of registered patients are collected at 3, 6, and 12 months after initiation of biologic therapy and recorded annually at participating institutes.

Database management

Data are maintained by the TBCR Center (hereafter, the Center) located in the Department of Orthopedic Surgery and Rheumatology at the Nagoya University School of Medicine. In addition, all data regarding registered patients collected at participating institutes are transferred to the Center every July. The Center checks all data and combines them for statistical analysis, which is conducted at the Department of Public Health, Nagoya City University, Graduate School of Medical Science. Access to combined data and its release are controlled by the Center; however, all members of the management committee can access the data. The registry was initially funded by a grant from the Ministry of Health, Labour and Welfare of Japan, "Study for mortality-based optimal management of patients with rheumatoid arthritis in the biologic era" (chaired by Professor H. Yamanaka, Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan).

The registry and study design were approved by the Ethics Committee of Nagoya University, School of Medicine. Patient anonymity was maintained during data collection, and the security of personal information is strictly controlled.

Statistical analysis

To examine baseline characteristics by age and initiation period of biologics, patients who were retrospectively registered were divided into three groups based on age tertiles: the young- ($\leq$53 years, $n = 292$), middle- (>53 to $\leq$64 years, $n = 309$), and old-aged (>64 years, $n = 259$) groups. To examine baseline characteristics by initiation period of biologics, we divided registered patients into four groups based on the year of initiation ($\leq$2005, 2006, 2007, and 2008). Differences among the groups were analyzed with general linear models for continuous variables and the χ^2test for categorical variables. As for the incidence of adverse events, we collected information on adverse events that resulted in the discontinuation of the 1st biologic treatment within 1 year and classified them according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision Version for 2007 (ICD-10). Baseline characteristics for the incidence of adverse events were analyzed using the Cox proportional-hazards regression model. All data were analyzed using SPSS version 19.0 (IBM, Armonk, NY, USA). $P < 0.05$ was considered statistically significant.

Results

A total of 964 patients were identified retrospectively through the established database system at thirteen institutes. After excluding 98 subjects with missing values and 6 patients younger than 17 years of age, the mean age and disease duration $\pm$ SD of the 860 subjects were 56.4 $\pm$ 13.8 and 11.5 $\pm$ 9.8 years, respectively.

Baseline characteristics are summarized by age group in Table 1. Significant differences by age were observed in sex, disease duration, stage of joint damage and class of dysfunction, patient's global assessment score for health, CRP, concomitant use of MTX, and the MTX dose at first administration of biologics. Patients in the young age group were more likely to be female, have shorter disease duration, less severe joint damage, and less dysfunction in daily life, and lower CRP levels. In particular, the proportion of patients with disease duration of <2 years was significantly higher in the young age group. There was no difference in DAS28-CRP by age. The use of MTX as a concomitant drug was more frequent and the dose higher in the young- and middle-aged groups than in the old-aged group.

The most popular of the biologics were etanercept (62.8%) and infliximab (32.0%). The proportion of etanercept as the first prescribed biologic treatment was higher in the young and old age groups than in the middle age group.

Differences in baseline characteristics by initiation year of treatment with biologics are shown in Table 2. Significant differences by initiation year were observed in the stage of joint damage, DAS28-CRP, CRP, concomitant use of PSL, and the PSL dose at first biologic administration. The proportion of etanercept as the 1st prescribed biologic treatment increased until 2007. In 2008, when other new biologics (adalimumab and tocilizumab) became available, the proportion of etanercept decreased while that of infliximab did not change significantly.

Adverse events within 1 year from the initiation of biologics which resulted in discontinuation of the 1st biologic treatment are summarized in Table 3. Notably, 75% of the adverse events that occurred within 1 year from the initiation of biologics occurred within 6 months of their initiation. Diseases of the respiratory system and infection (43.0%) were the main adverse events. Also included in the adverse events were one case (0.11%) of tuberculosis, two cases of *Pneumocystis jiroveci* pneumonia (0.23%), and three cases (0.35%) of nontuberculous mycobacterial infection. From 6 months to 1 year, 63% of the adverse events were categorized as infectious and parasitic diseases and diseases of the respiratory system.

We also examined the factors that influenced the incidence of adverse events (Table 4). Older age (per year) was

Table 1 Differences in baseline patient characteristics by age at initiation of biologics

Variables		Total all ages ($n = 860$)	Young ≤53 ($n = 292$)	Middle >53 to ≤64 ($n = 309$)	Old >64 ($n = 259$)	*P* value
Age (years)		56.4 (13.8)	40.8 (9.4)	59.1 (3.2)	70.9 (4.7)	
Women (%)		82.8	88.7	82.7	76.0	0.001
Disease duration (years)		11.5 (9.8)	9.0 (7.6)	13.0 (10.7)	12.5 (10.5)	<0.001
Disease duration ≤2 years (%)		16.8	22.9	12.0	15.7	0.004
Stage (%)	I	8.2	12.8	5.8	6.1	0.002
	II	14.1	14.6	13.9	13.8	
	III	37.0	41.2	35.6	34.0	
	IV	40.7	31.4	44.7	46.2	
Class (%)	I	15.6	25.9	14.6	5.3	<0.001
	II	46.8	53.3	46.4	40.1	
	III	36.0	20.4	36.9	52.2	
	IV	1.6	0.4	2.0	2.4	
DAS28-CRP		4.98 (1.14)	4.86 (1.18)	5.04 (1.14)	5.04 (1.09)	ns
Patient's global score (mm)		60.5 (21.8)	57.0 (23.6)	61.5 (20.4)	63.5 (21.0)	0.045
CRP (mg/dl)		3.8 (3.2)	3.3 (2.9)	3.9 (3.4)	4.2 (3.3)	0.02
MTX use (%)		74.9	81.9	80.9	59.3	<0.001
MTX dosage (mg/week)		7.2 (1.9)	7.6 (2.0)	7.1 (1.7)	6.7 (1.8)	<0.001
PSL use (%)		82.5	78.8	83.0	86.1	ns
PSL dosage (mg/day)		5.1 (2.3)	5.0 (2.0)	5.1 (2.7)	5.2 (1.9)	ns
Biologics						
Infliximab (%)		32.0	26.0	38.5	30.9	0.025
Etanercept (%)		62.8	68.5	57.0	63.3	
Others (adalimumab, tocilizumab, abatacept) (%)		5.2	5.5	4.5	5.8	

Except where indicated otherwise, values are means (SD). Stage and class were defined using Steinbrocker's classification

DAS28-CRP, Disease activity score in 28 joints (DAS28) based on C-reactive protein (CRP) levels with 4 variables; *MTX*, methotrexate; *PSL*, prednisolone

P values for continuous variables were determined with the general linear model; *P* values for categorical variables were determined with the χ^2test

significantly related to a higher incidence of discontinuation because of adverse events [hazard ratio (HR) = 1.041, 95% confidence interval (CI) 1.006–1.076] while lower level of daily dysfunction (Class I and II) were clearly related to a lower incidence of discontinuation because of adverse events [HR = 0.406, 95% CI 0.193–0.856].

Discussion

We confirmed significant age differences in the baseline characteristics of patients registered with the TBCR retrospectively. Compared to old-aged patients, young-aged patients tended to have started biologic therapy at an early stage of RA and more aggressively with high-dose MTX. We found significant differences in patient characteristics by the initiation year of biologics. The profile of adverse events within 1 year from initiation of biologics and related baseline characteristics were also examined.

Biologics confer good disease control to many patients with RA, but are associated with rare but severe adverse events such as serious infections, lymphoma, or chronic heart failure [4]. Adverse events clearly increase with age. In fact, the British Society for Rheumatology Biologics Register (BSRBR) reported that incidences of severe infection markedly increased with age, although no significant difference was observed in the relative risk of infection in patients undergoing anti-tumor necrosis factor (TNF)-α therapy compared to patients treated with non-biologic disease-modifying anti-rheumatic drugs (DMARDs) among older populations [5]. In the present study, older age had a significant impact on the incidence of adverse events that resulted in the discontinuation of the 1st biologic treatment.

On the other hand, the BSRBR reported that age and disease duration did not predict response to anti-TNF-α therapy, while a better response to this therapy was associated with the concurrent use of nonsteroidal anti-inflammatory drugs (NSAIDs) and MTX in 2,879 patients

Table 2 Differences in baseline patient characteristics by year at initiation of biologics

Variables		≤2005 (n = 193)	2006 (n = 221)	2007 (n = 250)	2008 (n = 196)	P value
Age (years)		57.0 (12.1)	57.4 (13.5)	56.2 (14.1)	55.2 (15.1)	ns
Women (%)		82.0	82.1	82.4	84.7	ns
Disease duration (years)		11.2 (9.0)	12.1 (10.1)	12.2 (10.7)	10.3 (9.1)	ns
Disease duration ≤2 years (%)		22.4	20.8	29.6	27.2	ns
Stage (%)	I	4.4	4.2	10.4	14.0	0.001
	II	9.9	12.6	15.4	18.4	
	III	42.9	39.1	33.3	33.5	
	IV	42.9	44.2	40.8	34.1	
Class (%)	I	11.5	13.5	16.30	21.2	ns
	II	48.4	47.0	48.3	43.0	
	III	38.5	37.2	34.6	34.1	
	IV	1.6	2.3	.8	1.7	
DAS28-CRP		5.4 (1.2)	4.9 (1.2)	4.8 (.9)	4.8 (1.1)	<0.001
Patient's global score (mm)		64.8 (20.0)	61.4 (23.2)	59.8 (21.1)	56.5 (21.9)	ns
CRP (mg/dl)		4.9 (3.3)	3.8 (3.5)	3.4 (2.8)	3.1 (2.9)	<0.001
MTX use (%)		74.4	73.6	74.4	77.5	ns
MTX dosage (mg/week)		7.4 (1.8)	7.2 (1.7)	6.9 (1.9)	7.3 (2.0)	ns
PSL use (%)		91.5	89.3	83.5	67.8	<0.001
PSL dosage (mg/day)		6.2 (3.4)	5.1 (1.7)	4.7 (1.4)	4.4 (1.6)	<0.001
Biologics						
Infliximab (%)		49.2	30.8	25.2	25.0	<0.001
Etanercept (%)		47.7	68.3	74.0	57.1	
Others (adalimumab, tocilizumab, abatacept) (%)		3.1	0.9	0.8	17.9	

Except where indicated otherwise, values are means (SD). Stage and class were defined using Steinbrocker's classification

DAS28-CRP, Disease activity score in 28 joints (DAS28) based on C-reactive protein (CRP) levels with 4 variables; *MTX*, methotrexate; *PSL*, prednisolone

P values for continuous variables were determined with the general linear model; *P* values for categorical variables were determined with the χ^2test

Table 3 Adverse events within 1 year from initiation of biologics

ICD-10 categories	Events within 6 months n (%)	Events within 6 months to 1 year n (%)	Total events within 1 year n (%)
Certain infectious and parasitic diseases	7 (12.3)	4 (21.1)	11 (14.5)
Diseases of the respiratory system	14 (24.6)	8 (42.1)	22 (28.9)
Diseases of the skin and subcutaneous tissue	9 (15.8)	1 (5.3)	10 (13.2)
Diseases of the musculoskeletal system and connective tissue	6 (10.5)	1 (5.3)	7 (9.2)
Injury, poisoning, and certain other consequences of external causes	8 (14.0)	0 (0.0)	8 (10.5)
Diseases of the circulatory system	1 (1.8)	1 (5.3)	2 (2.6)
Neoplasms	3 (5.3)	1 (5.3)	4 (5.3)
Diseases of the genitourinary system	1 (1.8)	2 (10.5)	3 (3.9)
Others	8 (14.0)	1 (5.3)	9 (11.8)
All categories	57 (100.0)	19 (100.0)	76 (100.0)

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision Version for 2007. Infusion reaction is included in the category "Injury, poisoning and certain other consequences of external causes"

with RA [6]. Consistent with this finding, the South Swedish Arthritis Treatment Group Register reported that MTX use was associated with a good response to anti-TNF therapy [7]. In our cohorts, doctors may have been hesitant to aggressively treat older patients, given the fear of adverse side effects, while younger patients could have

Table 4 Factors associated with incidence of adverse events within 1 year from initiation of biologics

Factors	HR	95% CI	*P* value
Age/year	1.041	1.006–1.076	0.019
Disease duration/year	0.990	0.954–1.026	0.571
Stage I and II	1.292	0.535–3.123	0.569
Class I and II	0.406	0.193–0.856	0.018
PSL no use	0.257	0.061–1.083	0.064
MTX no use	0.735	0.310–1.745	0.485

HR was determined using the Cox proportional-hazards regression model. Stage and class were defined using Steinbrocker's classification

CI confidence interval, *MTX* methotrexate, *PSL* prednisolone

been treated more aggressively. However, the results of the British and Swedish studies suggest that these older patients potentially could have been brought to remission without initiating aggressive treatments by using biologics and concomitant MTX at an early stage. Based on accumulated evidence, the European League Against Rheumatism (EULAR) published recommendations in 2010 for the management of RA with synthetic and biological DMARDs, stating that the aim of treatment should be achieving remission or low disease activity as soon as possible in every patient [8, 9]. Further careful observation will be needed to determine the safety and efficacy of aggressive therapy in older patients.

Biologics have been available in Japan since 2003, which is later than their introduction in North America and Europe. Moreover, in Japan, the MTX dose for RA treatment has been much lower than the doses used in North America and Europe, because the approved upper limit was 8 mg/week. The mean dose of MTX in the present study was 7.2 mg/week, which is comparable to that in the PMS studies of infliximab (mean 7.3 mg/week) [1] and etanercept (mean 6.58 mg/week) [2]. In response to frequent and persistent requests by rheumatologists and RA patients, the Japanese government raised the upper dose limit of MTX to 16 mg/week in January 2011. As such, ongoing Japanese cohort data with RA patients will provide valuable information on various treatment courses and disease states.

Wolfe et al. [10] reported that the administration of PSL in RA treatment had a significant impact on the incidence of serious pneumonia (i.e., pneumonia that required hospitalization). We did not find a significant relationship between the concomitant use of PSL with biologics and the incidence of adverse events, although there was trend (*P* value = 0.064). In this analysis, the number of cases for determining the incidence of adverse events was small and the observation period was limited. Further studies with longer follow-up periods are needed.

To date, three observational cohort studies have been established in Japan: Institute of Rheumatology Rheumatoid Arthritis (IORRA) (since 2000) [11], NinJa (National Database of Rheumatic Diseases by iR-net in Japan; http://www.ninja-ra.jp) (since 2002) [12], and REAL (the Registry of Japanese Rheumatoid Arthritis Patients on Biologics for Long-term Safety; http://www.real-study.jp) (since 2005) [13]. Compared with these cohorts, the TBCR is unique in that it includes a variety of participating institutes, spanning a single university hospital, a national medical center, urban county hospitals, and clinics throughout Japan. Thus, the TBCR more accurately reflects the clinical setting with regard to patients with RA in Japan. However, members of the TBCR study group are orthopedic surgeons, which represents a unique situation for RA treatment. Thus, there is the possibility of selection bias for treatments, although the baseline patient characteristics and incidence of adverse events in our registry are comparable to those of the PMS study of infliximab and etanercept in Japan.

The TBCR is in its initial stages, and information on all patients newly starting biologic therapy at the participating institutes is being collected prospectively. Drug-related survival and long-term prognosis based on follow-up data will be reported in the near future.

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Young Investigator Award Winner's Special Article

Epidemiologic Studies of Psychosocial Factors Associated With Quality of Life Among Patients With Chronic Diseases in Japan

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ABSTRACT

A link between affective disturbances and physical disorders has been suggested since the Greco–Roman era. However, evidence supporting an association between mind and body is limited and mostly comes from North America and Europe. Additional local epidemiologic studies are needed so that more evidence can be collected on effective treatments and health management. Epidemiologic studies of Japanese with rheumatoid arthritis (RA) and those on chronic hemodialysis examined the association between psychosocial factors and patient quality of life (QOL). Strong associations among depression, social support, and patient QOL were confirmed, which supports the findings of studies performed in Western countries. In addition, disparities between the perspectives of patients with RA and their doctors were observed. Alexithymia, a personality construct that reflects a deficit in the cognitive processing of emotion, had a stronger independent association with increased risk of 5-year mortality than did depression among patients with chronic hemodialysis. Physiological, biological, and psychosocial factors are associated and independently and interactively determine our health. Epidemiology is a powerful tool for identifying effective points of intervention, after considering all possible confounders. Future studies must clarify how health can be improved by using a psychosocial approach.

Key words: depression; alexithymia; risk factors; hemodialysis; rheumatoid arthritis

NO HEALTH WITHOUT MENTAL HEALTH

The World Health Organization (WHO) defines health as "a complete state of physical, mental, and social well-being and not merely the absence of disease or infirmity".[1] Thus, health fundamentally consists of physical, psychological, and social factors. Links among affective disturbances, social factors, and physical disorders have been observed since the Greco–Roman era, and a 1990 editorial in *JAMA* maintained that the notion "that the brain can exert profound effects on the body" was "by no means a new idea".[2] Engel, a Nobel Prize-winning internist and psychiatrist, claimed that the development of chemistry and the physical sciences created a dominant biomedical model of disease that separated the mental and somatic aspects of disease, leaving no room within its framework for the social, psychological, and behavioral dimensions of illness.[3] He proposed a biopsychosocial model to provide a design for action in "the real world" of health care. Recent advances in neurosciences, including brain imaging, have revealed a close link between psychological perception and physical responses.[4] Moreover, the shift in the primary cause of death from infectious diseases to noncommunicable chronic diseases, such as heart disease, diabetes, and cancers, has strengthened the importance of a psychosocial approach to health management. The Global Health Risk Report by the WHO concluded that the most important global risks for mortality in the world are high blood pressure, tobacco use, high blood glucose, physical inactivity, and overweight and obesity.[5] The biological approach has a limited capacity to reduce these health risks. Attending to the mind and individual social background is essential in the treatment of noncommunicable chronic diseases.[4]

The WHO now maintains that there is "no health without mental health".[6] The contribution of mental health disorders to disease burden has been increasing worldwide.[6] According to the 2005 report of the WHO, 31.7% of all years lived with disability were attributed to neuropsychiatric conditions, among which depression was the leading cause.[7] However, the association between mental disorders and disability remains underestimated.[6] Affective disturbances can undermine long-term outcomes of physical disorders via behavioral and cognitive processes with specific and nonspecific

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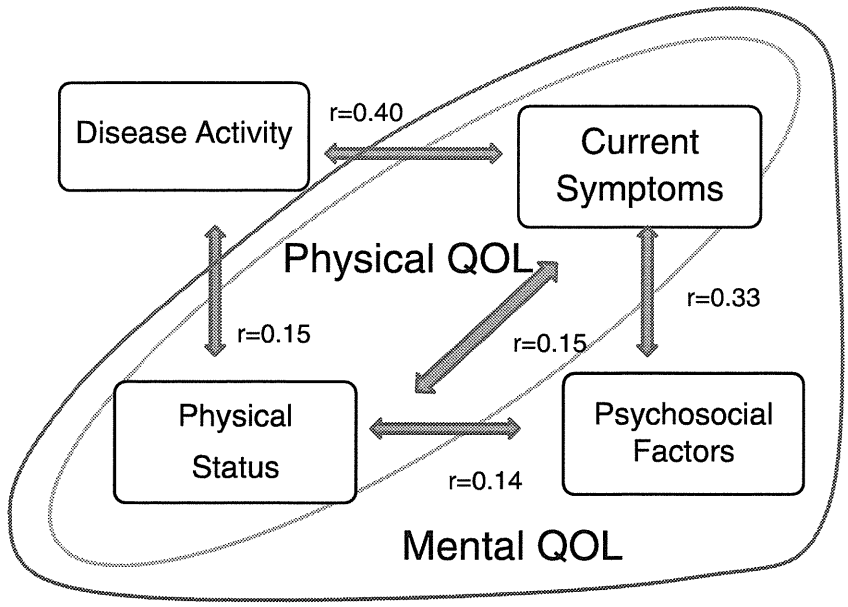

Figure 1. Interrelationships between psychosocial factors, disease activity, current symptoms, and physical status. The figure is based on the results of factor analysis of clinical and psychosocial data from 120 patients with rheumatoid arthritis. (Kojima M et al. J Psychosom Res. 2009;67(5):425–31. 2009, Elsevier Science Inc.)

biological responses.[8] Conversely, physical disorders increase the developmental and prognostic risk of mental disorders. Thus, comorbidity complicates health problems and increases the difficulties of individual patients.

Although an association between mental and physical health disorders has been strongly suggested, most of the available evidence for this association has come from North America and Europe, and investigations assessing the prognostic effects of mental illness on health outcomes are rare.[6] Psychosocial factors are potentially subject to ethnic, cultural, geographic, and economic factors. Moreover, health care and social systems vary by country. Additional local epidemiologic studies and international collaborative studies are needed to ensure effective integration of health care worldwide.

A series of epidemiologic studies of Japanese with rheumatoid arthritis (RA)[9,10] and those on chronic hemodialysis[11–13] examined the association between psychosocial factors and patient quality of life (QOL). The designs and major findings of these studies are summarized below.

EPIDEMIOLOGIC STUDY OF PATIENTS WITH RHEUMATOID ARTHRITIS

RA is a chronic disease that causes inflammation of the joints and surrounding tissues. It is believed to be an autoimmune disorder; however, its etiology is not fully understood. Patients with RA have pain, stiffness, swelling, and destruction of the joints. Those with severe chronic disorders accompanied by pain, disability, and disfigurement have a higher risk of emotional disturbances[8]; therefore, it is not surprising that patients with RA are twice as likely as the general population to be depressed.[14] Thus, the QOL of patients with RA is complicated with regard to the link between psychosocial and biological factors.

Study design

We performed a cross-sectional epidemiologic study of the interrelationships between the psychosocial and physiological factors that determine the disease status of people with RA.[9,10]

In total, 213 patients (mean age, 60 years; range, 18–85 years) completed a series of health examinations and questionnaires. Disease severity, functional disability, counts of swollen and/or tender joints, duration of RA, frequency of arthritis surgery, and C-reactive protein (CRP) levels were assessed by rheumatologists. Self-report inventories completed by the patients were used to assess the perceived degree of pain and fatigue (visual analog scales), depression (Beck Depression Inventory-II[15,16]), anxiety (Hospital Anxiety and Depression Scale[17]), and social support (Social Support Questionnaire[18,19]). Mental and physical components of health-related QOL were evaluated using the Short Form-36 Health Survey.[20–23]

Major findings

Principal axis factor analysis revealed a 4-factor structure in which the components reflected psychosocial factors, disease activity, current symptoms, and physical functional status. Disease activity was independent of psychosocial factors and failed to reflect the perceived physical or mental QOL of patients with RA[10] (Figure 1).

The associations among depression, pain, and inflammation were analyzed by multivariate analysis. Inflammation severity

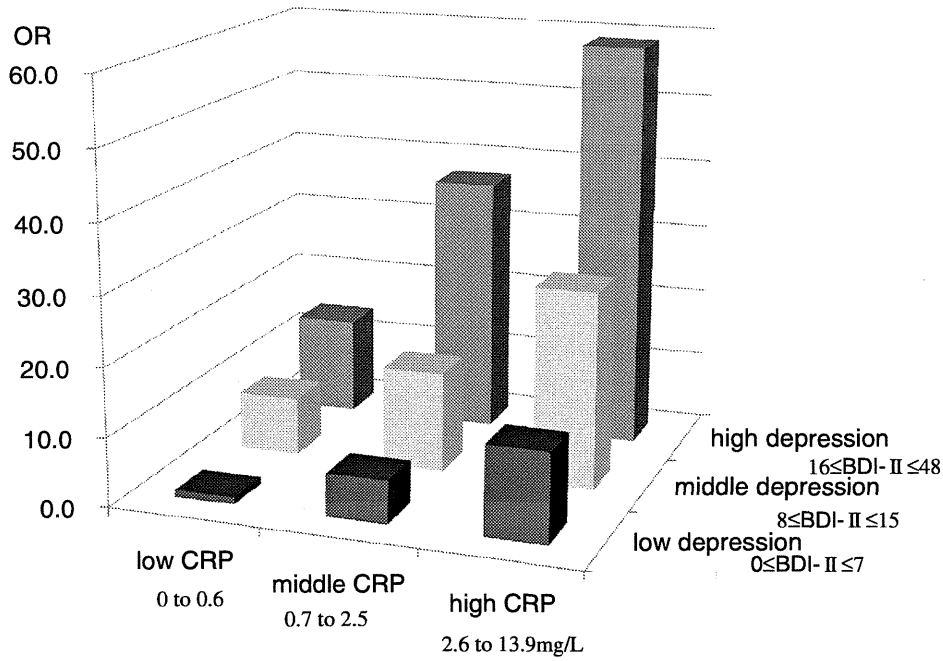

Figure 2. Impacts of depression and CRP on severe pain by tertiles of BDI-II score and CRP level. Using patients with a low BDI-II score and low CRP as the reference group, the odds ratios (ORs) for the presence of severe pain increased linearly with BDI-II score and CRP. (Kojima M et al. Arthritis Rheum. 2009;61:1018–24. 2009, American College of Rheumatology)

was evaluated by measuring the CRP level. Both depression score (standardized $\beta = 0.35$, $P < 0.001$) and CRP level (standardized $\beta = 0.35$, $P < 0.001$) were significantly associated with pain, even after adjusting for clinical covariates in the regression analysis. In logistic analysis, the combined effects on the risk of severe pain (pain score in the highest tertile) increased linearly with depression score and CRP level. Depression severity and inflammation were associated and appeared to have independent effects on perceived pain[9] (Figure 2).

Clinicians should therefore evaluate psychosocial factors and subjective disease status to improve the QOL of patients with RA. A clinical approach that considers both the body and mind might be needed in order to achieve optimal pain control.

EPIDEMIOLOGIC STUDY OF PATIENTS ON CHRONIC HEMODIALYSIS

Patients on chronic hemodialysis are at a high risk for emotional disturbances because of the burden due to illness, time constraints, diet restrictions, functional limitations, changes in self-perception, and fear of death. A positive association between depression and mortality has been reported in a population of such patients.[24] Alexithymia is a personality construct that reflects a deficit in the cognitive processing of emotion.[25] Alexithymic individuals tend to have difficulty identifying and describing their inner feelings, rarely fantasize, and have a utilitarian style of thinking. Alexithymia appears to be associated with various mental and physical health problems and to interfere with treatment compliance and treatment outcomes in clinical settings.[26] A study of a large cohort of the Finnish general population reported that alexithymic men had a 2-fold risk for all-cause death ($P < 0.001$).[27] However, it is not known if alexithymia is associated with other psychosocial factors and whether it influences long-term prognosis in patients on chronic hemodialysis.

Study design

We hypothesized that depression and alexithymia would be independently associated with increased 5-year mortality among patients on chronic hemodialysis. We collected extensive psychosocial and clinical data at baseline to adjust for the influence of possible confounding factors.[11–13]

In total, 230 outpatients on hemodialysis (mean age, 56 years; range, 23–71 years) completed a battery of self-report measures, including the Beck Depression Inventory-II (BDI-II),[15,16] 20-item Toronto Alexithymia Scale (TAS-20),[28,29] Social Support Questionnaire,[18,19] and Short Form-36 Health Survey.[20–23] Laboratory data, including a 24-hour electrocardiogram, were also collected at baseline. Survival status was confirmed every 6 months for up to 5 years.

Major findings

Baseline depression was significantly and independently associated with alexithymia ($P = 0.004$), and low satisfaction was associated with available social support ($P = 0.01$). Worsening of depressive symptoms after 6 months was

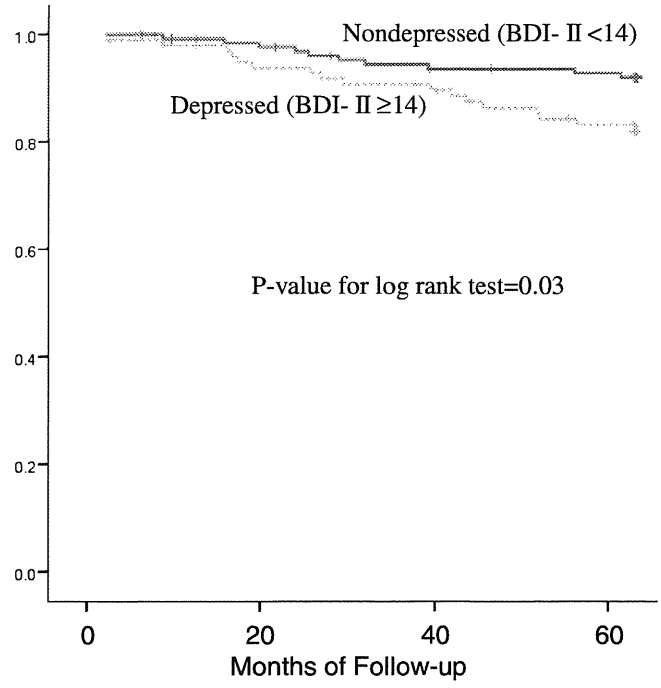

Figure 3. Kaplan-Meier survival curves by depression status. All-cause death-free survival by dichotomized level of BDI-II score in hemodialysis patients. (Kojima M et al. Psychother Psychosom. 2010;79:303–11. 2010, S. Karger AG, Basel)

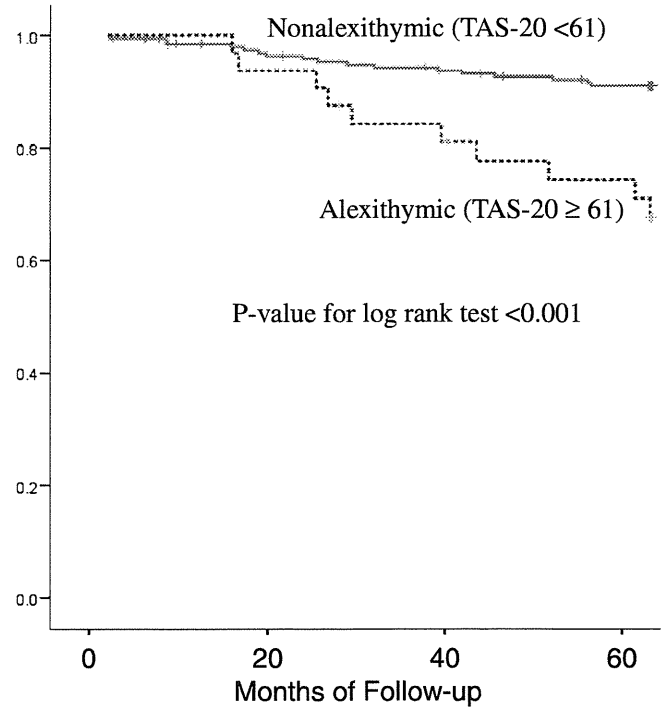

Figure 4. Kaplan-Meier survival curves by alexithymia status. All-cause death-free survival by dichotomized level of TAS-20 score in hemodialysis patients. (Kojima M et al. Psychother Psychosom. 2010;79:303–11. 2010, S. Karger AG, Basel)

Table. Multivariate adjusted hazard ratios (HRs) for 5-year mortality associated with alexithymia and depression among 230 hemodialyzed patients

	Variables in model	Alexithymia TAS-20 ≥61			Depression BDI-II ≥14			Change from previous step		
		HR[a]	95% CI	*P* value	HR[b]	95% CI	*P* value	χ^2	*df*[c]	*P* value
Model 1	Alexithymia, depression, age, and sex	3.54	1.55–8.11	0.003	1.75	0.77–3.99	0.18			
Model 2	Model 1 + PCS[d] and MCS[e] scores	3.64	1.48–8.96	0.005	2.13	0.86–5.23	0.10	7.86	2	0.02
Model 3	Model 2 + covariates[f]	3.62	1.32–9.93	0.012	1.70	0.64–4.48	0.29	15.90	6	0.01

[a]Hazard ratio shows increased mortality risk associated with presence of alexithymia (TAS-20 ≥61); [b]Hazard ratio shows increased mortality risk associated with presence of depression (BDI-II ≥14); [c]Degrees of freedom; [d]Physical component summary score of SF-36; [e]Mental component summary score of SF-36; [f]Variables included in Model 3 as covariates were education ≥12 years, interdialytic weight gain, having comorbidity, hematoclit, calcium, and diastolic blood pressure. (Adapted from Kojima et al, "Depression, alexithymia and long-term mortality in chronic hemodialysis patients", Psychotherapy and Psychosomatics 2010;79:303–11 2010 S. Karger AG, Basel.)

predicted by alexithymia (adjusted odds ratio [OR], 2.6; 95% confidence interval [CI], 1.1–5.9) and social support (adjusted OR, 2.1; 95% CI, 1.0–4.4).[11]

Analysis of heart rate variability (HRV) and dynamics with the help of the 24-hour electrocardiogram ($n = 119$) revealed a clear association of depression with reduced HRV and loss of fractal HR dynamics.[12]

Baseline depression and alexithymia were associated with an increased risk for all-cause 5-year mortality (Figures 3 and 4). However, only the association with alexithymia remained statistically significant after adjusting for baseline depression, health status (the SF-36 summary scores), marital status, and clinical covariates (multivariate adjusted hazard ratio, 3.62; 95% CI, 1.32–9.93; $P = 0.01$).[13]

Thus, depression, social support, and alexithymia were strongly associated and determined the QOL of patients on chronic hemodialysis (Table).

Conclusion and future implications

Physiological, biological, and psychosocial factors are associated and determine our health independently and interactively. Epidemiology is a powerful tool for identifying effective points of intervention, after considering all possible confounders. Additional prospective studies are needed to

identify variables that might be changed by intervention. We urgently need to develop effective psychosocial educational programs that improve the patient–doctor relationship and treatment outcomes and promote the health of the general population. Future studies are likely to clarify how we can improve our health by using a psychosocial approach.

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Conflicts of interest: None declared.

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Patellar Fracture After Total Knee Arthroplasty for Rheumatoid Arthritis

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Abstract: Patellar fracture is one of the most challenging complications of total knee arthroplasty, but relatively, little is known about it in patients with rheumatoid arthritis. We retrospectively analyzed 329 total knee arthroplasties performed in 230 female patients with rheumatoid arthritis to identify the incidence and risk factors for postoperative patellar fractures. The mean age was 61.8 years, and the mean follow-up period was 6.2 years. Patellar resurfacing was performed in all cases. Five postoperative patellar fractures (1.51%) were identified, and a thin residual patellar thickness and the use of posterior-stabilizing components were identified as significant risk factors, although the number of fractures was small in both groups. There was also tendency of higher age and greater joint line change observed in patients with fracture compared with those without fracture. **Keywords:** patellar fracture, total knee arthroplasty, rheumatoid arthritis, postoperative complication, risk factor.

Total knee arthroplasty (TKA) is an effective treatment option relieving arthritic pain and restoring the function and activity of daily living in patients with osteoarthritis (OA) and rheumatoid arthritis (RA). Although patellar resurfacing is a common surgical procedure in TKA, it is sometimes associated with complications such as fracture, subluxation, component loosening, and patellar clunk syndrome. Patellar fractures are rare but also comprise one of the most challenging complications of TKA. Previous reports have provided valuable information concerning the prevalence and risk factors for postoperative patellar fractures. However, most of the studies have focused on patients with OA, and only a few studies analyzed patients with RA [1-3]. In the present study, we examined the incidence of patellar fractures in female patients with RA after TKA with patellar resurfacing, and analyzed the risk factors. We also discuss the treatment strategy and the outcome in these fracture cases.

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Materials and Methods

This is a retrospective study and was approved by the research ethics committee of our hospital. Three hundred twenty-nine TKAs, which had been performed in 230 female patients with RA between 1992 and 2009 at one hospital, were retrospectively analyzed. Patients with less than 1 year of follow-up or with infection were excluded. Surgeries were performed by 4 orthopedic surgeons. The mean age at the time of surgery was 61.8 years (range, 30-85 years), and the mean follow-up period after TKA was 6.2 years. One hundred twenty of the implants were NexGen (Zimmer, Warsaw, IN), 105 were Scorpio (Stryker), 61 were AGC (Biomet, Warsaw, IN), 42 were Maxim (Biomet), and 1 was Miller-Galante (Zimmer). Three hundred six cruciate-retaining (CR) prostheses and 23 posterior-stabilizing (PS) prostheses were used. Patellar resurfacing was performed in all cases, and all of the components were cemented.

The Insall-Salvati ratio was calculated by dividing the patellar length by the patellar tendon length, as seen in the postoperative lateral radiographs taken with a measure. The change in the vertical level of the femorotibial joint line (joint line change) was measured by comparing the preoperative and postoperative lateral radiographs as previously reported [4]. In brief, preoperative joint line represents the distance from the tibia tubercle to the tibia plateau, and postoperative joint line is measured from the tibia tubercle to the weight-bearing surface of the tibial prosthesis. Residual bone thickness of the patella (patellar thickness) was measured from outer surface to the bone-cut line in the

Table 1. Patients with Patellar Fracture After TKA

Case	Age (y)	Time to Fracture (mo)	Trauma	Fracture Type	Implant
1	67	26	Yes	II	NexGen CR
2	64	1	No	II	NexGen CR
3	69	8	No	II	Scorpio PS
4	77	2	No	II	Scorpio PS
5	68	60	No	III	Miller-Galante PS

postoperative radiographs. The data on the lateral retinacular release (ie, performed or not) were collected from the surgical records.

For the assessment of risk factors associated with patellar fractures, the baseline characteristics, intraoperative factors, and radiographic parameters were compared between patients with and without patellar fracture, using the χ^2 test for the categorical variables and nonpaired *t* tests for numerical variables. Univariate logistic regression models were used to test the association between patellar fracture and risk factors. Then, the receiver operating characteristic curves were used to determine the optimal cutoff values.

Multivariable models were used to adjust for age and confounding factors. All analyses used a 2-sided type I error rate of 0.05 as the threshold for statistical significance and were performed with the use of JMP software (version 8.0; SAS Institute, Cary, NC).

Results

Five postoperative patellar fractures (1.51%) were identified during the observation period (Table 1). The mean age of these patients was 69.0 years (range, 64-77 years) at the time of TKA. Three fractures were identified within a year of the surgery. Of the 5 fractures, 4 occurred without any traumatic episode, and 2 of them were unexpectedly diagnosed by routine radiographic assessment. Four fractures were classified as type II in the Ortiguera and Berry Classification system, and the other was type III. Three components were the PS type, and the other 2 were the CR type.

Table 2. Characteristics of Participants

Characteristic	Fracture (−)		Fracture (+)		*P*
Participants	324		5		
Age (y)	61.7	(10.8)	69.0	(4.8)	.13
Insall-Salvati ratio	0.98	(0.15)	1.1	(0.15)	.29
Joint line change (mm)	7.8	(4.3)	10.8	(1.9)	.13
Patellar thickness (mm)	12.2	(1.6)	10.4	(1.8)	.01
Lateral release	158	(48.8%)	2	(40.0%)	.7
Implant					
PS	20	(6.2%)	3	(60.0%)	<.001
CR	304	(93.8%)	2	(40.0%)	

Data are expressed as mean (SD) or number of patients (%).

For the assessment of factors associated with patellar fracture, the baseline characteristics, intraoperative factors, and radiographic parameters were compared between the patients with and without a patellar fracture (Table 2). Patellar thickness was significantly lower in the group with than without fracture (mean, 10.4 vs 12.2 mm; $P = .01$), and the proportion with PS was significantly higher in the group with fracture ($P < .001$). Using the receiver operating characteristic curve, we determined that the cutoff point for the patellar thickness was 11 mm (area under the curve, 0.78; sensitivity, 80.0%; specificity, 67.9%). There was tendency of higher age (mean, 69.0 vs 61.7 years; $P = .13$) and greater joint line change (mean, 10.8 vs 7.8 mm; $P = .13$) in the fracture group. There was no tendency that 1 specific surgeon used specific type of prosthesis nor had higher prevalence of patellar fracture.

We constructed a multivariate logistic regression model to examine the correlation of the incidence of patellar fracture with patellar thickness and the use of PS components after adjusting for age and found that both patellar thickness and the use of the PS prosthesis were positively associated with the incidence of patellar fracture (Table 3).

We then reviewed the outcome of the fracture cases (Table 4). One type III fracture case was treated surgically by retrieving the patellar component, and the others were treated conservatively by applying knee braces for 2 to 3 weeks. No surgical procedures were performed in these cases. At the time of the latest follow-up, bone union was not observed in any of the cases, but all 5 patients reported that they had no pain and were ambulant; 2 of them used canes, and 3 did not. Extensor lag was less than 10° in all of the cases.

Discussion

Total knee arthroplasty with patellar resurfacing is generally favored in patients with RA [5-8], but we must be aware of the risk of postoperative patellar fracture. The reported prevalence of patellar fracture after TKA with patellar resurfacing ranges from 0.12% to 3.9%, which is higher than TKA without patellar resurfacing [3,9-12]. Little is known about patients with RA, but Grace and Sim [3] reported the incidence was 0.12% in patients with RA and 0.18% in patients with OA, with no significant difference between them. Scott et al [11] reported the incidence of postoperative patellar fracture

Table 3. Multivariate Logistic Regression Analysis for Odds Ratio and 95% Confidence Interval of the Risk Factors for Patellar Fracture

	Odds Ratio for Pain	95% CI	*P*
Implant: PS (vs CR)	30.30	3.85-311.68	.002
Patellar thickness	1.60	1.00-2.89	.049

Data were calculated by logistic regression analysis after adjustment for age and confounding. Abbreviation: CI, confidence interval.

Table 4. Treatment and Outcome in Each Fracture Case

Case	Treatment	Follow-Up (y)	Range of Motion (°)		Extensor Lag (°)	Bone Union	Pain	Walking Aid
			Before fracture	After fracture				
1	Knee brace	4	0-95	0-120	0	No	None	None
2	Knee brace	6	0-90	0-110	0	No	None	None
3	Knee brace	4	0-95	10-100	10	No	None	Cane
4	Knee brace	6	0-110	5-125	5	No	None	Cane
5	Patellar implant retrieval	10	0-90	0-90	0	No	None	None

to be 0.7% in patients with RA and 3.5% in patients with OA, suggesting a lower fracture risk in patients with RA. In our series, the prevalence of patellar fracture after TKA in female patients with RA was 1.5% (5/329 knees), which was within the range of the reported prevalence among the combined groups of patients with OA and RA.

Previous studies have reported risk factors for patellar fracture after TKA [13-15]. These include patient factors (RA, male sex, and osteoporosis), technical factors (excessive resection of patellar bone, lateral retinacular release, and revision surgery), and implant factors (PS type prosthesis, central peg, and cementless fixation). In the current study limiting the subjects to female RA patients with primary TKA, thinner postoperative patellar thickness and the use of a PS type of prosthesis were independently and significantly associated with patellar fracture. In addition, 4 (80%) of 5 fracture cases in our series occurred without a traumatic event. These findings imply that the increased patellofemoral contact stress, which results from using the PS type of prosthesis, and the reduced mechanical strength of the patella due to an excessive resection of the bone lead to stress fracture of the patella. However, we have to consider that there still have been an error of measurement using radiographs and that PS component could be preferred for patients with relatively severe deformity, which might have affected our result. In addition, it is possible that the higher frequency of patellar fractures in PS type of prosthesis is specific for the Japanese patients with a relatively wide intercondylar notch relative to the medial-lateral width of the femur.

In addition to these factors, there was a tendency of higher age and joint line change in the group with fracture. Excessive joint line change may exert an effect on the tibial-patellofemoral mechanical axis and increase the stress on the patella, as in the report by Figgie et al [4], where they found that an excessive joint line change (>8 mm) in TKA was associated with poor clinical results.

Ortiguera and Berry [10] proposed a classification system for postoperative patellar fracture. Using this system, in our series, 4 fractures (80%) were type II (implant intact/extensor mechanism disrupted), and 1 was type III (implant loose). In previous reports, type II fractures were relatively rare (15%-22%) [9,10,16], which is different from our cases. Therefore, our findings might reflect a special characteristic of female patients with RA.

The choice of treatment strategy for patellar fractures after TKA is controversial, but previous reports have tended to favor conservative treatment because of the considerable possibility of nonunion and infection after operative treatment [9,10,16,17]. Chalidis et al [17], in a systematic review, indicated that the mean nonunion rate after internal fixation with a tension-band technique or cerclage wire was 92%, with poor results in most cases. We treated 4 type II fractures nonoperatively with a knee brace for 2 to 3 weeks, and 1 type III fracture was treated operatively by retrieving the patellar component. Bone union was not observed in any case, yet all of these patients were ambulant, without reported pain, and exhibited only limited extensor lag (<10°) at the time of the last follow-up. Our clinical experience supports nonoperative treatment option.

In summary, we have described the prevalence, risk factors, and outcome of patellar fractures after primary TKA with patellar resurfacing in female patients with RA. Our analysis suggests that the residual bony thickness of the patella should not be less than 11 mm and that PS-type prostheses should be avoided if possible, especially in patients with a thin patella. In the event that a fracture does occur, conservative treatment seems a favorable choice.

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ORIGINAL ARTICLE

Analysis of the affected joints in rheumatoid arthritis patients in a large Japanese cohort

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Abstract
Objective Rheumatoid arthritis (RA) is a chronic inflammatory disorder involving multiple joints. We investigated the distribution of the affected joints and the relationships among this distribution, the disease activity, and the disease duration in Japanese RA patients by cross-sectional analysis using the National Database of Rheumatic Diseases by iR-net in Japan.
Materials and methods A total of 6408 RA patients registered in the database were analyzed. In each patient, the location of joint swelling and joint tenderness of 68 joints was examined, and the relationships among the distribution of the affected joints, the disease activity as determined using the DAS28-ESR, and the disease duration were analyzed statistically.
Results For the 6408 RA patients examined, the wrist was the most frequently affected site. There were some differences in the prevalence of tenderness and swelling; tenderness was frequently observed in large joints such as the knee, elbow and shoulder, while swelling was frequently observed in small joints such as the metacarpophalangeal joints. Although the frequency of involvement increased in all joints as disease activity increased, the pattern of distribution was not affected by disease activity. Furthermore, the distribution was not influenced by disease duration.
Conclusions Based on the results of this study, we can draw the following conclusions: (1) the wrist was the most affected joint; (2) there was a discrepancy between the distribution of swollen joints and that of tender joints; and (3) the distribution of affected joints was uniform regardless of disease activity.

Keywords Cohort · Distribution · Rheumatoid arthritis · Swelling · Tenderness

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Introduction

Rheumatoid arthritis (RA) is an inflammatory disorder involving multiple joints [1, 2]. Persistent synovitis leads to massive joint destruction, and eventually causes irreversible disability in patients. Recently, there has been remarkable progress in the pharmacological treatment of RA, and the present treatment goal is the remission of the disease and the amelioration of the quality of life of patients [3–5].

The degree of disability of RA patients is greatly affected by the distribution and severity of destruction of the affected joints [6]. In particular, large joint destruction in RA markedly compromises the activities of daily living and the quality of life of patients. Drossaers-Bakker et al. [7] reported that large joint damage accounted for 16 % of

the variation in Health Assessment Questionnaire (HAQ) scores, whereas small joint damage accounted for only 3 %. However, there is little information regarding the relationships among the distribution of the affected joints in RA patients, disease activity, and disease duration.

Therefore, we determined the overall frequency of joint involvement and the distribution of affected joints, as well as the relationships among the distribution of affected joints, disease activity, and disease duration of RA, using a large-cohort cross-sectional analysis of the National Database of Rheumatic Diseases by iR-net in Japan (NinJa) [8, 9].

Materials and methods

Patients

The data source employed in this study was a nationwide multicenter observational cohort database of rheumatic diseases established in 2002 in Japan, referred to as NinJa. The collected data consist of two components: (1) patient information over the course of the 1-year investigation period [e.g., outcome, death, hospitalization, operation, number of total joint arthroplasties in large joints (hip, knee, shoulder and elbow), malignancy and tuberculosis]; (2) information collected on an arbitrary day in daily clinical practice [e.g., the count of tender joints and swollen joints, responses to a modified HAQ, Steinbrocker's functional classification (class), patient global and pain visual analog scales (VAS), doctor VAS, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, disease activity score ((DAS)28-ESR), DAS28-CRP, and the use of corticosteroids, disease-modifying antirheumatic drugs and nonsteroidal anti-inflammatory drugs].

A total of 6408 RA patients registered in the NinJa database in the fiscal year 2008 were analyzed. Before enrollment, written informed consent was obtained from each patient. We investigated the location of joint swelling and joint tenderness in 68 joints and the relationships among the distribution of affected joints, disease activity as determined using the DAS28-ESR, and disease duration.

Statistical analysis

All statistical comparisons were made using a nonparametric test. Involved joints were compared according to the area of occurrence to calculate the prevalence of swelling and tenderness for each joint. The Pearson product–moment correlation coefficient between disease activity and the total number of involved joints in each individual was also calculated. The scale distribution of involved joints (large or small) was compared by the chi-square test among the groups classified according to disease activity. Statistical analysis was performed using the PASW Statistics 18 software package (IBM, Armonk, NY, USA), with the significance level set at 0.05.

Table 1 Characteristics of the study population

Patient characteristics ($N = 6408$)	Statistical data
Age (years)	62.7 ± 12.6 (6–95)
Disease duration (years)	13.6 ± 11.0 (0–62)
ESR (mm/1st hour)	33 ± 23 (0–99)
CRP (mg/dl)	0.9 ± 1.50 (0–14.2)
DAS28-ESR	3.7 ± 1.30 (0.07–8.20)
MHAQ	0.6 ± 0.69 (0–3.0)
Prednisolone equivalent dose (mg/day)	4.5 ± 2.48 (0–30)

Table 2 List of drugs and the number of patients prescribed

Drug	*N* (%)	Drug	*N* (%)
DMARDs	5557 (86.7)	Biologics	882 (13.8)
Methotrexate	3283 (51.2)	Etanercept	425 (6.6)
Salazosulfapyridine	1119 (17.5)	Infliximab	231 (3.6)
Bucillamine	1057 (16.5)	Tocilizumab	130 (2.0)
Tacrolimus	402 (6.3)	Adalimumab	66 (1.0)
Sodium aurothiomalate	230 (3.6)	Abatacept	18 (0.3)
Leflunomide	83 (1.3)	Others	12 (0.2)
Auranofin	70 (1.0)	NSAIDs	3423 (53.4)
Actarit	69 (1.0)	Corticosteroids	3624 (56.6)
Mizoribine	65 (1.0)		
D-Penicillamine	49 (0.8)		
Cyclosporin	14 (0.2)		
Cyclophosphamide	6 (0.1)		

Table 3 Order of frequency of joint swelling and tenderness

Swelling	% of patients affected	Tenderness	% of patients affected
Wrist	21.4	Wrist	24.5
MCP2	13.7	Knee	15.5
MCP3	11.1	Elbow	15.3
Ankle	9.3	Ankle	13.8
Knee	8.9	Shoulder	12.3
PIP3 (hand)	8.5	MCP2	9.2
Elbow	8.4	PIP3 (hand)	7.8
MCP1	5.7	MCP3	7.5
PIP2 (hand)	5.4	MCP1	7.5
MCP4	5.2	MTP3	6.8

Results

Patients

Of the 6408 patients enrolled in the study, 5255 (82.0 %) were women. Table 1 shows the characteristics of all the patients. The mean age [standard deviation (SD)] of all the patients was 62.7 (12.6) years (range 6–95 years), and the mean disease duration was 13.6 (11.0) years (range 0–62 years). Of these 6408 patients, 882 patients (13.8 %) were treated with biologics, 5557 patients (86.7 %) with disease-modifying antirheumatic drugs, 3624 patients (56.6 %) with corticosteroids, and 3423 patients (53.4 %) with nonsteroidal anti-inflammatory drugs, as shown in Table 2.

Table 4 Order of frequency for joint swelling and tenderness (disease duration < 1)

Swelling	% of patients affected	Tenderness	% of patients affected
PIP3 (hand)	18.5	Wrist	22.2
Wrist	18.0	Knee	20.6
PIP2 (hand)	13.3	Shoulder	18.5
Knee	13.0	PIP3 (hand)	17.4
PIP4 (hand)	11.7	Elbow	15.2
MCP2	10.9	MTP3	15.2
MCP3	10.9	PIP2 (hand)	14.8
PIP5 (hand)	7.8	MCP1	14.1
MCP1	6.9	Ankle	12.6
Ankle	6.3	PIP4 (hand)	12.4

Distribution of affected joints

Tenderness was most frequently observed in the wrist joint (24.5 %), followed by the knee (15.5 %), elbow (15.3 %), ankle (13.8 %), and shoulder (12.3 %) joints (Table 3). Small joints were less frequently affected. Swelling was most frequently observed in the wrist joint (21.4 %), followed by the second metacarpophalangeal (MCP) joint (13.7 %), the third MCP (11.1 %) joint, ankle (9.3 %), knee (8.9 %), and the third proximal interphalangeal (PIP) joint (hand) (8.5 %). Unlike in the case of tenderness, small joints were mainly involved in the case of swelling. Similar results were obtained when only early RA patients with <1 year of disease duration were analyzed (Table 4).

Relationship between distribution of affected joints and disease activity

We examined the relationship between the distribution of affected joints and disease activity. The number of affected joints (joints with either tenderness or swelling) in each individual was significantly correlated with disease activity

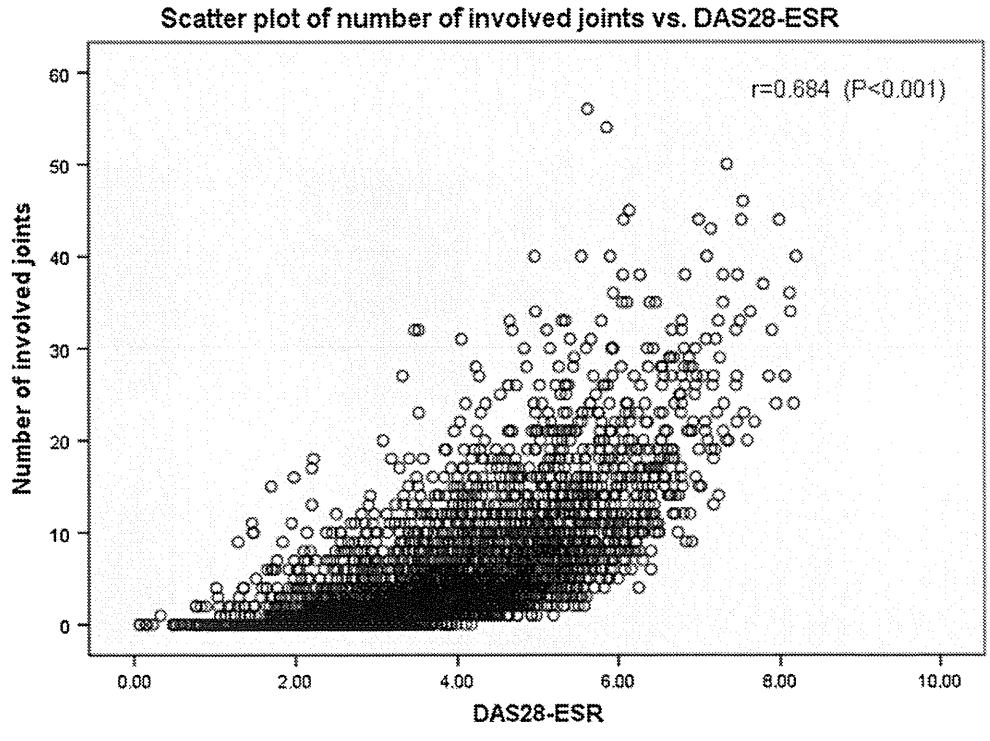

Fig. 1 Relationship between the Disease Activity Score 28–Erythrocyte Sedimentation Rate values and the number of involved joints

as measured using the DAS28-ESR ($r = 0.684$, $p < 0.001$, Fig. 1). Subjects were divided into 3 groups—a low disease activity group, a moderate disease activity group, and a high disease activity group—in accordance with the European League Against Rheumatism (EULAR) disease activity criteria [10], and the distribution of affected joints was examined in each group. Although the frequency of involvement increased in all joints as disease activity increased, the distribution of affected joints did not appear to differ among the 3 groups (Fig. 2a). In all 3 groups, the wrist joint was the most frequently affected site, followed by the knee joint, MCP joint, PIP joint (hand), and metatarsophalangeal joint (Fig. 2a). When the joints were divided into large (e.g., wrist, elbow, shoulder, hip, knee, ankle, and subtalar joints) and small (e.g., MCP) joints, the frequency of large joint involvement did not significantly differ among the 3 groups ($p = 0.362$, chi-square test, Fig. 2b).

Relationship between distribution of affected joints and disease duration

We examined whether the distribution of affected joints was associated with disease duration. Subjects were divided into 4 groups on the basis of disease duration (<3, 3–15, 15–25, ≥25 years). The pattern of joint involvement did not appear to differ among the 4 groups (Fig. 3a). Furthermore, the frequency of large joint involvement was not significantly different among the 4 groups ($p = 0.577$, chi-square test, Fig. 3b).

Subsequently, we analyzed the prevalence of swelling and tenderness for each large joint. The prevalence of swelling peaked at approximately 20 years in most joints and decreased at later stages. The prevalence of tenderness tended to increase in the later stages in the shoulder, elbow, knee, and ankle joints (Fig. 4a, b).

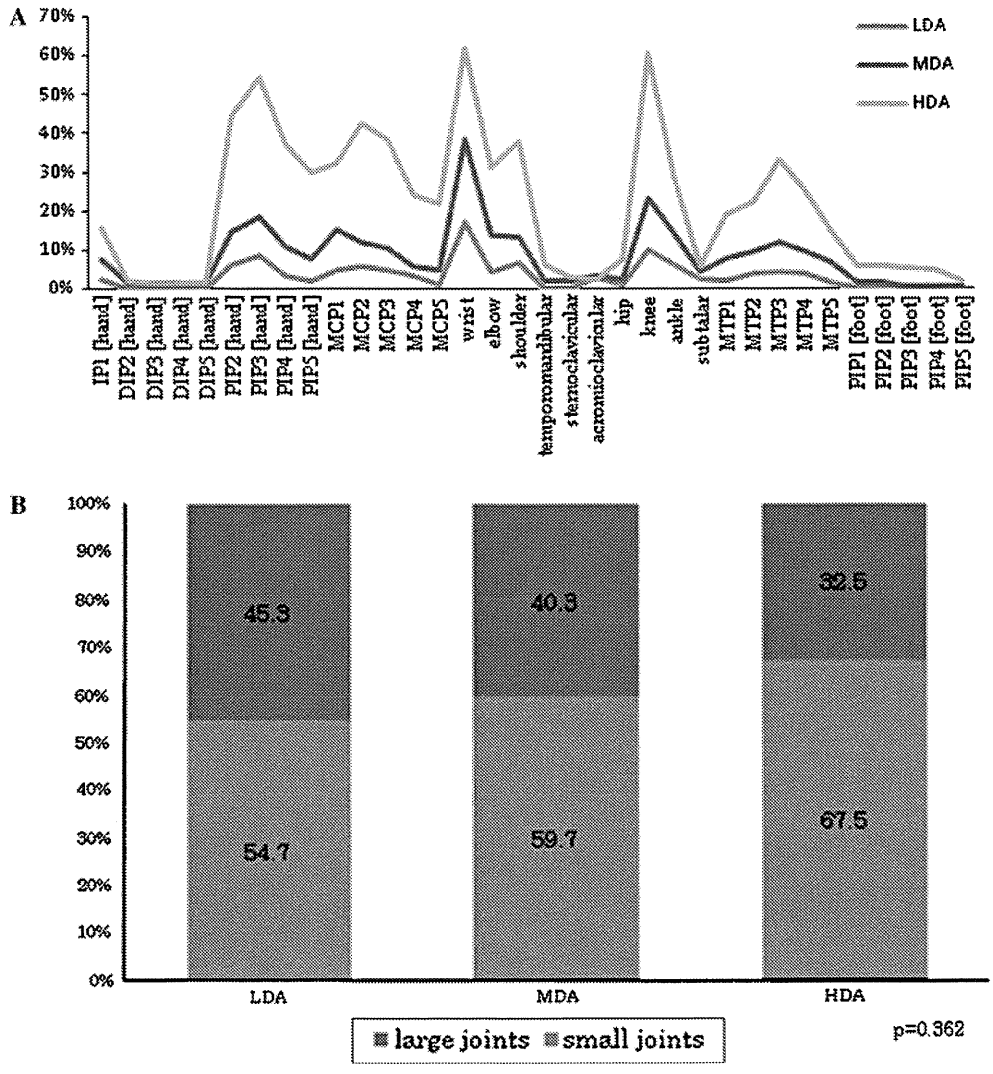

Fig. 2 Effect of disease activity on joint involvement. **a** Distribution of affected joints. **b** Proportions of large and small joint involvement. *LDA* low disease activity, *MDA* moderate disease activity, *HDA* high disease activity. No significant difference was detected among the 3 groups ($p = 0.362$)

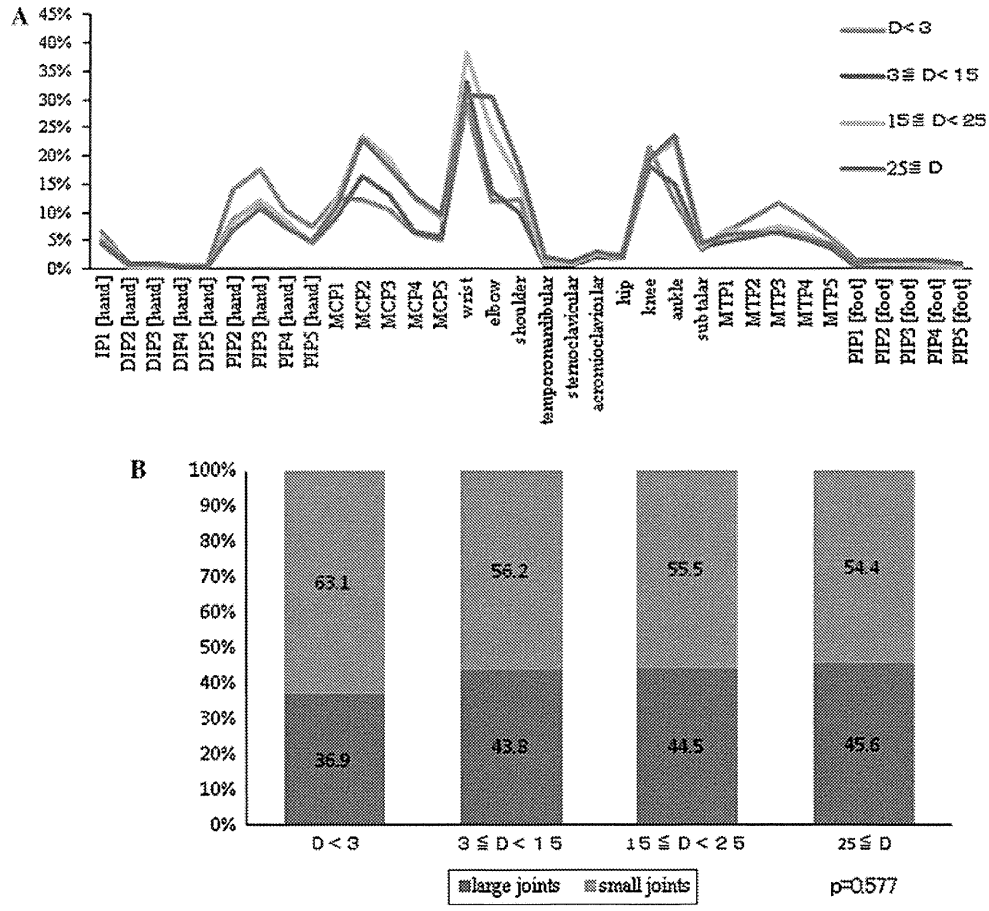

Fig. 3 Effect of disease duration on joint involvement. **a** Distribution of affected joints. **b** Proportions of large and small joint involvement. No significant difference was detected among the 4 groups ($p = 0.577$)

Discussion

We set out to analyze the frequency of joint involvement in Japanese RA patients using a national database. Although the wrist joint was the most frequently affected site, there were differences in the frequency of swelling and tenderness of the joints. Tenderness was frequently observed in large joints such as the knee, elbow, ankle, and shoulder joints, while swelling was frequently observed in small joints such as the MCP joints (Table 3). Similar results were obtained when only early RA patients with <1 year of disease duration were analyzed (Table 4). Furthermore, there are reports of lowered mechanical thresholds in primary afferent neurons of different species following inflammation or tissue damage [11–15]. The prevalence of tenderness in these joints might be higher than that of swelling, since large joints are subjected to higher mechanical loading than smaller joints and are therefore more susceptible to tenderness. Late-stage RA patients are likely to stand up using a bar and walk with a cane because of lower extremity joint destruction. Therefore, we can regard the shoulder and elbow joints as weight-bearing joints in such cases. Accordingly, our observation that late-stage RA with a disease duration of 25 years or more was associated with an increase in the prevalence of tenderness, especially in weight-bearing joints, may be attributable to the similar causes of these RAs (Fig. 4b). Furthermore, an increase in the prevalence of tenderness in late-stage RA may be caused by an increased number of structurally damaged joints but without inflammation, although radiographic data were not analyzed in the current study. It is also possible that the deep location of the joint makes the determination of swelling in the shoulder joint difficult (Fig. 4a). This suggests that analysis using ultrasound imaging may be necessary for the accurate diagnosis of joint swelling.

Ochi et al. previously reported that a subset of RA with more erosive disease tends to affect large joints compared with another subset with less erosive disease [16]. Although the current analysis does not include radiographic evaluations, we did not find any correlation between the distribution of affected joints and disease activity or disease duration, despite the fact that the prevalence of involvement of each joint increased as the disease activity increased. These results suggest that the distribution of affected joints is uniform throughout the course of RA.

There are several limitations of this study. The present study was a cross-sectional analysis of a cohort in a particular year (i.e., 2008), rather than a long-term study. Moreover, the patients registered in this database were

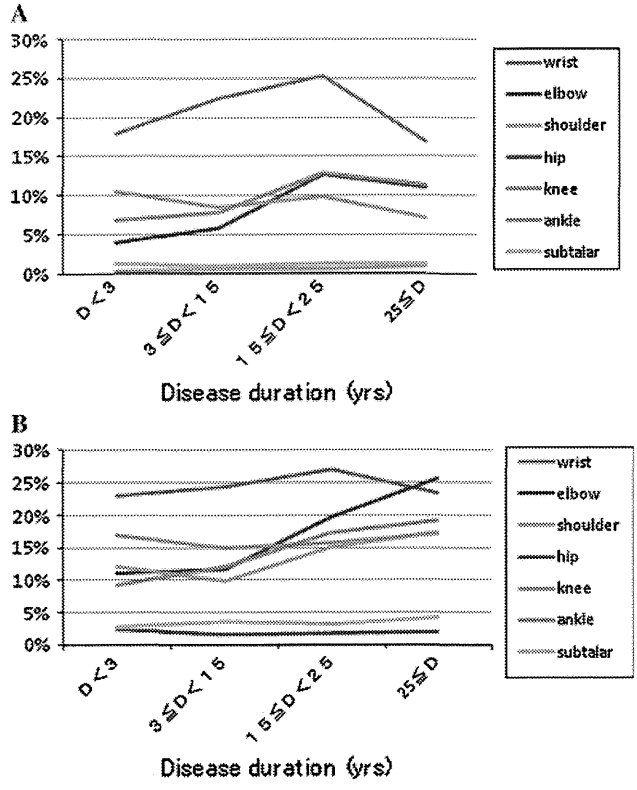

Fig. 4 **a** Prevalence of swelling in large joints. **b** Prevalence of tenderness in large joints

managed by rheumatologists in each organization, and so the data may have had selection bias. In addition, joints on which surgery had been performed were not counted as affected joints, so the prevalence may have been underestimated in the hip, knee, wrist, elbow, and toe joints. The abovementioned results must be further confirmed by future longitudinal analysis.

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Conflict of interest None.

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