ARP Rheumatology 2024;3:189-195
https://doi.org/10.63032/HLRQ1951

ORIGINAL ARTICLES

High disease activity influences the presence of vertebral fractures in rheumatoid arthritis

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ABSTRACT

Introduction: It is important to assess the risk of vertebral fractures (VFs) in patients with rheumatoid arthritis (RA), as RA is associated with a high risk of VFs. However, the epidemiology and risk of VFs in patients with RA remain inconclusive. The present study therefore clarified the prevalence and associated factors of VFs in patients with RA.
Methods: We included 107 patients (19 men and 88 women) and retrospectively investigated the number and location of VFs, bone mineral density (BMD), RA disease activity score for 28 joints based on C-reactive protein (DAS28-CRP), and history of medication for RA and osteoporosis. Based on the investigated items, we assessed the prevalence of VFs in patients with RA and the association between the clinical parameters of RA patients and VFs.
Results: The average age, disease duration, and DAS28-CRP were 67.9 years old, 14.9 years, and 2.2, respectively. We found that the prevalence of VFs in patients with RA was 30.8%, and 84.8% of patients with VFs and 62.2% of those without VFs had been treated for osteoporosis. We further found that the prevalence of VFs in patients with RA with a history of anti-osteoporotic agent use was 37.8%. In univariate analyses, patients with RA with VFs had significantly higher DAS28-CRP values, a higher rate of corticosteroid use, and lower BMD ($p = 0.018$, $p = 0.004$, and $p < 0.001$, respectively) than those without VFs. A multivariable logistic regression analysis and ordinal logistic analysis revealed that the DAS28-CRP and BMD were independent factors associated with the presence ($p = 0.042$ and $p = 0.011$, respectively) and number ($p = 0.036$ and $p = 0.048$, respectively) of VFs.
Conclusions: The prevalence of VFs was relatively high in patients with RA, regardless of the use of anti-osteoporotic agents. A high disease activity score and low BMD are associated with the presence and number of VFs in patients with RA. Based on these findings, to reduce VFs in RA patients, it is important to tightly control the disease activity of RA in addition to osteoporosis treatment.

Keywords: Anti-osteoporotic agent; Disease activity; Osteoporosis; Rheumatoid arthritis; Vertebral fracture.

BACKGROUND

Patients with rheumatoid arthritis (RA) are more likely to have osteoporosis than the general population, and RA is considered a risk factor for fragility fractures, including vertebral fractures (VFs)[1-3]. Inflammatory cytokines, activated osteoclasts, and steroids use have been reported as plausible explanations for osteoporosis in RA[1-4].

VFs are associated with a reduced functional status[5-12], and the presence of existing VFs is a risk factor for new VF and other fragile fractures[13, 14]. Therefore, it is important to assess the risk of VFs, particularly in patients with RA.

The arrival of biological agents has dramatically changed the treatment strategy for RA and the use of biological agents has also been reported to influence bone mineral density (BMD) improvement[15]. However, the relationship between biological agents and VFs has not been sufficiently investigated, the assessment of the risk of VFs remains important in RA patients.

Nevertheless, the epidemiology and risk factors for VFs in patients with RA have not been adequately elucidated. The present study therefore clarified the prevalence and associated factors of VFs in patients with RA.

This article was previously posted to the Research Square preprint server on January 7, 2024.

MATERIALS AND METHODS

Patients

We retrospectively reviewed 426 patients with RA who were treated at an outpatient RA clinic at our university

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Submitted: 21/04/2024
Accepted: 01/07/2024

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hospital between July 2017 and June 2020. All patients met the American College of Rheumatology classification criteria established in 1987[16]. Among them, we included 107 patients who underwent lateral radiography of the thoracolumbar spine and dual-energy X-ray absorptiometry (DEXA). Patients with a history of thoracolumbar surgery were excluded (Fig. 1).

The research protocol was approved by the Institutional Review Board of Gunma University Hospital (IRB No. HS2019-117), and written informed consent for participation was obtained from all patients.

The assessment of VFs

We assessed VFs from T4 to L5 using Genant's semi-quantitative classification based on the last available lateral radiograph of the thoracolumbar spine[17]. Vertebral deformities were classified into four grades: grade 0 (normal), grade 1 (mild), grade 2 (moderate), and grade 3 (severe) according to vertebral height reduction (vertebral height reductions of >20% to 25%, >25% to 40%, and >40%). Grade ≥1 was classified as VF in this study. The number of VFs was categorized as 0, 1, 2, or ≥3, according to a previous report[14].

The measurement of the BMD

We measured the BMD of the femoral neck using DEXA (Discovery A System; Hologic, Inc., Waltham, MA, USA), which was performed within 6 months of the VFs assessment. We also calculated T-scores based on normative data for Asian women.

Clinical parameters

We collected clinical data within three months of the VF assessment from medical records. The clinical data included the following: age, sex, body mass index (BMI), duration of RA, rheumatoid factor (RF), anti-cyclic citrullinated peptide antibody (ACPA), C-reactive protein (CRP), tender joint count, swollen joint count, visual analog scale (VAS) of patients' global assessment, and use of medication for RA and osteoporosis for ≥3 months. We further calculated the disease activity score for 28 joints based on C-reactive protein (DAS28-CRP) and the Health Assessment Questionnaire-Disability Index (HAQ-DI) to assess the functional status of patients with RA.

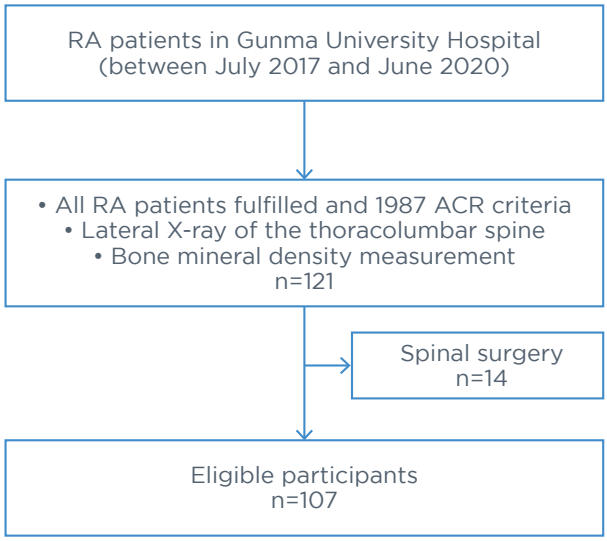

Figure 1. Flow diagram of the present study. ACR, American College of Rheumatology; RA, rheumatoid arthritis.

Statistical analyses

We performed univariate and logistic regression analyses using the STATA/SE software program (version 15; StataCorp, College Station, TX, USA). The Mann-Whitney U test was used to compare continuous data, and the chi-square test or Fisher's exact test was used for categorical variables. To identify associated factors for VFs in RA patients, a multivariable logistic regression analysis was performed with VFs as the dependent variable and the age, sex, BMI, history of corticosteroid use, history of biologic use, anti-osteoporotic agent use, DAS28-CRP, and BMD as independent variables. To identify factors associated with the number of VFs in patients with RA, an ordinal logistic regression analysis was also performed with the categorized number of VFs as the dependent variable. Statistical significance was set at $P < 0.05$. The observed power of the findings was calculated using a post-hoc power analysis with alpha = 0.05 representing the statistical power.

RESULTS

The demographics and clinical characteristics of the patients with RA in the study population are shown in Table I. Of the 107 patients with RA, 19 were men, and 88 were women. The mean age was 67.9 years old. The average disease duration was 14.9 years, and the average DAS28-CRP level was 2.2.

At the time of the VF assessment, 74 patients (69.2%) had a history of anti-osteoporotic agent use. A total of 95 VFs were identified in 33 patients (30.8%). The VFs showed a bimodal distribution, with peaks at the middle thoracic spine and thoracolumbar junction (Fig. 2). Of the 33 patients with VF, 28 (84.8%) were being treated for osteoporosis. Among those with a history of anti-osteoporotic agent use, 37.8% (28/74) had VFs.

As shown in Table II, in patients with VFs, the DAS28-CRP and the prevalence of a history of corticosteroid use were significantly higher ($p = 0.018$ and $p = 0.004$, respectively) and the BMD was significantly

TABLE I. Characteristics of the RA patients in the study population

N=107	Value
Age (years), mean ± SD	67.9 ± 10.9
Female, n (%)	88 (82.2)
BMI (kg/m²), mean ± SD	23.3 ± 3.9
Disease duration (years), mean ± SD	14.9 ± 11.2
RF positivity, n (%)	74 (69.3)
ACPA positivity, n (%)	83 (77.6)
Steinbrocker class (1/2/3/4)	17/65/24/1
Steinbrocker stage (I/II/III/IV)	14/21/39/33
Tender joint count, 28 joints, mean ± SD	1.6 ± 3.0
Swollen joint count, 28 joints, mean ± SD	1.0 ± 2.8
Global assessment score, mean ± SD	22.7 ± 24.7
CRP (mg/dl), mean ± SD	0.4 ± 0.5
DAS28-CRP, mean ± SD	2.2 ± 1.0
MTX use, n (%)	85 (79.4)
History of corticosteroid use, n (%)	66 (61.7)
Current users, n (%)	47 (46.6)
Daily dose for current users (mg/day), mean ± SD	3.9 ± 2.4
Long users (≥12months), n (%)	61 (57.0)
History of biologic agent use, n (%)	61 (57.0)
TNF inhibitor, n (%)	46 (43.0)
Tocilizumab, n (%)	26 (24.3)
Abatacept, n (%)	17 (15.9)
Anti-osteoporotic agent use, n (%)	74 (69.2)
Activate vitamin D3, n (%)	56 (52.3)
Bisphosphonate, n (%)	41 (38.3)
Denosumab, n (%)	22 (20.6)
Prevalence of vertebral fracture, n (%)	33 (30.8)
Number of vertebral fractures	
1, n	15
2, n	10
≥3, n	8
BMD (T-score at femoral neck), mean ± SD	-2.0 ± 1.0
HAQ-DI, mean ± SD	0.8 ± 0.8

ACPA, anti-cyclic citrullinated peptide antibody; BMD, bone mineral density; BMI, body mass index; CRP, C-reactive protein; DAS28-CRP, disease activity score for 28 joints based on C-reactive protein; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; MTX, methotrexate; RA, rheumatoid arthritis; RF, rheumatoid factor; SD, standard deviation; TNF, tumor necrosis factor

lower (p <0.001) than in patients without VFs.

A multivariable logistic regression analysis revealed that the DAS28-CRP (odds ratio [OR]: 1.82, p = 0.042, 95% confidence interval [CI]: 1.023-3.224) and BMD (OR: 0.36, p = 0.011, 95% CI: 0.161-0.794) were statistically significant factors for VFs in RA patients (Table III). An ordinal logistic regression analysis revealed that the DAS28-CRP (OR: 1.77, p = 0.036, 95% CI: 1.039-3.000) and BMD (OR: 0.51, p = 0.048, 95% CI: 0.263--0.994) were statistically significant factors associated with the number of VFs in RA patients (Table IV).

DISCUSSION

Our study has two main findings. First, we determined the prevalence of VFs in patients with RA (30.8%) and found that the prevalence remained almost the same (37.8%), even when patients with RA had a history of guideline-recommended anti-osteoporotic agent use. Second, a high DAS28-CRP and low BMD were independent factors associated with the presence and number of VFs.

The prevalence of VFs in patients with RA has been reported to be 13%-45.5%, which is higher than that in the general population or in the control group[4, 18-23]. In our study, the prevalence of VFs in patients with RA was consistent with that reported previously. In patients with VFs, the prevalence of a history of anti-osteoporotic agent use were significantly higher in the univariate analysis. The reason for this result in the univariate analysis is probably because the majority of VF patients with a history of anti-osteoporotic agent use began taking the medication after VF was diagnosed. Further research is needed on the relationship between the presence of VFs and osteoporosis treatment.

Some studies have reported a relationship between VFs and a high disease activity in RA patients[21, 23, 24]. In line with previous studies, RA disease activity was found to be a risk factor for VFs in patients with RA in this study. Thus, this result suggests that it is important not only to use anti-osteoporotic agents but also to reduce RA disease activity for the prevention of VFs in RA patients.

In our study, low BMD were independent factors associated with the presence and number of VFs. Although there is certainly evidence in the general population that low BMD is a risk factor for VFs[14, 25], there is still no consensus regarding the relationship between BMD and VFs in RA patients. While there are several papers showing results indicating that low BMD was a risk factor for VFs in RA patients[4, 18, 24], Başkan BM et al. reported that low BMD is not related to a risk factor for VFs[26]. Therefore, we believe that this study can contribute to the accumulation of evidence on this issue although further research is needed in the future.

In our study, the use of corticosteroids was a significant factor for VFs in the univariate analysis; however, it was not identified as an independent factor associated with VFs after adjusting for confounders in multivariable logistic regression analyses. The discrepancy be-

TABLE II. Demographic and clinical parameters of RA patients with and without vertebral fractures

	without vertebral fractures (n=74)	with vertebral fractures (n=33)	*p* value	Observed power
Age (years), mean ± SD	67.0 ± 11.8	70.2 ± 8.5	0.254	30.02%
Female, n (%)	61 (82.4)	27 (81.8)	0.939	5.30%
BMI, kg/m², mean ± SD	23.5 ± 4.0	23.0 ± 3.6	0.791	8.25%
Disease duration of RA, years, mean ± SD	13.8 ± 10.4	17.1 ± 12.5	0.248	26.38%
Tender joint count, 28 joints, mean ± SD	1.1 ± 1.8	2.7 ± 4.6	0.155	54.75%
Swollen joint count, 28 joints, mean ± SD	0.8 ± 2.8	1.3 ± 2.6	0.351	12.15%
Global assessment score, mean ± SD	19.2 ± 20.7	31.0 ± 31.2	0.190	54.28%
CRP, mg/dl, mean ± SD	0.31 ± 0.53	0.45 ± 0.57	0.216	21.83%
DAS28-CRP, mean ± SD	2.1 ± 0.9	2.7 ± 1.2	0.018	78.30%
History of corticosteroid use, n (%)	39 (52.7)	27 (81.8)	0.004	99.99%
History of biologic agent use, n (%)	38 (51.4)	23 (69.7)	0.078	97.57%
Anti-osteoporotic agent use, n (%)	46 (62.2)	28 (84.8)	0.020	99.84%
Activate vitamin D3, n (%)	34 (45.9)	22 (66.7)		
Bisphosphonate, n (%)	24 (32.4)	17 (51.5)		
Denosumab, n (%)	12 (16.2)	10 (30.3)		
BMD (T-score at femoral neck), mean ± SD	-1.7 ± 1.0	-2.5 ± 0.9	< 0.001	95.93%
HAQ-DI, mean ± SD	0.6 ± 0.7	1.0 ± 1.0	0.111	57.36%

BMD, bone mineral density; BMI, body mass index; CRP, C-reactive protein; DAS28-CRP, disease activity score for 28 joints based on C-reactive protein; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; RA, rheumatoid arthritis.

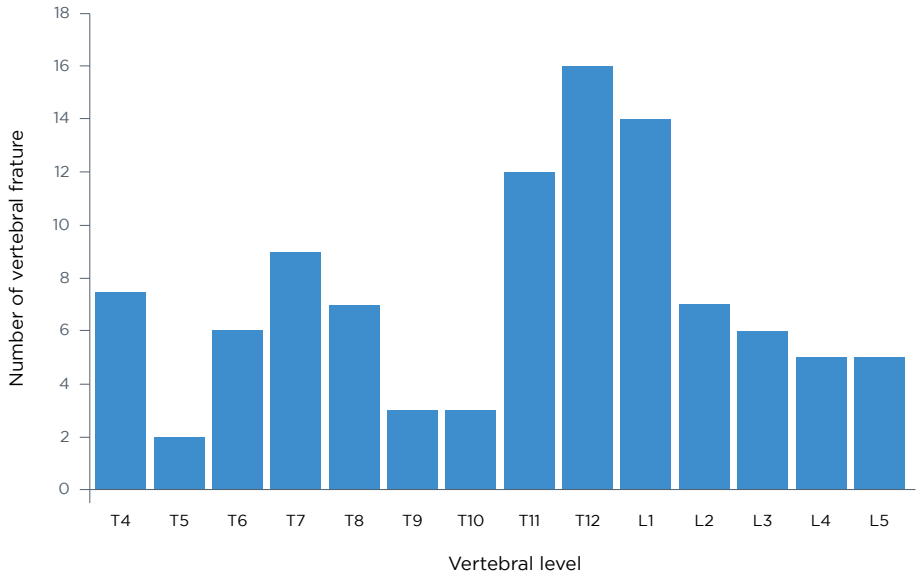

Figure 2. Number of vertebral fractures in patients with rheumatoid arthritis

tween the univariate analysis and the logistic regression analysis may be attributed to the potential confounding effects of other variables. The confounding effects of other variables such as age, sex, disease activity, and BMD could have acted as confounding factors for both vertebral fracture and corticosteroid use, leading to the loss of significance for corticosteroid use in the multivariable model. There are several previous studies that have found no significant association between the use of corticosteroids and VFs in RA patients[23, 24]. In line with our findings, El Maghraoui A et al. reported a significant association between the use of corticosteroids

TABLE III. Multivariable logistic regression of factors associated with vertebral fractures in RA patients

	OR	95% CI	*p* value
Age	0.98	0.931-1.052	0.732
Female	2.38	0.513-11.081	0.268
BMI	1.06	0.919-1.229	0.411
History of corticosteroid use	0.62	0.141-2.738	0.530
History of biologic agent use	1.59	0.477-5.332	0.449
Anti-osteoporotic agent use	4.62	0.743-28.764	0.101
DAS28-CRP	1.82	1.023-3.224	0.042
BMD (T-score at femoral neck)	0.36	0.161-0.794	0.011

BMD, bone mineral density; BMI, body mass index; DAS28, disease activity score for 28 joints based on C-reactive protein; OR, Odds ratio; 95% CI, 95% confidence interval; RA, rheumatoid arthritis.

TABLE IV. Multivariable ordinal logistic regression model of factors associated with the number of vertebral fractures in RA patients

	OR	95% CI	*p* value
Age	1.02	0.962-1.076	0.550
Female	2.40	0.529-10.920	0.256
BMI	1.02	0.896-1.168	0.734
History of corticosteroid use	0.71	0.175-2.855	0.625
History of biologic agent use	1.57	0.518-4.733	0.427
Anti-osteoporotic agent use	4.65	0.735-29.460	0.103
DAS28-CRP	1.77	1.039-3.000	0.036
BMD (T-score at femoral neck)	0.51	0.263-0.994	0.048

BMD, bone mineral density; BMI, body mass index; 95% CI, 95% confidence interval; DAS28-CRP, disease activity score for 28 joints based on C-reactive protein; OR, Odds ratio; RA, rheumatoid arthritis.

and VFs in univariate analysis, but no significant association in multivariate analysis. In patients with long-term RA, corticosteroids can reduce inflammation, increase activity, and prevent VF[24]. Ausaf Mohammad et al. also reported that no association between the use of corticosteroids and VFs was found. In this study, VFs in RA patients are not related to corticosteroid use, but are instead influenced by low bone density presumably due to chronic inflammation[23]. On the other hand, the use of corticosteroids has also been reported to affect VFs[4, 18, 19, 21], so further research is needed regarding corticosteroids and VFs.

Anti-rheumatic biological drugs have been reported to prevent bone loss in RA patients[27], and a previous study found that tumor necrosis factor inhibitors were associated with a reduced incidence of VF[28]. In contrast, other reports have demonstrated that biological agents do not contribute to increased BMD or reduce the risk of fractures[29]. However, these references investigated the incidence of VFs and BMD change after starting anti-rheumatic biological the drug, which differs from our study, which investigated the prevalence of VFs and BMD at the time of survey, we found no significant association between the use of biologics and VFs in this study.

Several limitations associated with the present study warrant mention. First, there may have been some selection bias, as this was a retrospective study. In this study, we only included patients who underwent an assessment of VFs and osteoporosis. Second, we lacked baseline data on VFs in patients with RA. It is possible that the presence of VFs before the diagnosis of RA influenced the results of this study. However, given the age of onset of RA, we assume that the majority of VFs in this study occurred after the diagnosis of RA, since the prevalence of VFs in the Japanese general population under 60 years old is <10%[12]. Further prospective studies are needed on this point. Third, the study population was relatively small. Thus, the statistical power may have been associated with some non-significant results or some of the investigated factors.

Despite these limitations, we believe that this study provides significant information regarding the treatment strategy for RA.

CONCLUSIONS

We retrospectively investigated the number and location of VFs, BMD, the RA disease activity score, and a history of RA and osteoporosis medication. Furthermore, we assessed the prevalence of VFs in patients with RA and the association between the clinical parameters of RA patients and VFs. We found that the prevalence of VFs in patients with RA was relatively high, regardless of the use of anti-osteoporotic agents. The presence and number of VFs in RA patients were associated with a high disease activity and low BMD. Based on these findings, to reduce VFs in RA patients, it is important to tightly control the disease activity of RA in addition to osteoporosis treatment.

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