model 1		Model 2	
	Odds ratio (95% CI)		p value	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
non-remission	0.80	(0.49, 1.34)	0.39	0.70 (0.40, 1.22)	0.21	0.61 (0.34, 1.07)	0.09
	1.18	(1.01, 1.38)	0.04	1.03 (0.87, 1.24)	0.70	1.04 (0.87, 1.24)	0.68
	2.37	(1.47, 3.82)	<0.01	1.45 (0.81, 2.61)	0.22		
	1.10	(0.97, 1.25)	0.14			0.96 (0.81, 1.14)	0.63
	1.06	(0.92, 1.21)	0.40			0.94 (0.78, 1.14)	0.55
	1.01	(0.74, 0.99)	0.96			0.71 (0.50, 1.01)	0.06
	1.27	(1.17, 1.38)	<0.01			1.21 (1.09, 1.35)	<0.01
sion	2.96	(1.96, 4.53)	<0.01	2.65 (1.56, 4.50)	<0.01	1.95 (1.15, 3.31)	0.01
	1.13	1.05, 1.22)	<0.01	0.98 (0.88, 1.09)	0.77		
s	0.92	(0.61, 1.37)	0.68	0.84 (0.53, 1.33)	0.45	0.88 (0.55, 1.40)	0.58
	0.60	(0.40, 0.90)	0.01	0.72 (0.45, 1.14)	0.16	0.76 (0.48, 1.22)	0.26
	1.87	(1.24, 2.81)	<0.01	1.48 (0.93, 2.34)	0.09	1.66 (1.03, 2.67)	0.04

age (stratified in 10 decades), Pain-VAS, HAQ-DI-based remission, and treatment type. 95% CI: 95% confidence interval; DAS28-activity Score 28 joints C-reactive protein; TJC: tender joint count; SJC: swollen joint count; PtGA: patient global assessment; CRP: C-IAQ-DI: Health Assessment Questionnaire Disability Index, Pain VAS: Visual Analogue Scale (range. 0 [no pain] to 10 [maximum])MARDs: biological disease-modifying anti-rheumatic drugs; DAS28 was used for gauging clinical remission (score <2.6); DAS 4 comprising TJC, SJC, CRP, and PGA).

correlation coefficients between

	Sex	Age	Disease duration	DAS28-CRP	TJC	SJC	CRP	PGA (0-100)	HAQ-DI	Pain VAS (0-100)	Biological DMARDs	Methotrexate	Steroid	Anxiety	Depression
	1														
	-0.10	1													
	0.16	0.28	1												
ESR	-0.01	0.20	0.22	1											
	0.03	0.10	0.12	0.81	1										
	-0.01	0.14	0.17	0.67	0.53	1									
	-0.14	0.13	0.08	0.39	0.21	0.27	1								
CRP	0.03	0.17	0.19	0.77	0.43	0.35	0.19	1							
	0.06	0.31	0.40	0.56	0.42	0.36	0.24	0.58	1						
PGA	-0.06	0.14	0.20	0.67	0.41	0.31	0.15	0.78	0.54	1					
	0.11	-0.16	-0.09	-0.07	-0.04	-0.03	-0.06	-0.05	-0.02	-0.04	1				
HAQ-DI	-0.02	-0.10	-0.09	-0.10	-0.05	-0.04	-0.19	-0.17	-0.17	-0.10	-0.01	1			
	-0.08	0.13	0.10	0.22	0.13	0.20	0.23	0.16	0.22	0.14	-0.02	-0.17	1		
	0.03	-0.01	0.06	0.21	0.13	0.07	0.02	0.32	0.31	0.28	-0.01	-0.11	0.07	1	
Biological DMARDs	-0.04	0.09	0.09	0.22	0.12	0.05	0.03	0.33	0.34	0.24	-0.01	-0.12	0.13	0.56	1

ESR: Disease Activity Score 28 joints C-reactive protein; TJC: tender joint count; SJC: swollen joint count; PGA: patient global assessment; CRP: C-reactive protein; HAQ-DI: Health Assessment Questionnaire Disability Index, Pain VAS: Visual Analogue Scale (range, 0 [no pain] to 100 [maximum pain]). DMARDs: biological disease-modifying anti-rheumatic drugs; Anxiety and depression were measured using the Hospital Anxiety and Depression Scale (Anxiety/Depression: HADS ≥ 8).

Figures

Figure 1

Flowchart of patient selection (HADS: Hospital Anxiety and Depression Scale)