

Trends in Treatment, Outcomes, and Incidence of Orthopedic Surgery in Patients with Rheumatoid Arthritis: An Observational Cohort Study Using the Japanese National Database of Rheumatic Diseases

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ABSTRACT. Objective. In this study, we investigated the changes in clinical outcome, treatment, and incidence of orthopedic surgery in patients with rheumatoid arthritis (RA) from 2004 to 2014.

Methods. Data were studied from the Japanese nationwide cohort database, NinJa (National Database of Rheumatic Diseases by iR-net in Japan), from 2004 to 2014. The time trends in the incidence of orthopedic procedures were analyzed using linear regression analysis. The cross-sectional annual data were compared between 2004 and 2014 to analyze the changes in clinical outcome and treatment.

Results. The incidence of orthopedic surgeries in patients with RA consistently decreased from 72.2 procedures per 1000 patients in 2004 to 51.5 procedures per 1000 patients in 2014 (regression coefficient = -0.0028 , 95% CI -0.0038 to -0.0019 , $p < 0.001$). The greatest reduction was found in total knee arthroplasty and total hip arthroplasty. Disease activity and functional disability improved significantly over this decade. The proportions of patients receiving methotrexate and biologic disease-modifying antirheumatic drugs significantly increased from 39.6% and 1.7% in 2004 to 63.8% and 27.4% in 2014, respectively.

Conclusion. The overall incidence of orthopedic surgeries in patients with RA significantly decreased, accompanied by improved clinical outcomes because of the expanded use of effective drugs; however, the declining trend differed between procedures or locations. The results from the present study suggest that there might be a change in supply and demand for orthopedic surgeries. (First Release September 1 2017; J Rheumatol 2017;44:1575–82; doi:10.3899/jrheum.170046)

Key Indexing Terms:

DISEASE ACTIVITY

EPIDEMIOLOGY

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Improvement in rheumatoid arthritis (RA) control using conventional synthetic and biological disease-modifying antirheumatic drugs (bDMARD), with a new treatment strategy consisting of early aggressive treatment and treating patients toward remission or low disease activity if remission is unavailable, has led to a substantial change in the clinical disease status of patients with RA¹. In accordance with the improvement in the disease status of patients with RA, a decreased incidence of orthopedic surgery in patients with RA has been reported in recent years by many studies from different countries^{2,3,4,5,6}.

In Japan, the use of methotrexate (MTX) and bDMARD for patients with RA was approved in 1999 and 2003, respectively, a delay of several years compared with some Western countries. We are now able to observe outcomes over the 10 years after the introduction of bDMARD. Two studies have reported the trends in orthopedic surgeries for patients with RA in Japan; however, one was from a single institution using data from 2003 to 2012⁷, while the other was a multicenter study including 5 university hospitals and 1 metropolitan

hospital in Japan presenting the data from 1998 to 2008⁸. There is still no study, to our knowledge, revealing the change in clinical outcome and trend in surgeries for patients with RA in the general population in Japan over a more recent decade.

In 2002, we created a nationwide, multicenter, observational cohort database of rheumatic diseases called NinJa (National Database of Rheumatic Diseases by iR-net in Japan), which included 44 institutions throughout Japan by 2014⁹. The aim of our present study was to investigate the changes in clinical outcome, treatment, and incidence of RA-related surgeries over 10 years in Japan using the NinJa database.

MATERIALS AND METHODS

Data source. The data source used in our study was a nationwide, multicenter, observational cohort database of rheumatic diseases in Japan (NinJa) collecting annual data since 2002⁹. The data are composed of 2 types: (1) patient outcomes over the course of the fiscal year including death, hospitalization, operation, number of total joint arthroplasties in large joints (hip, knee, shoulder, elbow), malignancy, and tuberculosis, and (2) the information collected all at once on an arbitrary day in daily clinical practice including the tender joint count, swollen joint count, a modified Health Assessment Questionnaire (MHAQ), patient's global and pain visual analog scales (VAS), doctor VAS, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Disease Activity Score in 28 joints (DAS28)-ESR, DAS28-CRP, and use of corticosteroids, DMARD, and nonsteroidal antiinflammatory drugs. All the patients included in our present study fulfilled the American College of Rheumatology classification criteria¹⁰. The study protocol was approved by the Institutional Review Board of The University of Tokyo [approval no.: 2185-(3)] and by all local ethics committees of the other 43 participating hospitals. All patients provided written informed consent before enrollment.

Patients. To analyze the prevalence and trend of orthopedic surgeries, the data of patients with RA enrolled in the fiscal years from 2004 to 2014 (a fiscal year is from April to March) were used. Orthopedic surgeries were recorded using category classifications including implant arthroplasty, revision implant arthroplasty, implant arthroplasty removal, RA-related orthopedic surgeries other than implant arthroplasties, surgeries for osteoporotic fractures, and others. For instance, synovectomies, arthroplasties without artificial implants, and arthrodeses were included in the category of RA-related orthopedic surgeries, and surgeries for fractures other than osteoporotic fractures were included in the category of "others." Locations operated were recorded as follows: cervical spine, thoracic spine, lumbar spine, shoulder, elbow, wrist, fingers, humerus, forearm, hip, knee, femur, neck of femur, supracondylar femur, lower leg, ankle, toes, and others. Procedures in the fingers performed at the same time were registered together as 1 procedure, as were the procedures in toes. Joint replacement, revision arthroplasty, and arthroplasty removal in the large joints including the shoulder, elbow, hip, knee, and ankle were counted together as joint replacement surgeries with respect to each joint. Orthopedic surgeries other than joint replacement were counted together with respect to each region including the spine, shoulder and elbow, hand and wrist, hip and knee, foot and ankle, and others. Bilateral procedures were counted as two. To investigate the changes in patient demographics and disease characteristics in the recent decade, the subjects enrolled in the NinJa in fiscal years of 2004 and 2014 were compared. In addition, we compared the demographics between the patients operated on more than once in the fiscal years of 2004 and 2014, which consisted of 222 and 614 patients, respectively, using the most recent data of each patient before surgery. If data for these years were unavailable, data from 2003 and 2013 were used. Some cases had missing data regarding certain variables and in some patients, data before surgery were not obtained. The percentages of the patients with available data were also reported for all variables.

Statistics. Continuous variables were reported as the mean \pm SD. Differences between groups were examined using 1-way ANOVA for continuous variables. Proportions were summarized using counts and percentages. The chi-square test or Fisher's exact test was conducted for univariate comparisons of the proportions between groups. The linear regression model was used to analyze trends over the 10-year period in the incidence of each RA-related surgery. A p value < 0.05 was defined as significantly different. Statistical analyses were performed using the statistical software JMP9 (SAS Institute Inc.).

RESULTS

The annual numbers of patients registered in the database and each procedure during the entire study period is shown in Table 1. The number of surgeries per 1000 patients declined significantly during the entire study period by 28.7% from 72.2 in 2004 to 51.5 in 2014 [regression coefficient (β) = -0.0028 , 95% CI -0.0038 to -0.0019 , $p < 0.001$; Table 2 and Figure 1A]. Joint replacements of the knee and hip were the most frequent procedures among joint replacements throughout the study period; however, both significantly decreased from 30.1 and 8.5 procedures per 1000 patients, respectively, in 2004 to 11.5 and 6.1 procedures per 1000 patients, respectively, in 2014 [total knee arthroplasty (TKA): $\beta = -2.00$, 95% CI -2.41 to -1.60 , $p < 0.001$; total hip arthroplasty (THA): $\beta = -0.573$, 95% CI -0.835 to -0.310 , $p < 0.001$; Table 2 and Figure 1A]. There were no significant changes in the performance of arthroplasties for the shoulder, elbow, and ankle during the study period (Table 2, Figure 1A). For surgeries other than joint replacements, a statistically significant change in incidence was not observed except for spine surgery, which showed a slow but significantly increasing trend ($\beta = 0.188$, 95% CI 0.045 – 0.331 , $p = 0.016$; Table 2, Figure 1B).

The demographic and disease characteristics of all registered patients and the patients who underwent orthopedic surgeries in 2004 and 2014 are shown in Table 3 and Table 4. The proportion of female patients was significantly decreased from 82.9% in 2004 to 80.4% in 2014 among all registered patients as well as among the patients who underwent orthopedic surgeries from 91.4% in 2004 to 86.5% in 2014. The mean age and age of disease onset were significantly higher in 2014 (64.3 yrs, 51.4 yrs, respectively) compared with 2004 (61.4 yrs, 48.2 yrs, respectively) among all registered patients. The same also held in the patients who underwent orthopedic surgeries with higher age and age of disease onset in 2014 (66.8 yrs, 48.6 yrs, respectively) compared with 2004 (61.9 yrs, 45.2 yrs, respectively). No significant difference was observed between 2004 and 2014 regarding disease duration.

The proportions of patients receiving MTX significantly increased over the 10-year period from 39.6% in 2004 to 63.8% in 2014, accompanied by a significant increase of weekly dose from 5.9 mg to 8.3 mg. The same trend was also observed in the patients who underwent orthopedic surgeries. A significant increase was observed in the proportions of patients treated with bDMARD from 1.7% in 2004 to 27.4%

Table 1. Numbers of enrolled patients with rheumatoid arthritis and their orthopedic surgeries in a nationwide, multicenter, observational cohort database of rheumatic diseases in Japan (NinJa) for each year from 2004 to 2014.

Year	No. Registered Patients	Total No. Surgeries	THA	TKA	TSA	TEA	TAA	Surgeries Other than Large-joint Arthroplasties						
								Spine	Osteoporotic Fracture	Hip and Knee	Shoulder and Elbow	Hand and Wrist	Foot and Ankle	Others
2004	4019	290	34	121	0	12	0	12	10	7	9	39	32	14
2005	4643	328	49	125	5	17	1	7	23	7	3	43	44	4
2006	5100	338	48	124	3	29	1	10	18	10	5	40	40	10
2007	5676	335	46	125	2	13	5	12	24	3	9	53	33	13
2008	6484	378	48	108	0	33	3	20	28	10	5	64	41	18
2009	7189	401	43	134	4	20	4	22	27	13	4	58	66	6
2010	7320	421	36	114	5	38	2	29	32	15	16	57	62	15
2011	10,377	503	46	145	3	38	9	46	34	8	10	67	80	17
2012	11,952	540	54	144	10	26	6	42	44	8	4	97	94	11
2013	13,231	526	52	113	4	34	3	48	46	16	15	82	92	21
2014	15,021	773	91	173	8	42	10	51	72	16	15	135	138	22

THA: total hip arthroplasty; TKA: total knee arthroplasty; TSA: total shoulder arthroplasty; TEA: total elbow arthroplasty; TAA: total ankle arthroplasty.

Table 2. Numbers of orthopedic surgeries performed per 1000 patients in a nationwide, multicenter, observational cohort database of rheumatic diseases in Japan (NinJa) for each year from 2004 to 2014.

Year	Total No. Surgeries	THA	TKA	TSA	TEA	TAA	Surgeries Other than Large Joint Arthroplasties						
							Spine	Osteoporotic Fracture	Hip and Knee	Shoulder and Elbow	Hand and Wrist	Foot and Ankle	Others
2004	72.2	8.5	30.1	0.0	3.0	0.0	3.0	2.5	1.7	2.2	9.7	8.0	3.5
2005	70.6	10.6	26.9	1.1	3.7	0.2	1.5	5.0	1.5	0.6	9.3	9.5	0.9
2006	66.3	9.4	24.3	0.6	5.7	0.2	2.0	3.5	2.0	1.0	7.8	7.8	2.0
2007	59.0	8.1	22.0	0.4	2.3	0.9	2.1	4.2	0.5	1.6	9.3	5.8	1.8
2008	58.3	7.4	16.7	0.0	5.1	0.5	3.1	4.3	1.5	0.8	9.9	6.3	2.8
2009	55.8	6.0	18.6	0.6	2.8	0.6	3.1	3.8	1.8	0.6	8.1	9.2	0.8
2010	57.5	4.9	15.6	0.7	5.2	0.3	4.0	4.4	2.0	2.2	7.8	8.5	2.0
2011	48.5	4.4	14.0	0.3	3.7	0.9	4.4	3.3	0.8	1.0	6.5	7.7	1.6
2012	45.2	4.5	12.0	0.8	2.2	0.5	3.5	3.7	0.7	0.3	8.1	7.9	0.9
2013	39.8	3.9	8.5	0.3	2.6	0.2	3.6	3.5	1.2	1.1	6.2	7.0	1.6
2014	51.5	6.1	11.5	0.5	2.8	0.7	3.4	4.8	1.1	1.0	9.0	9.2	1.5
Regression													
coefficient*	-0.0028	-0.573	-2.00	0.0079	-0.118	0.037	0.188	0.038	-0.068	-0.055	-0.208	0.018	-0.103
95% CI	-0.0038 to -0.0019	-0.835 to -0.310	-2.41 to -1.60	-0.067 to 0.083	-0.387 to 0.151	-0.022 to 0.096	0.045-0.331	-0.122 to 0.199	-0.178 to 0.043	-0.191 to 0.082	-0.441 to 0.025	-0.250 to 0.286	-0.271 to 0.066
p	<0.001	<0.001	<0.001	0.817	0.347	0.189	0.016	0.603	0.198	0.389	0.075	0.879	0.201

*Linear regression analysis was used to analyze trends in the performance of each procedure. THA: total hip arthroplasty; TKA: total knee arthroplasty; TSA: total shoulder arthroplasty; TEA: total elbow arthroplasty; TAA: total ankle arthroplasty.

in 2014 among all registered patients, and from 1.4% in 2004 to 36.5% in 2014 among the patients who underwent orthopedic surgeries. The proportions of patients using oral corticosteroids significantly decreased from 62.9% in 2004 to 40.5% in 2014 accompanied by a significant decrease of the daily dose from 5.2 mg to 4.2 mg among all registered patients. The same trend was also noted in the patients who underwent orthopedic surgeries.

Disease activity data including laboratory data, joint scores, and composite scores significantly improved in comparison between 2004 and 2014 among all registered patients and among patients who underwent orthopedic

surgeries. The proportions of patients in remission according to DAS28-ESR increased significantly from 13.1% in 2004 to 39.3% in 2014 among all registered patients (Figure 2). The same was true in the patients who underwent orthopedic surgeries with a significant increase from 3.4% in 2004 to 16.3% in 2014 (Figure 2). As for functional disability score, MHAQ significantly decreased over the 10-year period in all registered patients from 0.66 in 2004 to 0.42 in 2014, as well as in the patients who underwent orthopedic surgeries, from 1.03 in 2004 to 0.76 in 2014, indicating improved activities of daily living in patients with RA.

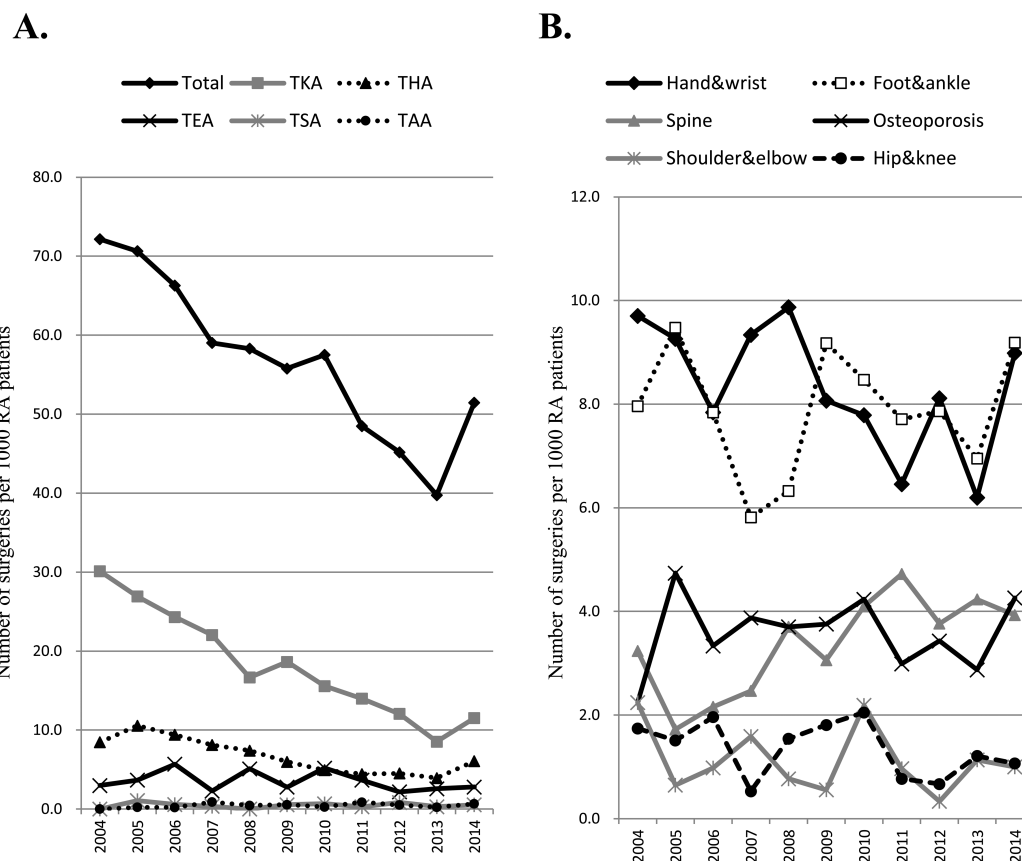


Figure 1. (A) Overall incidence of procedures and joint replacement procedures including TKA, THA, TEA, TSA, and TAA per 1000 patients with RA. (B) Incidence of each procedure for hand and wrist, foot and ankle, spine, osteoporotic fracture, shoulder and elbow, and hip and knee per 1000 patients with RA. TKA: total knee arthroplasty; THA: total hip arthroplasty; TEA: total elbow arthroplasty; TSA: total shoulder arthroplasty; TAA: total ankle arthroplasty; RA: rheumatoid arthritis.

DISCUSSION

Our present study demonstrated a significant improvement in disease activity and functional disability for Japanese patients with RA accompanied with the expanded use of MTX and bDMARD in a recent decade. There was a significant decrease in the prevalence of orthopedic surgeries from 2004 to 2014. In particular, the decrease of TKA was notable, with a reduction of 60%. Patients with RA who underwent orthopedic surgeries in 2014 had milder functional disability and disease activity status compared with those who had orthopedic surgeries in 2004.

The treatment of RA has markedly evolved over the past 2 decades because of aggressive treatment strategies using MTX as an anchor drug and the introduction of bDMARD. Many studies from Europe and the United States, including patients with RA treated in the 1980s and 1990s, reported improved disease activity, function, and joint damage associated with the expanded use of MTX^{11,12,13}. It was in 1999 that MTX was approved by the Japanese Ministry of Health, Labor, and Welfare for the treatment of patients with RA in Japan. First, the upper limit of the dosage was set at

8 mg/week; it was expanded to 16 mg/week in 2011. Our present study demonstrated a significantly increased usage and dosage of MTX in the study decade. The introduction of bDMARD in the late 1990s has been proven to achieve marked improvement in the longterm outcomes for patients with RA in Europe and the United States^{14,15,16,17}. Infliximab (IFX), which was the first bDMARD introduced into Japan, was approved for the treatment of RA in 2003, followed by etanercept (ETN) in 2005. As of 2016, 7 bDMARD are available, including 5 tumor necrosis factor (TNF)- α inhibitors (IFX, ETN, adalimumab, golimumab, and certolizumab pegol) and 2 agents having an alternative mechanism of action other than TNF inhibitors (tocilizumab; interleukin-6 receptor antibody, and abatacept; CTLA4-Ig). About 30% of the patients in 2014 received bDMARD, which indicates that Japan is now in the era of mature biologic agents after a decade since the introduction of IFX. However, the usage and dosage of corticosteroids decreased significantly in the study decade, which is consistent with previous studies revealing the recent trends in the treatment of RA^{1,11}. The result from our present study indicating significantly improved outcomes

Table 3. Comparison of background data of all registered patients and patients who underwent orthopedic surgeries between 2004 and 2014.

Characteristics	All Registered Patients		p	Patients with Orthopedic Surgeries		p
	2004	2014		2004	2014	
No. patients	4019	15,021	—	222 (5.5%)	614 (4.1%)	—
Female:male, n	3330:689	12,076:2945	< 0.001	203:19	531:83	0.046
Female, %	82.9	80.4	—	91.4	86.5	—
Age, yrs, mean \pm SD	61.4 \pm 11.9	64.3 \pm 12.9	< 0.001	61.9 \pm 10.1	66.8 \pm 11.3	< 0.001
Disease onset, yrs, mean \pm SD	48.2 \pm 14.2	51.4 \pm 15.0	< 0.001	45.2 \pm 12.7	48.6 \pm 15.3	0.003
Disease duration, yrs, mean \pm SD	13.2 \pm 10.6	13.0 \pm 11.0	0.145	16.7 \pm 9.7	18.2 \pm 11.6	0.090
No. patients using MTX, n (%)	1591 (39.6)	9584 (63.8)	< 0.001	94 (42.3)	369 (60.1)	< 0.001
Weekly amount of MTX, mg/week, mean \pm SD	5.9 \pm 1.9	8.3 \pm 3.1	< 0.001	5.9 \pm 1.8	8.2 \pm 3.2	< 0.001
No. patients using biologics, n (%)	69 (1.7)	4115 (27.4)	< 0.001	3 (1.4)	224 (36.5)	< 0.001
Infliximab	58	490		2	23	
Etanercept	5	1153		1	58	
Adalimumab	5	321		0	14	
Tocilizumab	1	1038		0	65	
Abatacept	0	629		0	35	
Golimumab	0	278		0	16	
Certolizumab pegol	0	120		0	13	
Patients using oral corticosteroids, n (%)	2504 (62.9)	6055 (40.5)	< 0.001	172 (78.2)	346 (56.4)	< 0.001
Dosage of corticosteroids, mg/day, mean \pm SD	5.2 \pm 14.8	4.2 \pm 2.9	< 0.001	5.3 \pm 2.2	4.3 \pm 2.6	< 0.001

MTX: methotrexate.

Table 4. Comparison of corrected variables of all registered patients and patients who underwent orthopedic surgeries between 2004 and 2014. Values are mean \pm SD [percentage of available data] unless otherwise specified.

Characteristics	All Registered Patients		p	Patients with Orthopedic Surgeries		p
	2004	2014		2004	2014	
Tender joint count	4.9 \pm 6.7 [95.4]	2.2 \pm 4.5 [97.2]	< 0.001	6.8 \pm 7.7 [74.3]	4.0 \pm 6.2 [60.3]	< 0.001
Swollen joint count	3.4 \pm 4.6 [95.3]	1.7 \pm 3.0 [97.2]	< 0.001	5.0 \pm 6.0 [73.9]	2.8 \pm 3.8 [60.3]	< 0.001
Pain VAS	3.7 \pm 2.5 [92.4]	2.5 \pm 2.3 [93.0]	< 0.001	5.1 \pm 2.2 [68.9]	3.9 \pm 2.5 [58.1]	< 0.001
MHAQ	0.66 \pm 0.70 [91.2]	0.42 \pm 0.63 [89.6]	< 0.001	1.03 \pm 0.66 [67.6]	0.76 \pm 0.67 [56.8]	< 0.001
CRP, mg/dl	1.4 \pm 3.4 [95.9]	0.6 \pm 1.3 [98.7]	< 0.001	2.5 \pm 2.7 [73.9]	0.8 \pm 1.3 [72.5]	< 0.001
ESR, mm/h	43.3 \pm 30.0 [91.8]	27.1 \pm 24.1 [84.7]	< 0.001	54.0 \pm 29.1 [71.6]	33.9 \pm 26.1 [61.6]	< 0.001
DAS28-ESR	4.2 \pm 1.4 [88.2]	3.0 \pm 1.2 [80.2]	< 0.001	4.9 \pm 1.3 [66.8]	3.8 \pm 1.2 [59.0]	< 0.001
SDAI	14.4 \pm 11.2 [91.0]	7.6 \pm 7.5 [92.2]	< 0.001	21.3 \pm 12.5 [68.5]	12.4 \pm 8.6 [70.0]	< 0.001
CDAI	13.0 \pm 9.9 [91.2]	7.1 \pm 7.0 [90.6]	< 0.001	19.0 \pm 11.3 [68.2]	11.6 \pm 8.1 [70.2]	< 0.001

VAS: visual analog scale; MHAQ: modified Health Assessment Questionnaire; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; DAS28: Disease Activity Score in 28 joints; SDAI: Simple Disease Activity Index; CDAI: Clinical Disease Activity Index.

could be largely attributed to modern therapeutic concepts as indicated by previous studies^{11,12,13}.

Orthopedic surgeries in patients with RA can be thought as the essential marker of joint failure. Some prospective studies following up with early-onset patients with RA reported the prevalence of orthopedic surgeries during their disease course as 17% in a 5-year followup⁵ and 48% in a 16-year followup⁶, and the prevalence of joint replacement surgeries as 17% in a 10-year³, 24% in a 16-year⁶, 25% in a

23-year², and 27% in a 25-year followup⁴. These previous prospective reports included many patients who could not receive the benefits of modern therapeutics in their early stage. The patients in the mature biologic era should have changing predictions. A prospective study comparing radiographic disease progression in patients with disease onset in the 1970s, 1980s, and 1990s showed a trend toward less radiographic progression, which could be attributable to improved treatment¹². Studies from several countries show

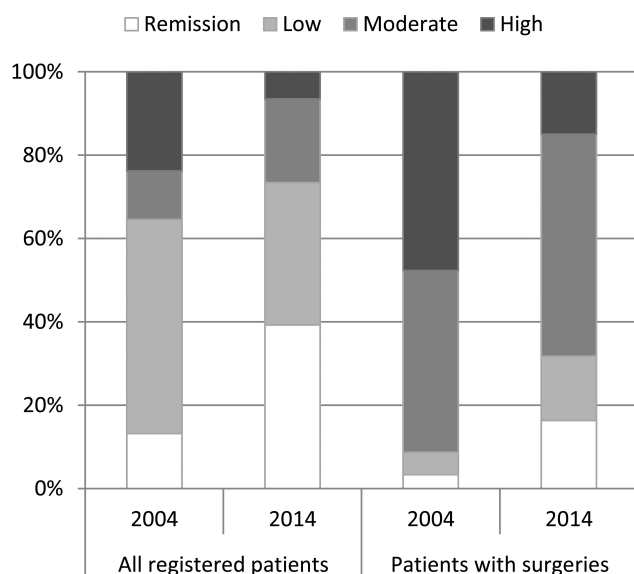


Figure 2. Proportion of disease activity status measured according to the Disease Activity Score in 28 joints with erythrocyte sedimentation rate, in patients with rheumatoid arthritis registered with the NinJa (National Database of Rheumatic Diseases by iR-net in Japan) database in 2004 and 2014, and patients with RA who underwent surgeries in 2004 and 2014.

that the rates of orthopedic surgery in patients with RA have been decreasing in recent years^{17,18,19,20,21,22}. A population-based cohort of patients with RA from Rochester, Minnesota, USA, demonstrated that the cumulative incidence of orthopedic surgeries at 10 years in the patients diagnosed between 1985–1994 was about one-third of the incidence of those diagnosed in previous decades including 1955–64, 1965–74, and 1975–84¹⁸. A cross-sectional national study in Spain revealed that the percentage of patients with RA who had undergone any orthopedic surgery during their disease course dramatically decreased from 26% in 2000 to 7.4% in 2010²¹. The Swedish inpatient registry data reported a significant decrease of 29% for all RA-related upper limb surgeries over the entire study period from 1998 to 2004²⁰, as well as a significant decrease of 24% for all lower limb surgeries during 1987 to 1996¹⁹. An observational cohort of patients with RA from a single institution in Japan showed that the number of orthopedic surgeries decreased from its peak in 2002 to about one-half in 2007 and gradually increased since 2008, but not reaching the peak in 2012⁷. A multicenter report including 6 institutions demonstrated that the number of orthopedic surgeries was stable from 1998 to 2008⁸. These reports containing data from a limited number of hospitals are likely to be influenced by the capacity for operation in each institution. We believe that our nationwide, multicenter, observational cohort better reflects the current condition of patients with RA among the general population in Japan.

TKA and THA account for a large portion of orthopedic surgeries for patients with RA^{5,6,7,18,19}. Both procedures are

established treatments for arthrosis of the hip and knee, and their overall rates in the entire population have increased remarkably since the early 1980s in many countries with an aging population^{23,24,25,26}. However, many studies have reported that these procedures for patients with RA have decreased in recent years^{19,22,27,28} (as is the case with our present study) or have remained stable²⁹. Our present study demonstrated a marked decrease in the incidence of TKA of 18.6 procedures per 1000 patients from 2004 to 2014, which accounted for the majority of the change in the overall number of orthopedic surgeries during this period (a decrease of 20.7 procedures per 1000 patients). The previous NinJa database study investigating the effect of biologics on the prevalence of orthopedic surgery in patients with RA from 2004 to 2007 reported that neither the number nor type of RA-related surgery significantly changed during the survey period, although the proportion of patients using bDMARD linearly increased from 2004 (1.8%) to 2007 (10.0%)³⁰. Since their introduction, bDMARD have tended to be prescribed for patients with higher disease activity and lower physical function, and having irreparable joint damage³⁰. The result of our present study implied that the use of bDMARD has expanded and has helped to prevent joint damage progression for patients in the early phase of the disease. Contrary to our present study, a report using the United States Nationwide Inpatient Sample data showed a significant increase in THA and TKA performed in patients with RA from 1992 through 2005, although the degree of their increase was much smaller compared with the general population³¹. This discrepancy might be partly attributed to the incidence of osteoarthritis that is greatly influenced by obesity. Obesity is still not a big problem in Japan compared with Western countries; the numbers of TKA and THA per general population are 3- to 5-fold bigger in the United States than in Japan^{32,33}.

Because the hand and foot are often affected in the early phase of RA, a greater decline of surgeries for the small joints was expected. However, our present study demonstrated no significant change in the incidence of surgeries for the small joints over the recent study decade. Swedish registry data reported a decrease in hand surgery of 27% for patients with RA from 1998 to 2004²⁰. Contrarily, an observational cohort from a single institution in Japan reported the gradual increase of surgeries for the hand and foot⁷. Direct comparisons between these studies would be difficult because of the differences such as data collection methods, clinical practice, and availability of orthopedic surgery. There are some possible explanations for the unchanged prevalence of hand and foot surgeries in our present study. First, the small joints and large joints possibly have considerably different responsiveness to treatment by MTX or bDMARD. However, the effectiveness of MTX and bDMARD in preventing joint damage progression has been well demonstrated by several studies, mainly using the Sharp score of the hand and foot^{34,35,36}. The second possible explanation would be

concerning the priority in selecting which joints should be reconstructed first. In the clinical practice of orthopedic surgeons, there is a prevailing principle in which large joint replacements of the lower extremities are performed preferentially in patients with polyarticular involvement. The decreasing demand for large joint replacements might enable the allocation of capacity for operations on the small joints. Third, patients may desire a better quality of life, which was supported by the results of our present study showing better function and disease activity status in the patients who underwent surgeries in 2014 compared to those in 2004.

The involvement of the cervical spine is common in patients with RA, and the severity of RA activity has been shown to correlate with the progression of cervical spine instability³⁷. At present, few studies have investigated the trend in spine surgery for patients with RA before and during the biologic era. Contrary to expectations, our present study demonstrated no decrease in spine surgery during the study period. Surgeries for the cervical spine accounted for 45% of the entire spine surgeries in our present study (data not shown). Factors other than a change in RA severity may have contributed to the result in our present study such as a change of operative indication, improved surgical technique, and developed instruments³⁸.

The large size of the study population is one of the notable advantages of our study. NinJa is the only Japanese cohort of patients with RA covering almost the entire nation; therefore, our present results could be regarded as representing the recent trends of treatments and outcomes among the general RA population across Japan. Some limitations of our study must be acknowledged. First, the observed trend toward improved patient outcomes and decreased orthopedic surgeries over the recent study decade cannot be definitively attributed to the new treatment strategies with MTX and/or bDMARD. We were unable to perform multivariate analysis adjusting for sociodemographic, clinical, and treatment variables because of the cross-sectional design of the database and absence of a national joint replacement registry system in Japan. However, it appears likely that modern therapeutic concepts may play at least some role in these improved outcomes. Second, we could not obtain clinical data about disease status in patients who underwent surgeries immediately before surgery because the clinical appraisal of patients was conducted on an arbitrary day in each fiscal year that tended to concentrate on the last quarter of each fiscal year. We used the data of the previous year as a substitute in cases that did not have clinical data about disease status before surgery. This method was applied for patients who underwent surgeries between 2004 and 2014; therefore, we believe that the comparisons performed in our present study are still meaningful. Third, the NinJa database might include surgeries from other pathologies than RA such as degenerative changes. Because the improved control of disease in patients with RA is expected to expose osteoarthritic change,

the downward trend in surgeries would not be changed even if we focused on RA-related surgeries, excluding surgeries related to other pathologies.

We have documented a substantially decreasing trend of orthopedic surgeries for patients with RA accompanied by improved disease control and functional disability in the analysis of a large observational cohort in Japan. Reduction in TKA and THA was predominant while the number of surgeries for the small joints was stable during the study period. The improved outcomes in patients with RA achieved in the biologic era might have brought some changes in supply and demand for orthopedic surgeries.

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