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

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Abstract

Background Management of anxiety and depressive symptoms 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 depressive symptoms after controlling for physical disability, pain, and treatment.

Methods 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 that DAS28-based non-remission was not statistically associated with anxiety symptoms (odds ratio [OR] [95% confidence interval {CI}], 0.93 [0.48–1.78]: $p = 0.82$) and depressive symptoms (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 symptoms (OR [95% CI], 1.15 [1.02–1.29]; $p = 0.03$) and depressive symptoms (OR [95% CI], 1.21 [1.09–1.35]; $p < 0.01$). Additionally, HAQ-DI-based non-remission was associated with anxiety symptoms (OR [95% CI], 3.51 [1.85–6.64]; $p < 0.01$) and depressive symptoms (OR [95% CI], 2.65 [1.56–4.50]; $p < 0.01$). Patients using steroids had a closer association with depressive symptoms than those not using them (OR [95% CI], 1.66 [1.03–2.67]; $p = 0.04$).

Conclusions As per the multivariable logistic regression analysis, there was no association between DAS28-based-non-remission and anxiety and depressive symptoms; however, the univariate analysis revealed such association. In the multivariate analysis, PtGA and non-remission on HAQ were associated with anxiety and depressive symptoms. Rather than focusing solely on controlling disease, activity and treatment should focus on improving or preserving physical function and patient's overall sense of well-being.

Background

Anxiety and depressive symptoms 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 symptoms, and 14.8%–34.2% have depressive symptoms [1]. RA patients with these conditions have worse outcomes, including poor medication adherence [3], worse treatment response [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.

However, it is difficult for a rheumatologist to notice anxiety and depressive symptoms in ambulatory care. In this study, self-reported questionnaires such as the Hospital Anxiety Depression Scale (27) were used to assess anxiety and depressive symptoms in RA patients. Considering the burden on patients and the time required, it is difficult to use it in daily medical situations. Therefore, we focused on the disease activity evaluated in each medical examination. If it is clear that disease activity and its components correlate with anxiety and depressive symptom in RA patients, excluding the effects of other factors that affect anxiety and depressive symptoms, disease activity can be assessed as anxiety and depressive symptoms in RA patients. It can be used in daily medical care as an index for anxiety and depressive symptoms.

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 depressive symptoms 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 [20]. Other studies have reported that C-reactive protein (CRP) levels are associated with anxiety and depressive symptoms in RA patients [21].

Disease activity reflecting the above factors may be associated with anxiety and depressive symptoms 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 depressive symptoms [22, 23], while others have not found this association [24]. A key reason is that other factors such as physical disability, pain, and medication associated with anxiety and depressive symptoms have not been investigated [22-24] in previous studies.

Our study's hypothesis is that disease activity and its components are associated with anxiety and depressive symptoms even if the effects of disease activity such as pain, disability, and treatments are excluded. The present study aimed to determine the factors

associated with anxiety and depressive symptoms 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 such bipolar disorder and schizophrenia, 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 this study.

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 depressive symptoms 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 depressive symptoms as a HADS anxiety score ≥8 and HADS depression score ≥8 [27].

Statistical analysis

Unless otherwise stated, data are presented as mean ± standard deviation or number (%). First, we examined the associations between the RA patients' characteristics and both anxiety and depressive symptoms 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 depressive symptoms. Based on the 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 542 RA patients and excluded 25 because they had psychiatric disorders such bipolar disorder, and schizophrenia. Of the remaining 517, another nine were excluded from the anxiety analyses because of incomplete HADS anxiety questionnaires, for 508 patients, while 10 were excluded from the depression analyses because of incomplete HADS depression questionnaires, for 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 symptoms, and 143 (28.2%) had depressive symptoms, as measured by the HADS (Table 1).

Table 1. Characteristics of patients with rheumatoid arthritis

Characteristic	Overall N=517
Gender (female)	429 (83.0)
Age, years	62.5 ± 13.1
Disease duration, months	159.7 ± 139.7
stage	
	114 (22.1)
	125 (24.3)
	96 (18.6)
	180 (35.0)
Disease activity	
DAS28-CRP	1.91 ± 0.82
DAS28-CRP remission	360 (78.9)
Low disease activity	57 (12.5)
Moderate disease activity	37 (8.1)
High disease activity	2 (0.5)
TJC	0.8 ± 1.5
SJC	0.8 ± 1.5
PtGA	29.1 ± 24.4
CRP	0.4 ± 0.8
HAQ-DI	0.74 ± 0.77
HAQ-DI remission	252 (51.3)
Pain VAS	27.6 ± 25.7
Treatment	
Biological DMARD	187(36.2)
Methotrexate	345 (66.7)
Steroid	159 (30.8)
Anxiety and depression	
Anxiety	91 (17.9)
Depression	143 (28.2)

Data are presented as mean ± standard deviation or number (%). DAS28-CRP: Disease Activity Score in 28 joints, Remission: DAS28-CRP <2.6, TJC: tender joint count, SJC: swollen joint count, PtGA: patient global assessment; VAS: range 0 (best) to 100 (worst), CRP: C-reactive protein, HAQ DI: Health Assessment Questionnaire Disability Index, HADS-A: Hospital Anxiety and Depression Scale Anxiety subscale, HADS-D: Hospital Anxiety and Depression Scale Depression subscale, Anxiety: HADS-A ≥8, Depression: HADS-D ≥8.

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 symptoms. We then conducted multivariable logistic regression (Table 2). In Model 1, patients with DAS28-CRP-based non-remission was not associated with anxiety symptoms (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 symptoms (OR [95% CI], 0.83 [0.68–1.01]; $p = 0.07$). 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 symptoms (OR [95% CI], 1.15 [1.02–1.29]; $p = 0.03$). Similar to Model 1, patients with HAQ-DI-based non-remission had closer association with anxiety symptoms than those with HAQ-DI-based remission (OR [95% CI], 3.21 [1.69–6.08]; $p < 0.01$).

Table 2. Multivariate analyses of association between clinical factors and anxiety in patients with rheumatoid arthritis (N=508)

	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
gender	0.99 (0.55, 1.89)	0.98	0.88 (0.45, 1.71)	0.71	0.83 (0.43, 1.63)	0.59
Age (10 years)	1.01 (0.84, 1.29)	0.98	0.83 (0.68, 1.01)	0.07	0.83 (0.68, 1.01)	0.06
DAS28-CRP non-remission	1.99 (1.12, 3.36)	0.01	0.93 (0.48, 1.78)	0.82		
TJC	1.18 (1.03, 1.35)	0.02			1.02 (0.85, 1.22)	0.85
SJC	1.14 (0.98, 1.34)	0.08			0.97 (0.79, 1.19)	0.76
CRP	1.23 (0.90, 1.65)	0.17			1.01 (0.70, 1.43)	0.98
PGA (0-10)	1.29 (1.18, 1.42)	<0.01			1.15 (1.02, 1.29)	0.03
HAQ-DI non-remission	4.32 (2.59, 7.48)	<0.01	3.51 (1.85, 6.64)	<0.01	3.21 (1.69, 6.08)	<0.01
Pain VAS (0-10)	1.24 (1.14, 1.35)	<0.01	1.10 (0.98, 1.23)	0.12		
Biological DMARD	1.12 (0.69, 1.77)	0.65	1.07 (0.63, 1.80)	0.81	1.05 (0.62, 1.77)	0.85
Methotrexate	0.64 (0.40, 1.03)	0.06	0.67 (0.40, 1.13)	0.13	0.71 (0.42, 1.20)	0.20
Steroid	1.63 (1.01, 2.60)	0.04	1.12 (0.66, 1.92)	0.67	1.14 (0.66, 1.96)	0.64

Model adjusted for age (stratified in 10 decades), Pain-VAS, HAQ-DI remission and treatment type. Odds ratio (95% CI): Odds ratio (95% confidence interval). DAS28-CRP: 28-joint disease activity score, TJC: tender joint count, SJC: swollen joint count, PtGA: patient global assessment; VAS: range 0 (best) to 10 (worst), CRP: C-reactive protein, HAQ: Health Assessment Questionnaire, Pain; VAS: range 0 (no pain) to 10 (maximum), Anxiety is measured by using HADS, HADS = Hospital Anxiety and Depression Scale, Anxiety: HADS-A ≥8.
DAS28 was used for clinical remission (DAS28 score of< 2.6) ; DAS 4 variables (DAS4) include TJC, SJC, CRP, and PGA.

Association between clinical variables and depression

Similar analyses were conducted for depressive symptoms. 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 symptoms. We then conducted multivariable logistic regression (Table 3). In Model 1, patients with DAS28-CRP-based non-remission were not associated with depressive symptoms (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 depressive symptoms than HAQ-DI-based remission (OR [95% CI], 2.65 [1.56–4.50]; $p < 0.01$). In Model 2, pain was excluded from the explanatory variables for collinearity. As a result, patients with severe PtGA were more notably associated with depressive symptoms (OR [95% CI], 1.21 [1.09–1.35]; $p < 0.01$). Similar to Model 1, patients with HAQ-DI-based non-remission had a closer association with depressive symptoms than HAQ-DI-based remission (OR [95% CI], 1.95 [1.15–3.31]; $p = 0.01$). Patients taking steroids had a higher association with depressive symptoms than those not taking steroids (OR [95% CI], 1.66 [1.03–2.67]; $p = 0.04$).

variable 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
	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
ıased non-remission	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
ɛmission	2.96	(1.96, 4.53)	<0.01	2.65 (1.56, 4.50)	<0.01	1.95 (1.15, 3.31)	0.01
0)	1.13	1.05, 1.22)	<0.01	0.98 (0.88, 1.09)	0.77		
ARDs	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

d for age (stratified in 10 decades), Pain-VAS, HAQ-DI-based remission, and treatment type. 95% CI: 95% confidence interval;)isease Activity Score 28 joints C-reactive protein; TJC: tender joint count; SJC: swollen joint count; PtGA: patient global :RP: C-reactive protein; HAQ-DI: Health Assessment Questionnaire Disability Index, Pain VAS: Visual Analogue Scale (range. 0) [maximum pain]). Biological DMARDs: biological disease-modifying anti-rheumatic drugs; DAS28 was used for gauging clinical)re <2.6); DAS 4 variables (DAS4; comprising TJC, SJC, CRP, and PGA).

. Correlation coefficients between
es

	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													
n	0.16	0.28	1												
CRP	-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								
-100)	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						
S (0-	-0.06	0.14	0.20	0.67	0.41	0.31	0.15	**0.78**	0.54	1					
al s	0.11	-0.16	-0.09	-0.07	-0.04	-0.03	-0.06	-0.05	-0.02	-0.04	1				
exate	-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	
sion	-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

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

Discussion

This was a large cohort study using the KURAMA cohort [25]. We investigated the association of disease activity with anxiety and depressive symptoms, after adjusting for physical disability, pain, and treatment of RA patients. In this study, we used multiple models to investigate such associations and produced several interesting findings. (1) There was no association between DAS28-based-non-remission and anxiety and depressive symptoms according to multivariable logistic regression analysis, even though there was an association according to univariate analysis. (2) Severity of PtGA, a component of the DAS28 composite measure, was strongly associated with anxiety and depressive symptoms, whereas other individual elements of DAS28-CRP (CRP, SJC, and TJC) were not. (3) Non-remission on HAQ-DI was independently and significantly associated with anxiety and depressive symptoms. (4) Additionally, patients taking steroids had a higher association with depressive symptoms than those not taking steroids.

Previous studies investigating the association between disease activity and anxiety and depressive symptoms 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 depressive symptoms in RA patients. There were two key issues: (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 depressive symptoms was mainly 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, patients with DAS28-based non-remission were not an independent factor associated with anxiety and depressive symptoms. The average DAS28 CRP score in this study was 1.91 ± 0.82, which was lower than the previous study (DAS28 CRP score 6.26-6.77). In addition, almost 80% achieved remission of disease activity (42.4-56.3% in previous studies), the disease severity was low and controlled. Therefore, when adjusted for other factors, the effects of other factors associated with anxiety and depression may be more robust than disease activity.

We also found that PtGA—a component of the DAS28-CRP composite measure—was notably associated with anxiety and depressive symptoms. Factors suggesting inflammation—e.g., CRP, TJC, and SJC—were not associated with anxiety and depressive symptoms 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. The present study did not correlate the two variables because of low CRP. 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. Various factors are reflected in PtGA. For example, such as physical disability [32-33], pain [17, 32], and catastrophizing pain [34] are among factors that exacerbate PtGA. Santos et al. [35] excluded a priori to test the direct association between DAS28-CRP 3 variables and depressive symptoms but rather tested the influence of disease activity and the impact of the disease in patients. The results showed that there was no direct association between DAS28-CRP3V and depressive symptoms, and confirmed an indirect relationship between disease activity and depressive symptoms mediated by the impact of disease such as pain, physical well-being, functional disability and coping. Thus, the functional disability, pain, recognition, and self-evaluation of disease were reflected in PtGA, and related to anxiety and depression. In addition, there is a gap between doctor and patient PtGA assessments [36]. Therefore, in order to understand the anxiety and depressive symptoms of the patients, it is necessary to pay attention to the subjective experience of patients regardless of the disease activity. Additionally, to reduce anxiety and depressive symptoms 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 [37, 38, 39] relieve the tendency to catastrophize and subsequently reduce pain and distress; therefore, these approaches may be effective interventions in this case.

The present study found the HAQ-DI score, which identifies physical disability, was associated with anxiety and depressive symptoms in multivariable analysis. Previous studies found the HAQ-DI score [12-14] was a factor related to anxiety and depression. Regardless of acute disease activity score, functional disability measured by HAQ is a factor of depression[21, 22, 40]. In addition, with persistent disability, the possibility of concurrent anxiety and depressive symptoms increased, irrespective of disease activity remission. Physical disability 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 affected anxiety and depression [13, 40].

The effect of bone or joint damage was not clear because joint damage was not evaluated in this study. However, patients were older, had a longer disease duration, low disease activity and low inflammation. It was suggested that anxiety and depressive symptoms were caused by loss of activity in daily life due to prolonged limited function rather than acute symptoms of disease activity. It is important to confirm the effects of the disease on daily life. In T2T, the goal of treatment was to restore physical function to normal and to be able to participate in social activities again, thereby maintaining a long-term quality of life [41]. Improving quality of life by supporting daily activities and possibly replacing or recovering lost activities to maintain and improve physical functions may relief anxiety and depressive symptoms.

Finally, in Model 1, younger RA patients 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. In Model 2, patients taking steroids were associated with depression. Side effects of depression may be caused by the pharmacological actions of steroids [42]. Appropriate treatment is needed in considering this risk of side effects.

One of the strengths of this study is that it used a large cohort study to investigate the association between disease activity and anxiety and depressive symptoms for adjusted factors affecting the anxiety and depressive symptoms. Various scales are used to evaluate depression in RA patients. The HADS was used because it was 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 depressive symptoms. Using the HADS allows the prevalence of anxiety and depressive symptoms 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

There was no association between DAS28-based-non-remission and anxiety and depressive symptoms according to multivariable logistic regression analysis, even though there was an association according to univariate analysis. It was confirmed that almost 80% of patients

had achieved disease activity remission. In multivariate analysis, PtGA and non- remission on HAQ were factors associated with anxiety and depressive symptoms. Thus, the functional disability, pain, recognition, and self-evaluation of disease were reflected in PtGA, and related to anxiety and depressive symptoms indirectly. In order to understand the anxiety and depressive symptoms of the patients, it is necessary to pay attention to the subjective experience of patients regardless of the disease activity. It was suggested that anxiety and depressive symptoms were caused by loss of activity in daily life due to prolonged limited function rather than acute symptoms of disease activity. It is important to confirm the effects of the disease on daily life. Improving quality of life by supporting daily activities and possibly replacing or recovering lost activities to maintain and improve physical functions that may relieve anxiety and depressive symptoms.

List Of Abbreviations

RA: rheumatoid arthritis

DAS28: disease activity score

HAQ-DI: health assessment questionnaire disability index

OR: odds ratio

CI: confidence interval

PtGA: patient's global assessment

TNF: tumor necrosis factor

IL: interleukin

CRP: C-reactive protein

KURAMA: Kyoto University Rheumatoid Arthritis Management Alliance

HADS: hospital anxiety and depression scale

TJC: tender joint count

SJC: swollen joint count

VAS: visual analogue scale

CBT: cognitive behavioral therapy

bDMARDs: biological disease-modifying anti-rheumatic drugs

Declarations

Ethical approval and consent to participate

Kyoto University Graduate School and Faculty of Medicine, Ethics Committee approved this study.

Informed consent was obtained from study participants.

Availability of data and materials

All data generated or analyzed during this study are included in this published article [and its supplementary information files] or are available from the corresponding author on reasonable request.

Competing interests

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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References

1. Matcham F, Rayner L, Steer S, Hotopf M. The prevalence of depression in rheumatoid arthritis: a systematic review and meta-analysis. 2013;53:2136–2148. https://doi.org/10.1093/rheumatology/ket169
2. Marrie RA, Hitchon CA, Walld R, Patten SB, Bolton JM, Sareen J et al. Increased burden of psychiatric disorders in rheumatoid arthritis. Arthritis Care Res. 2018;70:970–978. https://doi.org/10.1002/acr.23539
3. Mattey DL, Dawes PT, Hassell AB, Brownfield A, Packham JC. Effect of psychological distress on continuation of anti-tumor necrosis factor therapy in patients with rheumatoid arthritis. J Rheumatol. 2010;37:2021–2024. https://doi.org/10.3899/jrheum.100050
4. Li X, Gignac MA, Anis AH. The indirect costs of arthritis resulting from unemployment, reduced performance, and occupational changes while at work. Med Care. 2006;44:304–310. https://doi.org/10.1097/01.mlr.0000204257.25875.04
5. Margaretten M, Julian L, Katz P, Yelin E. Depression in patients with rheumatoid arthritis: description, causes and mechanisms. Int J Clin Rheumtol. 2011;6:617–623. https://doi.org/10.2217/IJR.11.6
6. Matcham F, Scott IC, Rayner L, Hotopf M, Kingsley GH, Norton S et al. The impact of rheumatoid arthritis on quality-of-life assessed using the SF-36: a systematic review and meta-analysis. Semin Arthritis Rheum. 2014;44:123–130. https://doi.org/10.1016/j.semarthrit.2014.05.001
7. Ang DC, Choi H, Kroenke K, Wolfe F. Comorbid depression is an independent risk factor for mortality in patients with rheumatoid arthritis. J Rheumatol. 2005;32:1013–1019
8. Timonen M, Viilo K, Hakko H, Sarkioja T, Ylikulju M, Meyer-Rochow VB et al. Suicides in persons suffering from rheumatoid arthritis. Rheumatology. 2003;42:287–291. https://doi.org/10.1093/rheumatology/keg082
9. Ho RC, Fu EH, Chua AN, Cheak AA, Mak A. Clinical and psychosocial factors associated with depression and anxiety in Singaporean patients with rheumatoid arthritis. Int J Rheum Dis. 2011;14:37–47. https://doi.org/10.1111/j.1756-185X.2010.01591.x
10. Mikuls T, Saag K, Criswell L, Merlino L, Cerhan JR. Health related quality of life in women with elderly onset rheumatoid arthritis. J Rheumatol. 2003;30:952–957

11. Cutolo M, Kitas GD, van Riel PL. Burden of disease in treated rheumatoid arthritis patients: going beyond the joint. Semin Arthritis Rheum. 2014;43:479–488. https://doi.org/10.1016/j.semarthrit.2013.08.004
12. Margaretten M, Yelin E, Imboden J, Graf J, Barton J, Katz P et al. Predictors of depression in a multiethnic cohort of patients with rheumatoid arthritis. Arthritis Rheum. 2009;61:1586–1591. https://doi.org/10.1002/art.24822
13. Bacconnier L, Rincheval N, Flipo RM, Goupille P, Daures JP, Boulenger JP et al. Psychological distress over time in early rheumatoid arthritis: results from a longitudinal study in an early arthritis cohort. Rheum. 2015;54:520–527. https://doi.org/10.1093/rheumatology/keu371
14. Karpouzas GA, Dolatabadi S, Moran R, Li N, Nicassio PM, Weisman MH. Correlates and predictors of disability in vulnerable US Hispanics with rheumatoid arthritis. Arthritis Care Res. 2012;64:1274–1281. https://doi.org/10.1002/acr.21689
15. Dickens C, McGowan L, Clark-Carter D, Creed F. Depression in rheumatoid arthritis: a systematic review of the literature with meta-analysis. Psychosom Med. 2002;64:52–60. https://doi.org/10.1097/00006842-200201000-00008
16. Walsh DA, McWilliams DF. Mechanisms, impact and management of pain in rheumatoid arthritis. Nat Rev Rheumatol. 2014;10:581–592. https://doi.org/10.1038/nrrheum.2014.64
17. Odegård S, Finset A, Mowinckel P, Kvien TK, Uhlig T. Pain and psychological health status over a 10-year period in patients with recent onset rheumatoid arthritis. Ann Rheum Dis. 2007;66:1195–1201. https://doi.org/10.1136/ard.2006.064287
18. de Ridder D, Geenen R, Kuijer R, van Middendorp H. Psychological adjustment to chronic disease. Lancet. 2008;372:246–255. https://doi.org/10.1016/S0140-6736(08)61078-8
19. Liu Y, Ho RC, Mak A. Interleukin (IL)-6, tumour necrosis factor alpha (TNF-alpha) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: a meta-analysis and meta-regression. J Affect Disord. 2012;139:230–239. https://doi.org/10.1016/j.jad.2011.08.003
20. Du X, Pang TY. Is dysregulation of the HPA-Axis a core pathophysiology mediating co-morbid depression in neurodegenerative diseases? Front Psychiatry. 2015. https://doi.org/10.3389/fpsyt.2015.00032
21. Kojima M, Kojima T, Suzuki S, Oguchi T, Oba M, Tsuchiya H et al. Depression, inflammation, and pain in patients with rheumatoid arthritis. Arthritis Rheum. 2009;61:1018–1024. https://doi.org/10.1002/art.24647
22. Kekow J, Moots R, Khandker R, Melin J, Freundlich B, Singh A. Improvements in patient-reported outcomes, symptoms of depression and anxiety, and their association with clinical remission among patients with moderate-to-severe active early rheumatoid arthritis. Rheum. 2011;50:401–409. https://doi.org/10.1093/rheumatology/keq327
23. Overman CL, Bossema ER, van Middendorp H, Wijngaards-de Meij L, Verstappen SM, Bulder M et al. The prospective association between psychological distress and disease activity in rheumatoid arthritis: a multilevel regression analysis. Ann Rheum Dis. 2012;71:192–197. https://doi.org/10.1136/annrheumdis-2011-200338
24. Ho RC, Fu EH, Chua AN, Cheak AA, Mak A. Clinical and psychosocial factors associated with depression and anxiety in Singaporean patients with rheumatoid arthritis. Int J Rheum Dis. 2011;14:37–47. https://doi.org/10.1111/j.1756-185X.2010.01591.x
25. Terao C, Hashimoto M, Yamamoto K, Murakami K, Ohmura K, Nakashima R et al. Three groups in the 28 joints for rheumatoid arthritis synovitis–analysis using more than 17,000 assessments in the KURAMA database. PLoS One. 2013;8: e59341. https://doi.org/10.1371/journal.pone.0059341
26. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2010;69:1580–1588. https://doi.org/10.1136/ard.2010.138461
27. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67:361–370 https://doi.org/10.1111/j.1600-0447.1983.tb09716.x
28. Wells G, Becker JC, Teng J, Dougados M, Schiff M, Smolen J et al. Validation of the 28-joint Disease Activity Score (DAS28) and European League Against Rheumatism response criteria based on C-reactive protein against disease progression in patients with rheumatoid arthritis, and comparison with the DAS28 based on erythrocyte sedimentation rate. Ann Rheum Dis. 2009;68:954–960. https://doi.org/10.1136/ard.2007.084459
29. Fransen J, Creemers MC, Van Riel PL. Remission in rheumatoid arthritis: agreement of the disease activity score (DAS28) with the ARA preliminary remission criteria. Rheumatology. 2004;43:1252–1255. https://doi.org/10.1093/rheumatology/keh297
30. Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: a review of its history, issues, progress, and documentation. J Rheumatol. 2003;30:167–178

31. van Tuyl LH, Boers M. Patient-reported outcomes in core domain sets for rheumatic diseases. Nat Rev Rheumatol. 2015;11:705–712. https://doi.org/10.1038/nrrheum.2015.116
32. Khan NA, Spencer HJ, Abda EA, Alten R, Pohl C, Ancuta C et al. Patient's global assessment of disease activity and patient's assessment of general health for rheumatoid arthritis activity assessment: are they equivalent? Ann Rheum Dis. 2012;71:1942–1949. https://doi.org/10.1136/annrheumdis-2011-201142
33. Verschueren P, Esselens G, Westhovens R. Predictors of remission, normalized physical function, and changes in the working situation during follow-up of patients with early rheumatoid arthritis: an observational study. Scand J Rheumatol. 2009;38:166–172. https://doi.org/10.1080/03009740802484846
34. Boyden SD, Hossain IN, Wohlfahrt A, Lee YC. Non-inflammatory causes of pain in patients with rheumatoid arthritis. Curr Rheumatol Rep. 2016;18:30. https://doi.org/10.1007/s11926-016-0581-0
35. Santos EF, Duarte CM, Ferreira RO, Pinto AM, Geenen R et al. Multifactorial explanatory model of depression in patients with rheumatoid arthritis: a structural equation approach. Clin Exp Rheumatol. 2019;37(4):641-648.
36. Barton JL, Imboden J, Graf J, Glidden D, Yelin EH, Schillinger D. Patient-physician discordance in assessments of global disease severity in rheumatoid arthritis. Arthritis Care Res. 2010;62:857–864. https://doi.org/10.1002/acr.20132
37. 37. Beltman MW, Voshaar RC, Speckens AE. Cognitive-behavioral therapy for depression in people with a somatic disease: meta-analysis of randomized controlled trials. Br J Psychiatry. 2010;197:11–19. https://doi.org/10.1192/bjp.bp.109.064675
38. DiRenzo D, Crespo-Bosque M, Gould N, Finan P, Nanavati J, Bingham CO. Systematic review and meta-analysis: mindfulness-based interventions for rheumatoid arthritis. Curr Rheumatol Rep. 2018;20:75. https://doi.org/10.1007/s11926-018-0787-4
39. Hofmann SG, Gomez AF. Mindfulness-based interventions for anxiety and depression. Psychiatr Clin North Am. 2017;40:739–749 https://doi.org/10.1016/j.psc.2017.08.008
40. Katz PP, Yelin EH. Activity loss and the onset of depressive symptoms: do some activities matter more than others? Arthritis Rheum. 2001;44:1194–1202. https://doi.org/10.1002/1529-0131(200105)44:5<1194::AID-ANR203>3.0.CO;2-6
41. 41. Smolen JS, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas D, Burmester G et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis. 2010;69:631–637. https://doi.org/10.1136/ard.2009.123919
42. Wolkowitz OM, Burke H, Epel ES, Reus VI. Glucocorticoids, mood, memory, and mechanisms. Ann N Y Acad Sci. 2009;179:19–40. https://doi.org/10.1111/j.1749-6632.2009.04980.x

Figures

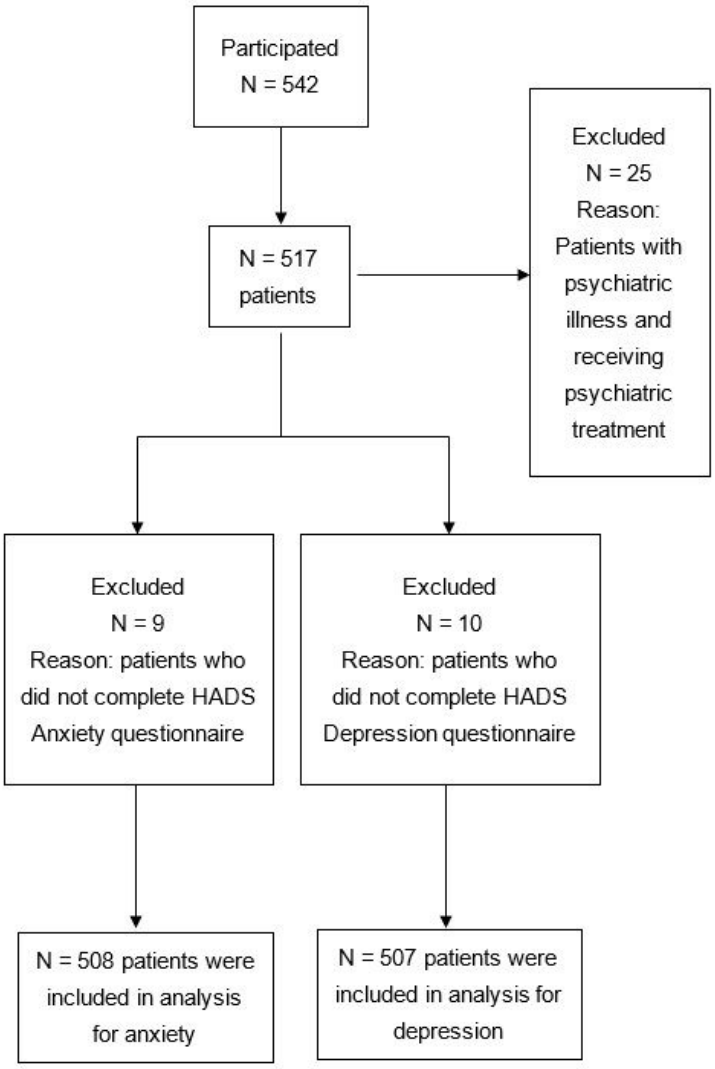

Figure 1

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