Egyptian Rheumatology and Rehabilitation

RESEARCH

Open Access

# The association between comorbidities and disease activity in patients with rheumatoid arthritis: a multicenter, cross-sectional cohort study in Japan with the highest proportion of elderly individuals

Takanori Miura[1,2*], Naohisa Miyakoshi[3], Takeshi Kashiwagura[2], Hiroyuki Tsuchie[3], Yusuke Sugimura[2] and Yoichi Shimada[2]

## Abstract

**Background:** This study aimed to assess the association of disease activity with the presence of comorbidities in patients with rheumatoid arthritis, using the Akita Orthopedic Group on Rheumatoid Arthritis (AORA) registry, a multicenter, cross-sectional registry in Japan with the highest proportion of elderly people. We included 1838 patients (mean age: 66.4 years old) who visited our affiliated institutions between April 2018 and March 2019. The patients were divided into two groups based on the disease activity in 28 joints based on the erythrocyte sedimentation rate (DAS28-ESR) into the remission or low disease activity group (L group) and the moderate or high disease activity group (H group). Patient demographics and comorbidities in the two groups were compared.

**Results:** The most common comorbidity was hypertension (33.7%), followed by renal disease (25.2%), respiratory disease (12.2%), diabetes mellitus (8.1%), cardiovascular disease (8.0%), malignancies (5.7%), and cerebrovascular disease (4.7%). The H group was older ($p<0.0001$); had a higher prevalence of hypertension ($p<0.0001$), diabetes ($p=0.0011$), respiratory disease ($p<0.0001$), cerebrovascular disease ($p<0.0001$), and cardiovascular disease ($p=0.0030$); and was less likely to use anti-rheumatic drugs. The prevalence of comorbidities other than renal disease and malignant tumor was higher in the H group. Multivariate logistic regression analysis showed that female sex ($p=0.0054$), advanced Steinbrocker class ($p<0.0001$), high anti-citrullinated protein antibody levels ($p=0.0211$), high prednisolone dose ($p<0.0001$), and absence of biologics' or JAK inhibitors' use ($p<0.0001$) were risk factors for high disease activity, and shorter treatment period was a low-risk factor for high disease activity ($p=0.0041$). Among comorbidities, the presence of cerebrovascular disease ($p=0.0334$) was the only independent risk factor for high disease activity.

**Conclusions:** In our registry study with a high proportion of elderly RA patients, cerebrovascular disease was associated with high disease activity in patients with RA. Therefore, when treating elderly patients with RA, we need to pay careful attention to cerebrovascular disease, and treatment should be aimed at achieving adequate control of RA.

**Keywords:** Rheumatoid arthritis, Comorbidity, Treatment strategy, Cerebrovascular disease, Treat to target, Multicenter study

*Correspondence: tmlucky8@gmail.com
[1] Department of Orthopedic Surgery, Kakunodate General Hospital, 3 Iwase Kakunodate, Senboku, Akita 014-0394, Japan
Full list of author information is available at the end of the article

## Background

Rheumatoid arthritis (RA) is a chronic inflammatory disease that can lead to joint destruction and dysfunction due to synovitis and bone erosion. However, in the last decade, the introduction of disease-modifying antirheumatic drugs (DMARDs), such as methotrexate (MTX), biologics (Bio), and Janus kinase inhibitors (JAK) has dramatically improved the long-term prognosis of patients with RA [1]. The concept of "treat-to-target" (T2T) in RA, which involves monitoring the disease activity in order to achieve remission or low disease activity, has been shown to be effective in improving pain and dysfunction [2, 3].

RA is more common in middle-aged people between the ages of 40 and 60 years [3], and treatment response to MTX and biologics has been reported to be similar among younger and older patients with RA [4]. However, the increased incidence of comorbidities, such as cardiovascular and respiratory diseases, with aging, often makes it difficult to introduce and continue these effective drugs [3, 4]. As a result, older patients with RA are more difficult to treat and have a higher disease activity [5–8]. Previous reports have also shown that patients with comorbidities have higher disease activity and poorer outcomes than those without comorbidities [5, 6, 9]. However, only few reports have examined the relationship between specific comorbidities and disease activity in RA [10]. Furthermore, there are no reports of studies that focus on elderly individuals with several comorbidities.

This study aimed to investigate which comorbidities affect disease activity in patients with RA using the Akita Orthopedic Group on Rheumatoid Arthritis (AORA) registry [11], a multicenter, cross-sectional RA cohort study in Japan with the highest proportion of elderly people.

## Methods

### The AORA registry

The AORA registry was established in 2010 as a multicenter cohort of Japanese patients with RA in Akita Prefecture, Japan. The AORA registry is maintained by the Department of Orthopedic Surgery at Akita University Graduate School of Medicine and covers 28 affiliated institutions. The data is collected once a year from the responsible physician at each institution. Japan is one of the world's most rapidly aging countries, and the Akita Prefecture has the highest rate of aging, with 33.8% of the population aged ≥65 years [12]. Therefore, compared to other cohort registries [13, 14], the AORA registry is novel, owing to its high proportion of elderly patients.

### Study design

We included 2175 patients with RA aged ≥18 years who visited our affiliated institutions between April 2018 and March 2019. Patients not assessed for comorbidities and those with insufficient clinical findings and laboratory data for assessment of disease activity were excluded; finally, 1838 patients (365 males and 1473 females) were included in this study. Patient information, including age, sex, medication, dosing period, disease stage and class as per the Steinbrocker classification system [15], serum levels of anti-citrullinated protein antibody (ACPA), the disease activity score in 28 joints based on the erythrocyte sedimentation rate (DAS28-ESR), simplified disease activity index (SDAI), the health assessment questionnaire disability index (HAQ), and comorbidities, were collected. We investigated the use of the following drugs for RA: DMARDs, MTX, glucocorticoids (prednisolone, PSL), Bio, and JAK inhibitors (Bio/JAK). Regarding comorbidities, we evaluated the presence of hypertension; diabetes mellitus (DM); respiratory disease (chronic obstructive pulmonary disease (COPD), interstitial pneumonia (IP), asthma, and pulmonary infection); cerebrovascular disease (cerebral infarction, cerebral hemorrhage, and subarachnoid hemorrhage); cardiovascular disease (myocardial infarction, heart failure, and cardiomyopathy); renal disease; and malignancy. We defined renal disease as an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73m$^2$ [16]. On the DAS28-ESR, remission was defined as <2.6, low disease activity as 2.6–3.2, moderate activity as 3.2–5.1, and high disease activity as >5.1 [17]. Therefore, we divided patients into two groups: the remission or low disease activity group (L group) and the moderate or high disease activity group (H group). We compared the measures between the two groups. Furthermore, factors that affected high disease activity were examined.

The study's retrospective protocol was approved by the Institutional Review Board for Clinical Research at Kakunodate General Hospital (approval number, 00409), and informed consent was obtained from all patients.

### Statistical analysis

Values are expressed as means and standard deviations (SD) for continuous variables and as percentages for categorical variables. Comparisons between groups were made using independent sample *t* tests in the case of continuous variables, and Pearson's chi-square tests for categorical variables. To investigate the association between RA disease activity and comorbidities, a multivariate logistic regression analysis was performed. All statistical analyses were completed using R version 3.5.1 software (R Foundation for Statistical Computing, Vienna,

Austria), and the statistical significance was considered at a $p$ value <0.05.

## Results

The mean age was 66.4 ± 13.0 years (range, 18–99 years), and the mean disease duration period was 151.3 ± 129.0 months (range, 20–1040 months) (Table 1). Among patients who used biologics, etanercept was used in 175 patients (34.9%); tocilizumab in 68 patients (22.7%); abatacept in 68 patients (13.6%); adalimumab in 51 patients (10.2%); golimumab in 46 patients (9.2%); infliximab in 30 patients (6.0%); and certolizumab in 15 patients (3.0%). The JAK inhibitor tofacitinib was used in only two patients (0.4%). The most common comorbidity was hypertension, followed by renal disease, respiratory disease, DM, heart disease, malignant tumor, and cerebrovascular disease, in decreasing order of prevalence (Table 1).

**Table 1** Clinical information for all patients

| Variable | Value |
|---|---|
| Total patients | 1838 |
| Age (years) | 66.4±13.0 (18–99) |
| Elderly (≥ 65) | 1103 (60.0) |
| Sex—male/female | 365 (19.9)/1473(80.1) |
| Disease duration (months) | 151±129 (20-1040) |
| Steinbrocker stage I/II/III/IV | 517 (28.2)/407 (22.2)/442 (24.0)/472 (25.6) |
| Steinbrocker class I/II/III/IV | 856 (46.5)/729 (39.7)/207 (11.3)/46 (2.5) |
| ACPA (U/ml) | 133±307 (0–7690) |
| DAS | 2.9±1.2 (0.28–7.9) |
| SDAI | 7.3±6.8 (0.01–57.4) |
| HAQ | 0.5±1.2 (0–49) |
| DMARDs usage | 1607 (87.4) |
| MTX usage | 1117 (60.8) |
| MTX dose (mg/week) | 7.2±2.3 (1–14) |
| PSL usage | 711 (38.7) |
| PSL dose (mg/day) | 3.8±2.1 (0–25) |
| Biologics/JAK usage | 501 (27.2) |
| Comorbidity | |
| Hypertension | 619 (33.7) |
| Diabetes mellitus | 149 (8.1) |
| Respiratory disease | 224 (12.2) |
| Cerebrovascular disease | 86 (4.7) |
| Cardiovascular disease | 174 (8.0) |
| Renal disease | 464 (25.2) |
| Malignant tumor | 105 (5.7) |

Values are expressed as the number of patients (%) or the mean ± SD (range)

*ACPA* anticyclic citrullinated peptide antibody, *DAS* Disease Activity Score-28 joint count, *HAQ* Health Assessment Questionnaire, *DMARDs* disease-modifying anti-inflammatory drugs, *MTX* methotrexate, *PSL* prednisolone, *JAK* Janus kinase inhibitors, *SD* standard deviation

On comparing the two groups, the H group was older ($p$<0.0001); had a higher proportion of women ($p$=0.0017); and had a longer disease duration ($p$=0.0055), more advanced stage ($p$<0.0001) and Steinbrocker class ($p$<0.0001), and higher ACPA levels ($p$=0.0034) than the L group. The usage rate of DMARDs ($p$=0.0017), MTX ($p$=0.0387), and Bio/JAK ($p$<0.0001) was lower in the H group; however, the usage rate and dose of PSL were higher in the H group ($p$<0.0001) than in the L group. Moreover, the H group had a higher prevalence of hypertension ($p$<0.0001), diabetes ($p$=0.0011), respiratory disease ($p$<0.0001), cerebrovascular disease ($p$<0.0001), and cardiovascular disease ($p$=0.0030) (Table 2). Multivariate logistic regression analysis revealed that female sex ($p$=0.0054), advanced Steinbrocker class ($p$<0.0001), high ACPA levels ($p$=0.0211), high PSL dose ($p$<0.0001), and absence of Bio/JAK use ($p$<0.0001) were risk factors for high disease activity; shorter treatment period was a low-risk factor for high disease activity ($p$=0.0041). Among comorbidities, the presence of cerebrovascular disease ($p$=0.0334) was associated with high disease activity (Table 3).

## Discussion

Using our patient registry with a high proportion of elderly patients, we found that cerebrovascular disease was associated with high disease activity in patients with RA, among the comorbidities studied. Since patients from the registry had a higher average age of 66.4 years, and a higher prevalence of cardiovascular disease (8.0%) and cerebrovascular disease (4.7%) than those in other reports [4, 8, 18], this finding has important implications for the treatment of rheumatoid arthritis in the elderly.

In the comparison between the two groups, the H group was older, had more comorbidities, used MTX and Bio less often, and used a higher dose of PSL. This result is consistent with that of a previous study [14] which suggested that the presence of comorbidities influenced the choice of treatment. In addition, it has been reported that female RA patients who have a longer disease duration and belong to a higher disease functional class as per the Steinbrocker criteria do not respond to treatment as well as those with a shorter disease duration [19]. The results of our multivariate logistic regression analysis support these previous findings, indicating that early and adequate therapeutic intervention is necessary in the treatment of RA.

Conversely, it has been reported that RA is an independent risk factor for cardiovascular and cerebrovascular disease due to the progression of arteriosclerosis caused by chronic inflammation and decreased physical activity [20–24]. Previously, Crepaldi et al. reported that ischemic heart disease was related to RA disease

**Table 2** Comparison between the remission or low disease activity group (L group) and moderate or high disease activity group (H group) by DAS28

| Variables | L group | H group | *p* value |
|---|---|---|---|
| Total patients | 1133 | 705 | |
| Age (years) | 64.2±13.0 | 70.0±12.2 | <0.0001* |
| Sex—male/female | 251 (22.2)/882 (77.8) | 114 (16.2)/591 (83.8) | 0.0017* |
| Disease duration (months) | 145±120 | 162±141 | 0.0055* |
| Steinbrocker stage I/II/III/IV | 33.8/21.9/21.9/22.4 | 18.8/22.7/27.5/31.0 | <0.0001* |
| Steinbrocker class I/II/III/IV | 59.5/33.5/5.7/1.3 | 25.8/49.5/20.3/4.4 | <0.0001* |
| ACPA (U/ml) | 114±173 | 181±436 | 0.0034* |
| DAS | 2.2±0.7 | 4.1±0.8 | <0.0001* |
| SDAI | 3.9±3.2 | 12.7±7.5 | <0.0001* |
| HAQ | 0.5±1.1 | 1.4±3.6 | <0.0001* |
| DMARDs usage | 1133 (61.6) | 705 (38.4) | 0.0017* |
| MTX usage | 711 (62.7) | 406 (57.6) | 0.0387* |
| MTX dose (mg/week) | 7.3±2.3 | 7.2±2.4 | 0.5686 |
| PSL usage | 370 (32.7) | 341 (48.4) | <0.0001* |
| PSL dose (mg/day) | 3.5±2.1 | 4.1±2.1 | <0.0001* |
| Biologics/JAK usage | 346 (30.5) | 155 (22.0) | <0.0001* |
| Comorbidity | | | |
| Hypertension | 312 (27.5) | 307 (43.5) | <0.0001* |
| Diabetes mellitus | 73 (6.4) | 76 (10.8) | 0.0011* |
| Respiratory disease | 104 (9.2) | 120 (17.0) | <0.0001* |
| Cerebrovascular disease | 32 (2.8) | 54 (7.7) | <0.0001* |
| Cardiovascular disease | 71 (6.2) | 72 (10.2) | 0.0030* |
| Renal disease | 310 (27.4) | 256 (36.3) | 0.0562 |
| Malignant tumor | 60 (5.3) | 45 (6.4) | 0.5695 |

Values are expressed as the number of patients (%) or the mean ± SD

*ACPA* anticyclic citrullinated peptide antibody, *DAS* Disease Activity Score-28 joint count, *HAQ* Health Assessment Questionnaire, *DMARDs* disease-modifying anti-inflammatory drugs, *MTX* methotrexate, *PSL* prednisolone, *JAK* Janus kinase inhibitors, *SD* standard deviation

*Statistically significant

activity [10]. However, in our study, cardiovascular disease, including ischemic heart disease, was not a risk factor for high disease activity. This may have been due to several reasons. First, Asians have a lower risk of developing ischemic heart disease than Westerners [25], and therefore, there may have been fewer patients with ischemic heart disease in our study. Second, in our registry, the category of "cardiovascular disease" included not only ischemic heart disease, but also heart failure and cardiomyopathy. Heart failure and cardiomyopathy do not directly correlate with RA disease activity, and this may have influenced our results.

The association between cerebrovascular disease and disease activity of RA has been previously reported, and proper treatment and maintenance of low disease activity in RA can suppress the progression of atherosclerosis [26], thereby reducing the risk of cerebrovascular events [27]. Our results suggest that cerebrovascular events may be more frequent in RA patients with high disease activity, and provide evidence for the effectiveness of appropriate treatment, including Bio, based on recent T2T strategies. Another possible interpretation is that patients with a history of cerebrovascular disease are not being treated appropriately. In fact, the physical limitations of patients have been reported to be barriers to achieving optimal disease activity [18], and the usage rate of biologics has been reported to be lower in patients with cerebrovascular disease because this comorbidity is attributed to increased fragility [28]. In this study as well, a high Steinbrocker class was a risk factor for high disease activity in the multivariate logistic regression analysis; impaired physical function was associated with high disease activity. Although the definition of patient fragility is unclear and the association between cerebrovascular disease and the patient's physical function and usage rate of biologics has not been investigated in this study, we hypothesized that the general health condition of patients with a history of stroke influenced the treatment choice of their physicians and resulted in high disease activity.

**Table 3** Multivariate logistic regression analysis for the moderate or high disease activity in rheumatoid arthritis patients

| Variables | OR | 95%CI | *p* value |
|---|---|---|---|
| Age | 1.0005 | 0.9923–1.0183 | 0.4303 |
| Female | 1.7759 | 1.1951–2.6826 | 0.0054* |
| Disease duration | 0.9979 | 0.9965–0.9993 | 0.0041* |
| Steinbrocker stage | 1.1723 | 0.9972–1.3786 | 0.0540 |
| Steinbrocker class | 2.4559 | 1.9617–3.0942 | <0.0001* |
| ACPA | 1.0008 | 1.0001–1.0016 | 0.0211* |
| MTX usage | 1.0330 | 0.7607–1.4072 | 0.8356 |
| PSL usage | 1.8142 | 1.3524–2.4352 | <0.0001* |
| Biologics/JAK usage | 0.4870 | 0.3431–0.6849 | <0.0001* |
| Hypertension | 1.0769 | 0.7698–1.5013 | 0.6632 |
| Diabetes mellitus | 1.2927 | 0.7782–2.1835 | 0.3182 |
| Respiratory disease | 1.4247 | 0.9261–2.1846 | 0.1053 |
| Cerebrovascular disease | 1.8682 | 1.0642–3.6347 | 0.0334* |
| Cardiovascular disease | 1.5137 | 0.8919–2.5645 | 0.1229 |
| Renal disease | 1.1947 | 0.8229–1.7320 | 0.3479 |
| Malignant tumor | 0.7047 | 0.3762–1.2753 | 0.2590 |

*OR* odds ratio, *CI* confidence interval, *ACPA* anticyclic citrullinated peptide antibody, *MTX* methotrexate, *PSL* prednisolone, *JAK* Janus kinase inhibitors

*Statistically significant

The presence of respiratory disease is the most important comorbidity to consider when treating patients with both MTX and biologics, as it increases the risk of drug-related risks, such as the development and exacerbation of IP and respiratory infections [28–30]. Therefore, respiratory disease could also be a risk factor for high disease activity in terms of drug selection. However, in this study, there was no statistically significant association between disease activity and respiratory disease in patients with RA. A previous study reported that respiratory comorbidity affected patient-reported outcomes [10]. However, to our knowledge, there are no studies that have revealed an association between RA disease activity and the presence of respiratory comorbidities. A variety of treatment options, including the careful use of MTX and biologics with close monitoring of symptoms [28, 31] and the use of some biologic agents with a low risk of infection but good efficacy in improving activity, could contribute to achieving low disease activity in patients with comorbid conditions [32, 33].

This study had several limitations. First, this was a cross-sectional observational study; hence, it was difficult to evaluate the influence of comorbidities on therapeutic response and selection of drugs, and to clearly establish a causal relationship between comorbidities, disease characteristics, and treatment. Second, we did not investigate other painful diseases, such as osteoarthritis and spondylosis, which may influence the assessment of disease activity. Although comorbidities generally increase in the elderly, we did not compare comorbidities in the non-RA group. Finally, our study was not limited to the elderly, as it included all RA patients older than 18 years. Finally, although our data is from the region with the highest rate of aging, our study is not limited to the elderly because we analyzed all registered cases, including all patients with RA aged 18 years and older. Further research is needed to confirm these findings by refining the registration methods, collecting more detailed data, and conducting longitudinal studies.

## Conclusions

In our registry study with a high proportion of elderly RA patients, we revealed that in patients with moderate-to-high disease activity as classified by DAS28-ESR, the prevalence of hypertension, diabetes mellitus, respiratory disease, and cardio-cerebrovascular disease, but not renal disease and malignant tumor, was significantly higher. Furthermore, multivariate logistic regression analysis showed that among the comorbidities, only cerebrovascular disease was associated with high disease activity in patients with RA. Therefore, when treating elderly patients with RA, we need to pay careful attention to cerebrovascular disease, and treatment should be aimed at achieving adequate control of RA.

#### Abbreviations

RA: Rheumatoid arthritis; AORA: Akita Orthopedic Group on Rheumatoid Arthritis; DAS28-ESR: Disease activity score in 28 joints based on the erythrocyte sedimentation rate; DMARDs: Disease-modifying antirheumatic drugs; MTX: Methotrexate; Bio: Biologics; JAK: Janus kinase inhibitors; T2T: Treat-to-target; ACPA: Anti-citrullinated protein antibody; SDAI: Simplified disease activity index; HAQ: The health assessment questionnaire disability index; PSL: Prednisolone; DM: Diabetes mellitus; COPD: Chronic obstructive pulmonary disease; IP: Interstitial pneumonia; eGFR: Estimated glomerular filtration rate; SD: Standard deviation.

#### Acknowledgements

The authors would like to thank Moto Kobayashi, Masakazu Urayama, Natsuo Konishi, Hiroki Ito, Takayuki Tani, Tsutomu Sakuraba, Toshiaki Aizawa, Hidekazu Abe, Norio Suzuki, Keiji Kamo, Hiroshi Aonuma, Tetuya Kawano, and Yosuke Iwamoto for data collection and sharing their dataset with us.

#### Authors' contributions

TM, NM, HT, and YS conceived and design the study, in addition to drafting the manuscript. TK data collected. YS gave final approval. All authors read and approved the final manuscript.

#### Funding

The authors received no specific funding for this work.

#### Availability of data and materials

All data generated or analyzed during this study are included in this published article.

## Declarations

### Ethics approval and consent to participate

The study's protocol was approved by the Institutional Review Board for Clinical Research at Kakunodate General Hospital (approval number, 00409), and informed consent was obtained from each individual patient in accordance with the Declaration of Helsinki.

### Consent for publication

Not applicable

### Competing interests

The authors declare that they have no competing interests.

### Author details

[1]Department of Orthopedic Surgery, Kakunodate General Hospital, 3 Iwase Kakunodate, Senboku, Akita 014-0394, Japan. [2]AORA (Akita Orthopedic Group on Rheumatoid Arthritis), 1-1-1 Hondo, Akita 010-8543, Japan. [3]Department of Orthopedic Surgery, Akita University Graduate School of Medicine, 1-1-1 Hondo, Akita 010-8543, Japan.

Received: 14 October 2021 Accepted: 28 December 2021
Published online: 15 February 2022

### References

1. Shourt CA, Crowson CS, Gabriel SE, Matteson EL (2012) Orthopedic surgery among patients with rheumatoid arthritis 1980-2007: a population-based study focused on surgery rates, sex, and mortality. J Rheumatol 39:481–485. https://doi.org/10.3899/jrheum.111056
2. Smolen JS, Aletaha D, Bijlsma JWJ, Breedveld FC, Boumpas D, Burmester G et al (2010) Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis 69:631–637. https://doi.org/10.1136/ard.2009.123919
3. Rasch EK, Hirsch R, Paulose-Ram R, Hochberg MC (2003) Prevalence of rheumatoid arthritis in persons 60 years of age and older in the United States: Effect of different methods of case classification. Arthritis & Rheumatism 48:917–916. https://doi.org/10.1002/art.10897
4. Köller MD, Aletaha D, Funovits J, Pangan A, Baker D, Smolen JS (2009) Response of elderly patients with rheumatoid arthritis to methotrexate or TNF inhibitors compared with younger patients. Rheumatology 48:1575–1580. https://doi.org/10.1093/rheumatology/kep291
5. Burmester GR, Ferraccioli G, Elipo R-M, Monteagudo-Sáez I, Unnebrink K, Kary S et al (2008) Clinical remission and/or minimal disease activity in patients receiving adalimumab treatment in a multinational, open-label, twelve-week study. Arthritis Rheum 59:32–41. https://doi.org/10.1002/art.23247
6. Sokka T, Makinen H, Hannonen P, Pincus T (2007) Most people over age 50 in the general population do not meet ACR remission criteria or OMERACT minimal disease activity criteria for rheumatoid arthritis. Rheumatology 46:1020–1023. https://doi.org/10.1093/rheumatology/kem051
7. Treharne GJ, Douglas KMJ, Iwaszko J, Panoulas VF, Hale ED, Mitton DL et al (2007) Polypharmacy among people with rheumatoid arthritis: the role of age, disease duration and comorbidity. Musculoskeletal Care 5:175–190. https://doi.org/10.1002/msc
8. Jung SM, Kwok SK, Ju JH, Lee SW, Song JJ, Yoon CH et al (2018) Risk factors associated with inadequate control of disease activity in elderly patients with rheumatoid arthritis: results from a nationwide KOrean College of Rheumatology BIOlogics (KOBIO) registry. PLoS ONE 13:e0205651. https://doi.org/10.1371/journal.pone.0205651
9. Ranganath VK, Maranian P, Elashoff DA, Woodworth T, Khanna D, Hahn T et al (2013) Comorbidities are associated with poorer outcomes in community patients with rheumatoid arthritis. Rheumatology (Oxford) 52:1809–1817. https://doi.org/10.1093/rheumatology/ket224
10. Crepaldi G, Scire CA, Carrara G, Sakellariou G, Caporali R, Hmamouchi I et al (2016) Cardiovascular comorbidities relate more than others with disease activity in rheumatoid arthritis. PLoS ONE 11:e0146991. https://doi.org/10.1371/journal.pone.0146991
11. Sugimura Y, Miyakoshi N, Miyamoto S, Kasukawa Y, Hongo M, Shimada Y (2016) Prevalence of and factors associated with lumbar spondylolisthesis in patients with rheumatoid arthritis. Mod Rheumatol 26:342–346. https://doi.org/10.3109/14397595.2015.1081326
12. Statistics Bureau Home Page/Population Census. 2020. http://www.stat.go.jp/english/data/kokusei/index.html. Accessed 5 Apr 2020.
13. Dougados M, Soubrier M, Antunez A (2014) Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring : results of an international, cross-sectional study (COMORA). Ann Rheum Dis 73:62–68. https://doi.org/10.1136/annrheumdis-2013-204223
14. Nakajima A, Inoue E, Shimizu Y, Kobayashi A, Shidara K, Sugimoto N et al (2014) Presence of comorbidity affects both treatment strategies and outcomes in disease activity, physical function, and quality of life in patients with rheumatoid arthritis. Clin Rheumatol 34:441–449. https://doi.org/10.1007/s10067-014-2750-8
15. Steinbrocker O, Traeger CH, Batterman RC (1949) Therapeutic criteria in rheumatoid arthritis. J Am Med Assoc 140:659–662. https://doi.org/10.1001/jama.1949.02900430001001
16. Hallan S, Matsushita K, Sang Y, Mahmoodi BK, Black C, Ishani A et al (2012) Age and the association of kidney measures with mortality and end-stage renal disease. J Am Med Assoc 308:2349–2360. https://doi.org/10.1001/jama.2012.16817
17. van der Heijde DM, van't Hof M, van Riel PL, van de Putte LB (1993) Development of a disease activity score based on judgment in clinical practice by rheumatologists. J Rheumatol 20:579–581
18. Owensby JK, Chen L, O'Beirne R, Ruderman EM, Harrold LR, Melnick JA et al (2019) Patient and rheumatologist perspectives regarding challenges to achieving optimal disease control in rheumatoid arthritis. Arthritis Care Res (Hokoben) 72:933–941. https://doi.org/10.1002/acr.23907
19. Anderson JJ, Wells G, Verhoeven AC, Felson DT (2000) Factors predicting response to treatment in rheumatoid arthritis: the importance of disease duration. Arthritis Rheum. 43(1):22–29. https://doi.org/10.1002/1529-0131(200001)43:1<22::AID-ANR4>3.0.CO;2-9
20. Arts EEA, Fransen J, den Broeder AA, Popa CD, van Riel PLCM (2015) The effect of disease duration and disease activity on the risk of cardiovascular disease in rheumatoid arthritis patients. Ann Rheum Dis 74:998–1003. https://doi.org/10.1136/annrheumdis-2013-204531
21. Solomon DH, Karlson EW, Rimm EB, Cannuscio CC, Mandl LA, Manson JE et al (2003) Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. Circulation 107:1303–1307. https://doi.org/10.1161/01.CIR.0000054612.26458.B2
22. Wiseman SJ, Ralston SH, Wardlaw JM (2016) Cerebrovascular disease in rheumatic diseases a systematic review and meta-analysis. Stroke 47:943–950. https://doi.org/10.1161/STROKEAHA.115.012052
23. Michaud K, Wolfe F (2007) Comorbidities in rheumatoid arthritis. Best Pract Res Clin Rheumatol 21:885–906. https://doi.org/10.1016/j.berh.2007.06.002
24. Peters MJL, Symmons DPM, McCarey D, Szekanecz Z, Sattar NG, McInnes MT et al (2010) EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Ann Rheum Dis 69:325–331. https://doi.org/10.1136/ard.2009.113696
25. Hirotsugu U, Akira S, Katsuyuki M, Turin TC, Takashima N, Kita Y et al (2008) Cardiovascular disease and risk factors in Asia: a selected review. Circulation 118:270227–270209. https://doi.org/10.1161/CIRCULATIONAHA.110.956839
26. Arida A, Protogerou AD, Konstantonis G, Fragiadaki K, Kitas GD, Sfikakis PP (2017) Atherosclerosis is not accelerated in rheumatoid arthritis of low activity or remission, regardless of antirheumatic treatment modalities. Rheumatology 56:934–939. https://doi.org/10.1093/rheumatology/kew506
27. Tang C-H, Yu F, Huang C-Y, Chen D-Y (2019) Potential benefits of biologics on stroke and mortality in patients with rheumatoid arthritis: A nationwide population-based cohort study in Taiwan. Int J Rheum Dis 22:1544–1552. https://doi.org/10.1111/1756-185X.13611
28. Bengtsson K, Jacobsson LTH, Rydberg B, Kvist G, Torstenson T, Dehlin M et al (2016) Comparisons between comorbid conditions and health care consumption in rheumatoid arthritis patients with or without biological disease-modifying anti-rheumatic drugs: a register-based study. BMC Musculoskelet Disord 17:1–10. https://doi.org/10.1186/s12891-016-1354

29. Tokuda H, Harigai M, Kameda H, Tomono K, Takayanagi N, Watanabe A et al (2017) Consensus statements for medical practice: Biological agents and Lung disease [Abridged English translation by the Japanese Respiratory Society]. Respir Investig 55:229–251. https://doi.org/10.1016/j.resinv.2017.01.002
30. Roubille C, Haraoui B (2014) Interstitial lung diseases induced or exacerbated by DMARDS and biologic agents in rheumatoid arthritis: a systematic literature review. Semin Arthritis Rheum 43:613–626. https://doi.org/10.1016/j.semarthrit.2013.09.005
31. Alarcon GS, Kremer JM, Macaluso M, Weinblatt ME, Cannon GW, Palmer WR (1997) Risk factors for methotrexate-induced lung injury in patients with rheumatoid arthritis. A multicenter, case-control study. Ann Intern Med. 127:356–364. https://doi.org/10.7326/0003-4819-127-5-199709010-00003
32. Yun H, Xie F, Delzell E, Levitan EB, Chen L, Lewis JD et al (2016) Comparative risk of hospitalized infection associated with biologic agents in rheumatoid arthritis patients enrolled in Medicare. Arthritis Rheumatol 68:56–66. https://doi.org/10.1002/art.39399
33. Ebina K, Hashimoto M, Yamamoto W, Hirano T, Hara R, Katayama M et al (2019) Drug tolerability and reasons for discontinuation of seven biologics in elderly patients with rheumatoid arthritis -The ANSWER cohort study. PLoS ONE 14:e0216624. https://doi.org/10.1371/journal.pone.0216624

## Publisher's Note