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ORIGINAL ARTICLE

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Disability and patient's appraisal of general health contribute to depressed mood in rheumatoid arthritis in a large clinical study in Japan

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Abstract The aim of this study was to evaluate the factors responsible for depressed mood in rheumatoid arthritis (RA). Clinical and laboratory measures were collected from 4558 RA patients enrolled in a large clinical cohort study for RA conducted at the Institute of Rheumatology, Tokyo Women's Medical University (IORRA study). A two-question depressed screening included in the U.S. Preventive Services Task Force recommendation were utilized to identify "depressed patients." A total of 1875 (41.1%) were identified as "depressed patients" who presented with symptoms suggestive of depression. Patient's Visual Analog Scale (VAS) for general health (43.3 mm vs 24.6 mm, $P < 0.0001$) and pain (40.9 mm vs 23.8 mm, $P < 0.0001$) and the disability index scores measured by the Health Association Questionnaire (HAQ) (0.986 vs 0.574, $P < 0.0001$) were significantly higher in depressed patients than in nondepressed patients. The presence of three or more comorbidities (odds ratio [OR] 2.157, $P < 0.0001$), infection (OR 1.754, $P < 0.0001$), and joint surgery (OR 1.878, $P < 0.0001$) were significantly correlated with depressed mood in RA. The results of the Generalized Linear Model analysis showed that HAQ disability index ($P < 0.0001$) and patient's VAS for general health ($P < 0.0001$) were also strongly and significantly associated to the response variable "probability of depressed patients." Patient appraisal of poor general health and greater disability were associated with depressed mood in RA.

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Introduction

Rheumatoid arthritis (RA) is characterized by chronic arthritis leading to joint deformity. Patients with RA are often debilitated by the continuous pain and the fear of becoming disabled. Therefore, the coexistence of depression in patients with RA is reported to be higher than that in the general population (2%–9%).[1] The prevalence of depression in RA patients is reported to be from 13% to 42% in which variance results form the methodology of diagnosis of depression.[2–5] Depression is often accompanied by physical symptoms, such as fatigue, stiffness, and joint pain; and these symptoms can debilitate symptoms of RA. In addition, depression inflicts enormous economic deprivation such as loss of income and increased medical expenses. In light of such consequences, recognizing and treating depression is crucial to the improvement of the quality of life (QOL) of RA patients.

Depression is difficult to diagnose as in an outpatient rheumatology clinic, even though proper management of depression in RA patients is very important. The Center for Epidemiologic Studies Depression Scale (CES-D)[6] and Beck Depression Inventory (BDI)[7] are instruments psychologists commonly use to assess depressive symptoms. However, even the short forms of CES-D[8] or BDI[9] are too cumbersome and time-consuming for routine use. In 2002, the U.S. Preventive Service Task Force (USPSTF) compressed the clinical guidelines for screening depression into a two-question form concerning mood and anhedonia.[10] An earlier study reported that a "yes" answer to either one of these two questions was 96% sensitive and 57% specific for depression,[11] and this screening is certified as a very convenient and reliable instrument.[10]

To evaluate depressed mood in RA patients, we screened RA patients enrolled in a single institute-based large-scale survey at the Institute of Rheumatology, Tokyo

Women's Medical University [Institute of Rheumatology, rheumatoid arthritis (IORRA) study] using this two-question depression screen. We then investigated the factors associated to depressed mood among the RA patients.

Methods

Medical survey system and measurement instruments

A single institute-based large cohort survey system at the Institute of Rheumatology, Tokyo Women's Medical University was started in October 2000 (IORRA study), and surveys were conducted every 6 months thereafter. During April and October, after obtaining informed consent for joining the IORRA study from each patient at each survey, the examining physician evaluated 66 joints for swelling and 69 joints for tenderness, and recorded which joints were swollen and tender. The physician also recorded the Visual Analog Scale (VAS) evaluation scores for disease activity on the each patient's chart. Laboratory studies included C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), complete blood cell count (CBC), blood chemistry, and urinalysis. Patients brought home a questionnaire to complete including their VAS scale for pain intensity and general health, and an assessment of their degree of physical disability by the Stanford Health Assessment Questionnaire functional index (HAQ disability) and Japanese version of HAQ (J-HAQ) scoring system. J-HAQ is the Japanese version of the HAQ scoring system that was translated, culturally modified, and validated by our group.[12] Disease Activity Score 28 (DAS28 score),[13] the most commonly used score for evaluating RA activity, is calculated by using the VAS scale for the patient's general health, swollen joints count, tender joints count, and ESR. The patients reported current comorbidities, such as hypertension, diabetes mellitus, asthma, and emphysema, and they also reported significant medical events occurring during the prior 6 months, including infections, joint surgery, concurrent development of malignancies, bone fractures, and hospitalizations. The brand names and doses of disease-modifying antirheumatic drugs (DMARDs), corticosteroids, and nonsteroidal anti-inflammatory drugs (NSAIDs) were also reported. Patients were expected to complete their questionnaires at home and to mail the completed forms within 2 weeks in a pre-addressed and pre-stamped envelope. These reported data were stored and linked to the laboratory data.

Screen for depressed state

The two-question screening for depression included in the clinical guidelines prepared by the USPSTF[10] was utilized in the questionnaire for the 5th IORRA survey conducted in October 2002. The first question was "Over the past 2 weeks, have you felt down, depressed, or hopeless?" The second was "Over the past 2 weeks, have you felt little interest or pleasure in doing things?" We used the translated Japanese version of these questions.[14] Patients who answered "yes" to at least one question are at high risk for depression or else actually exhibit symptoms suggestive of depression, as discussed by Whooley et al.[11] Therefore, we categorized patients into "depressed" RA patients who are positive to this screen and "nondepressed" RA patients who are negative to this screen.

Participants

The 5th IORRA study, conducted during October 2002, enrolled 5070 patients. The number of questionnaires returned was 4930, corresponding to a completion rate of 97.2%. Among the 4930 patients with RA, diagnosed according to the criteria of American College of Rheumatology in 1987[15] by established rheumatologists, 4558 (774 men and 3784 women) patients with RA answered at least one of the two screening questions for depression.

The mean age of these responded patients was 57.9 ± 12.7 years and average disease duration was 11.0 ± 8.8 years. The patient's VAS score for general health and pain, and doctor's VAS score for RA activities were 32.3 ± 25.4 mm, 30.8 ± 26.2 mm, and 16.7 ± 15.9 mm, respectively. HAQ score and J-HAQ score were 0.774 ± 0.773 and 0.790 ± 0.760, and ESR and CRP were 34.6 ± 23.8 mm/h and 1.3 ± 1.7 mg/dl.

Statistical analysis

Comparison of the demographic and clinical data of depressed patients with nondepressed patients was performed using the Wilcoxon Scores test analysis for continuous variables and the chi-squared test for categorical data. Fisher's exact test was used to analyze the relationship between depressed mood and the impact of events during the previous 6 months or the accompanying condition. To evaluate the relative contribution of demographic, clinical, and laboratory factors to the scoring of depressed mood, the Generalized Linear Model was used for analysis. The Generalized Linear Model[16] is a nonlinear model with the "link function" for the means of the response variables and allows models to be fit to data that follow probability distributions. In this case, we assumed that the response variables followed a binomial distribution since the response variables had binary values, either depressed mood or not. The logit function was therefore selected as the linking function. Parameters of the Generalized Linear Model were estimated using the principle of maximum likelihood. Deviances were helpful in assessing the goodness of fit of a given Generalized Linear Model. Deviance is defined as twice the difference between the maximum achievable log likelihood and the log likelihood at the maximum likelihood estimates of the regression parameters. The contribution of explanatory variables to the response variables can be evaluated by comparing the deviance of the null model with the deviance of a model with sequentially added terms. It is assumed that a variable with maximum deviance signifi-

Table 1. Demographic and clinical variables of depressed and nondepressed patients with rheumatoid arthritis

	Depressed patients (n = 1875)		Nondepressed patients (n = 2683)		P
	Mean	(SD)	Mean	(SD)	
Sex (female %)	83.9		82.4		0.203
Age (years)	57.5	(13.0)	58.1	(12.4)	0.333
Onset age (years)	46.0	(13.9)	47.2	(13.5)	0.010
Disease duration (years)	11.4	(9.1)	10.8	(8.5)	0.084
Pt's general VAS (range: 0–100)	43.3	(25.9)	24.6	(22.0)	<0.0001
Pt's pain VAS (range: 0–100)	40.9	(27.7)	23.8	(22.7)	<0.0001
Doctor's VAS (range: 0–100)	19.7	(17.6)	14.6	(14.3)	<0.0001
Tender joint score	3.7	(6.0)	2.4	(4.2)	<0.0001
Swollen joint score	3.1	(4.2)	2.6	(3.6)	0.0003
RF	77.3		73.8		0.008
ESR (mm/h)	37.6	(25.3)	32.6	(22.5)	<0.0001
CRP (mg/dl)	1.5	(2.0)	1.1	(1.5)	<0.0001
HAQ score (range: 0–3)	0.986	(0.771)	0.574	(0.653)	<0.0001
J-HAQ score (range: 0–3)	1.039	(0.795)	0.615	(0.684)	<0.0001
DAS28	4.15	(1.36)	3.54	(1.25)	<0.0001
Dose of daily prednisolone (mg)	2.6	(3.1)	1.9	(2.7)	<0.0001
Prednisolone intake (%)	68.5		58.8		<0.0001
NSAID intake (%)	79.3		73.3		<0.0001
DMARD intake (%)	92.7		92.6		0.7765

Pt, patient; VAS, visual analog scale; RF, rheumatoid factor; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; HAQ, Health Assessment Questionnaire; J-HAQ, Japanese version of HAQ; DAS28, Disease Activity Score; NSAID, nonsteroidal anti-inflammatory drug; DMARD, disease-modifying antirheumatic drug

cantly affects the response variable. We can also evaluate the relative contribution of explanatory variables to the response variable by using chi-squared statistics since deviance asymptomatically converges to the chi-squared distribution.

Results

Descriptive statistics

Among the 4930 patients enrolled in this study, 4558 patients (male 774, female 3784) answered at least one question from the screening for depression. For the first question "Over the past 2 weeks, have you felt down, depressed, or hopeless?" 1709 (37.5%, male 264, 34.1%, female 1445, 38.1%) patients answered yes. For the second question "Over the past 2 weeks, have you felt little interest or pleasure in doing things?" 1343 (29.5%; male 228, 29.5%; female 1115, 29.5%) patients answered yes. In all, 1875 patients (41.1%; male 302, 39.0%; female 1575, 41.6%) answered yes to at least one of these questions, and these were categorized as "depressed" RA patients. Table 1 compares the demographic and clinical variables of depressed and nondepressed RA patients. Age, disease duration, and sex were not related to depressed mood, but younger onset of disease was significantly related to depressed mood ($P < 0.05$). Patient's VAS for general health and pain and doctor's VAS for disease activity were significantly worse in depressed patients than in nondepressed patients ($P < 0.0001$). Tender joints count and swollen joints count, HAQ score and J-HAQ score, the level of ESR and CRP, and DAS28 score were significantly worse in depressed patients than in nondepressed patients. The daily dose of prednisolone was higher in depressed patients than in nondepressed patients. The percentage of patients currently taking steroids and NSAIDs was higher in depressed patients than in nondepressed patients. However, the percentage of patients currently receiving DMARDs did not significantly differ between depressed patients and nondepressed patients.

Figure 1 shows the prevalence of depressed mood as a function of the severity of the patient's VAS for general health, pain intensity, and the severity of the doctor's VAS for disease activity. The prevalence of depressed mood progressively increased for each measure as severity worsened. For the patient's VAS for general health, the prevalence of depressed mood was 25.7% in patients with VAS scores 0–2.5, increasing to 44.8% for scores 2.5–5.0, 58.0% for scores 5.0–7.5, and 79.3% for scores 7.5–10. This pattern of relationship between scores and prevalence of depressed mood was detected in all three VAS evaluations. Figure 1 also shows the increased prevalence of depressed mood as a function of HAQ score, J-HAQ score increased and disease activity score DAS28 worsened. Of the 667 patients with a DAS28 over 5.1, who were thought to have high disease activity,[17] 393 patients (58.9%) were categorized as depressed RA patients. This tendency is also seen with ESR but is not apparent with CRP, probably because only a small number of patients had high CRP levels in this study. The subjective variables indicated in VAS clearly reflected more of the depressed mood than the objective variables, such as ESR or CRP.

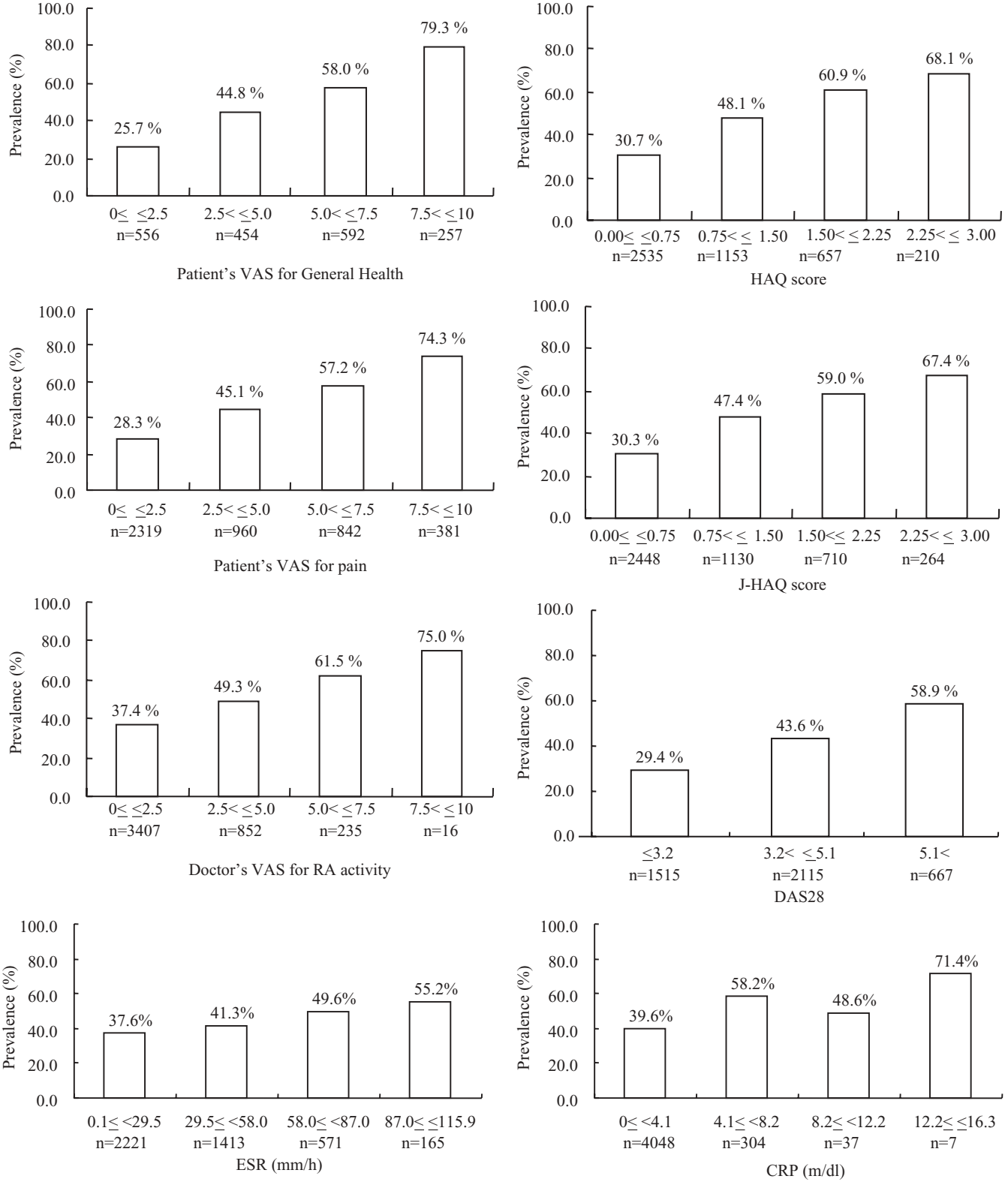

Fig. 1. Prevalence of depressed mood as a function of general health evaluated by the patient, severity of pain, disease activity evaluated by the doctor, Health Assessment Questionnaire (*HAQ*) score, Japanese HAQ (*J-HAQ*) score, Disease Activity Score (*DAS28*), erythrocyte sedimentation rate (*ESR*), and C-reactive protein (*CRP*). The percentage on each *bar* of the graph indicates the prevalence of depressed mood. *VAS*, visual analog scale; *RA*, rheumatoid arthritis

Table 2. Comorbidities and events that occurred in the previous 6 months correlated with depressed mood

	Odds ratio	95% CI	*P*
Comorbidity (3 or more)	2.157	1.475–3.175	<0.0001
Infection	1.754	1.409–2.186	<0.0001
Joint surgery	1.878	1.313–2.696	0.0004
Cancer	2.625	1.025–7.241	0.029
Bone fracture	1.676	1.033–2.730	0.032
Hospitalization	1.537	1.096–2.158	0.011
Unrelated to joint surgery			
Sex	0.899	0.765–1.056	0.200

CI, confidence interval

Table 3. Best associated factors for depressed mood under the generalized linear model

Order of entry	Explanatory variable	Coefficient	Deviance	*P*
1	HAQ	0.385	218.6	<0.0001
2	VAS for patient's GH	0.025	148.9	<0.0001
3	Infection+	0.343	5.0	<0.025
4	Cancer+	1.121	4.0	<0.046
5	Age	–0.014	2.8	0.1
6	Sex (female)	–0.228	0.1	0.8

GH, general health

Factors associated with depressive mood

During the course of RA, patients often have complicating comorbidities such as hypertension, diabetes mellitus, hyperlipidemia, asthma, and emphysema. Medical events such as bone fracture, joint operation, infection, onset of malignancy, and hospitalization may also occur. In this study, we asked patients to report events that occurred in the previous 6 months. We investigated the relationship between such events and depressed moods. Table 2 shows that having three or more comorbidities, infection, and/or joint surgery for RA were significantly correlated with depressed mood. Malignancy, bone fracture, and hospitalization except for joint surgery also showed high odds ratio for depressed moods.

The Generalized Linear Model was used to identify which variables significantly contributed to depressed mood in patients with RA. Since the VAS scores for patient's pain and general health and the VAS scores for doctor's evaluation were closely related to each other, we used patient's VAS for general health as the representative score among these three scores. HAQ score and J-HAQ score were also closely related to each other; we used the HAQ score as the representative score of the two. The explanatory variables included sex, age, disease duration, HAQ score, patient's VAS for general health, the presence of three or more comorbidities, malignancies, joint surgery, hospitalization, bone fracture, infection within 6 months, and current administration of NSAIDs, DMARDs, and steroids. Based on the Akaike's Information Criteria (AIC), we constructed a model comprising the best fit of the data. The relative importance of each of the explanatory variables was evaluated by Analysis of Deviance. Table 3 shows which variables were related to depressed mood. The coefficient column reports the estimated coefficient based on the maximum likelihood method for the Generalized Linear Model. The Deviance column reports the effect of sequentially adding each of these terms to the original model, starting from the null model as a constant model. The *P*-value column gives the tail probability of the chi-squared distribution corresponding to the values in the deviance column. The following valuables were found to significantly contribute to depressed mood, in decreasing order of significance: greater disability (higher HAQ score), worse patient appraisal for general health, infection, and malignancy. The probability of having depressed mood increased with higher HAQ or patient's VAS for general health scores because the deviance of HAQ and patient's VAS for general health were high. Patients who had infections and malignancy in the previous 6 months before this survey also tend to have depressed mood in terms of positivity of coefficient.

Discussion

To investigate depressed mood in patients with RA, we used the simple two-question recommended by the USPSTF 2002 for screening depressed patients.[10] This case-finding two-question screen instrument had been proved to be a useful measurement for detecting depression in primary care by comparing to six previously validated case-finding instruments.[11] The advantage of this screening tool is that it possesses a high sensitivity and the disadvantage is that it has a fair specificity. Given the low negative likelihood ratio (LR) at a titer of 0.07 for detecting major depression,[11] the major clinical value of this tool is to exclude depression[18] rather to detect depression. However, this instrument is reported as a good instrument for screening of depression in Japan[14] and in the United States.[19] Further accurate steps in diagnosing depression by Mini-Mental State Examination, BDI, or Short Form Geriatric Depression Scale (SFGDS) are needed.

Among the 4558 patients with RA in our institute, 41.1% of these patients were identified as "depressed" RA patients. Major depressive disorder is reported to affect between 13% and 42% of patients with RA, i.e., is two to three times more common in patients with RA than in the general population.[2,3] Considering that the specificity of this screening system for depression is 57%,[11] the identification of depressed mood in 41.1% of the RA patients was quite acceptable. Among other connective tissue diseases, patients with systemic sclerosis is reported to have high but almost the same prevalence of depression as in RA.[20,21] Depression in patients with systemic sclerosis

is also reported to be related to disability. Depression associated with pain is also seen in patients with fibromyalgia, although we have not evaluated the diagnostic criteria of fibromyalgia in this cohort. The possibility of coexistence of fibromyalgia would be of great interest for further investigation.

Concerning medical comorbidities and events coexisting or occurred within previous 6 months, coexistence of three or more comorbidities and newly onset infection are closely and significantly associated to depressed mood in our study. Joint surgery, newly onset of malignancy, bone fracture, and hospitalization are also associated factors. As these current cormorbidities and these medical events are all derived from patient's self-reporting, the real severity may not have been calculated objectively and this may attribute to the limitation of this study.

When all variables were taken into account, worse disability and worse patient appraisal for general health were strongly and significantly associated with depressed mood in our large-scale screen for depressed patients in RA. Coexistence of infection and malignancy were also significant but less associated factors of depressed mood; however, age and female sex were not factors. In several previous reports, female sex, present age,[22] younger onset, pain[2] and disability,[23,24] socioeconomic factors,[23,25] social isolation, and economic deprivation[23] are listed as the factors related to depression. There is a disagreement among some reports that some demographic factors are not agreed as associated factors; however, our study clearly demonstrated which factors are associated for depressed mood by using highly qualified large-scale single-institute cohort (IORRA).

The two-question assessment is a simple screening for depression and can easily be done in a daily clinical setting. When a physician suspects depression in a patient, adequate treatment should be carried out. Bird and Broggini reported that paroxetine showed a number of advantages in the management of depression in RA patients.[26] Parker et al. also reported that antidepressant intervention in patients with RA is effective.[27] In addition, Sharpe et al. reported in a blind, randomized, controlled trial that cognitive–behavioral intervention resulted in a significant improvement in joint involvement in patients with recent-onset RA.[28] Therefore, it is important to pay particular attention to patients with recent-onset RA and to examine their answers to the two-question screen to determine whether they are at risk of depression. If so, these patients should be referred to a psychiatrist.

In conclusion, using a large observational cohort of RA patients, we clearly demonstrated a relationship between disability, self-reporting of general health, and depressed mood in Japanese patients. To obtain a better QOL in patients with RA, adequate treatment to RA, both physically and psychologically, need to be provided.

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