Osteoporosis and Sarcopenia 9 (2023) 150–156

Contents lists available at ScienceDirect

Osteoporosis and Sarcopenia

journal homepage: www.elsevier.com/locate/afos

Original article

Pain score as a predictor of subsequent fragility fracture in postmenopausal patients with rheumatoid arthritis: A retrospective case-control study

Ichiro Yoshii [a,*], Naoya Sawada [b], Tatsumi Chijiwa [c]

[a] Department of Musculoskeletal Medicine, Yoshii Clinic, Shimanto, Japan
[b] Department of Rheumatology, Dohgo Onsen Hospital, Matsuyama, Japan
[c] Department of Rheumatology, Kochi Memorial Hospital, Kochi, Japan

ARTICLE INFO

Keywords:
Bone fragility
Female
Fracture
Pain
Rheumatoid arthritis

ABSTRACT

Objectives: Bone fragility fracture (BFF) is a serious incident in treating rheumatoid arthritis (RA). We hypothesized that pain degree during treatment RA correlated with incident BFF and validated how pain affects incident BFF (inc-BFF).

Methods: Postmenopausal RA patients treated for at least 3 years were recruited. The primary endpoint was the development of inc-BFF. Follow-up began with the first bone mineral density measurement (baseline) and continued until the development of the first BFF or termination of the study. Clinical indicators at baseline, including pain score using a visual analog scale (PS-VAS), were analyzed statistically using Cox regression analysis, receiver operation characteristics (ROC), Kaplan-Meier survival curve analysis (K-M), and chi-square test.

Results: A total of 239 patients were recruited. Using a multivariate Cox regression analysis, the baseline's PS-VAS and prevalent BFF (pr-BFF) demonstrated significantly higher risk ratios. For ROC, pr-BFF and PS-VAS had significant cutoff index (COI) (positive, 21.0) and an area under-curve of 0.692 ($P < 0.001$) and 0.616 ($P < 0.01$), respectively. PS-VAS > COI had a 2.24-fold higher hazard ratio than PS-VAS ≤ COI using K-M. When these 2 conditions were combined, patients with pr-BFF-positive and PS-VAS-positive had a sensitivity of 42.3% and a specificity of 88.8% for the inc-BFF. PS-VAS > COI had no statistical significance in the subgroup without pr-BFF, whereas the existence of pr-BFF had a significantly higher risk ratio in the PS-VAS ≤ COI.

Conclusions: The PS-VAS during RA treatment is a good indicator for predicting the inc-BFF in postmenopausal RA patients with pr-BFF.

1. Introduction

It is widely accepted that rheumatoid arthritis (RA) is a determinant risk factor of osteoporosis [1–4]. RA is associated with a high risk of bone fragility fracture (BFF); this is because of the identification of many other risk factors of osteoporosis involved in RA, such as glucocorticoid administration [5,6], chronic inflammation [7], impaired mobility due to joint deformity [8], sarcopenia (likely to be caused by decreased mobility), polypharmacy, and malnutrition cachexia [9]. Although RA has such a high risk of fragility fractures, few solid indicators are still linked to fracture risk. Although there are reports that continued clinical remission prevents fractures, there are few reports on other simple clinical indicators [10].

We focused on patient pain. Patient pain scores are linked to disease activity and daily living activities, which are related to patients' daily activity [11]. In addition, we speculate that intense pain correlates with difficulty in moving, which may lead to accidental falls [12].

The purpose of this study is to statistically investigate whether pain indicators in patients are linked to the risk of fragility fractures and to obtain warning indicators for fracture occurrence in pain indicators.

2. Methods

We recruited postmenopausal RA patients treated under a treat-to-target (T2T) treatment strategy [13,14]. The patients who were followed up at least 3 years from the first bone mineral density (BMD)

Peer review under responsibility of The Korean Society of Osteoporosis.
* Corresponding author. Department of Musculoskeletal Medicine, Yoshii Clinic, 6-7-5 Nakamura-Ohashidori, Shimanto City, 787-0033 Kochi, Japan.
E-mail address: ichiroyo@giga.ocn.ne.jp (I. Yoshii).

https://doi.org/10.1016/j.afos.2023.12.001
Received 2 October 2023; Received in revised form 22 November 2023; Accepted 3 December 2023
Available online 21 December 2023

measure (baseline) ranged from August 2010 to July 2018. The patients with RA were monitored for tenderness joint count, swollen joint count, patient's global assessment, evaluator's global assessment, serum C-reactive protein, Health Assessment Questionnaire Disability Index (HAQ), and pain scale by visual analog scale (PS-VAS) from the first visit to each follow-up visit. Every other year from baseline, radiographs of the hands and feet on both sides were taken for radiographic evaluation by Sharp/van der Heijde Score (SHS). Clinical goals were set for patients from baseline to be in remission with a clinical disease activity index (CDAI) $\leq$ 2.8 or simplified disease activity index (SDAI) $\leq$ 3.3 within 6 months of diagnosis.

BMD was measured using dual-energy X-ray absorptiometry (DXA) for postmenopausal patients or for whom glucocorticoids (GCs) are given. Osteoporosis is diagnosed when the T-score in the lumbar spine (LS) or the femoral neck (FM) is marked < -2.5, and an anti-osteoporotic drug is initiated. After the first measurement, DXA was tested every other half to 1 year.

Our institute is located in a rural area of Japan with a population of about 90,000. Our clinic is the only institute in this small community that treats RA systemically. Therefore, about 90% of RA patients are recruited. Thus, this dataset would be comparable to cohort study data.

The primary outcome was the development of BFF, and the following-up continued until the development of the first fracture, censoring at death, loss to follow-up, or end of the study in July 2022. Patients who lost to follow-up due to admission in nursing homes or chronic hospitals 3 years from the baseline were excluded from the study. BFF included proximal femoral fracture, vertebral body fracture, proximal humerus fracture, and distal radius fracture. In these patients, statistical examinations were performed as follows.

2.1. Risk factor extract using Cox regression analyses

Clinical indicators were picked up as candidate risk factors for incident BFF and examined using a Cox regression analysis with a univariate model. The presence of incident BFF was set as a dependent factor, and each candidate risk factor was selected as the independent factor. Listed independent factors were age, disease duration of RA, SDAI, HAQ-DI, SHS, PS-VAS, anti-citrullinated polypeptide antibodies (ACPA) level, rheumatoid factor (RF) level, body mass index (BMI), T-score in the LS, T-score in the FN, presence of prevalent BFF (pr-BFF), fracture memory of parents, GCs administration, estimated glomerular filtration ratio (eGFR), presence of comorbidities such as lifestyle-related diseases (LSDs) in which diabetes, hypertension, hyperlipidemia, and chronic obstructive pulmonary diseases were included, presence of easy-to-fall ability (Fallability) in which osteoarthritis, joint contracture in the lower extremity, parkinsonism, musculoskeletal ambulation disability symptom complex, and other neuromuscular diseases were included, and presence of cognitive impairment (CI) at baseline. Changes of these items during follow-up from the baseline, such as SDAI, HAQ-DI, SHS, PS-VAS, and T-scores in the LS and the FN, eGFR, and administration of anti-osteoporosis drugs were also picked up, and examined.

Then, a Cox regression analysis with a multivariate model was examined in the factors with significant regression in the univariate model. Factors that demonstrated significantly higher risk ratios were extracted as the risk factors.

2.2. The cutoff index determination using ROC

A receiver operation characteristics analysis (ROC) was examined to determine the risk factor's cutoff index (COI). The risk factor was rejected when the COI did not match statistical significance.

2.3. Hazard ratio, sensitivity, and specificity are determined using Kaplan-Meier survival curve analysis and chi-square tests

Kaplan-Meier survival analysis and chi-square test were examined to clarify the hazard ratio of the risk factors and to determine the sensitivity and specificity of the risk factors regarding the development of incident BFF.

2.4. Additional tests in the subgroups

A. Patients were divided into 2 subgroups according to the COI of the most potent risk factor, and these subgroups were further divided according to the COI of the second most potent risk factor. Then, ROC and chi-square tests were examined to determine the COI of the second most potent risk factor and to clarify sensitivity and specificity for the incidence of BFF in the subgroups.
B. Patients were divided into subgroups according to the COI of the PS-VAS at each period of the baseline and the mean value after the baseline. The COIs were determined using ROC analysis. Subgroups were defined as follows: A to A, a patient group whose PS-VAS at and after the baseline exceeded COI at both periods; A to B, a patient group whose PS-VAS at the baseline exceeded the COI and decreased to lower than the COI after the baseline; B to A, a patient group whose PS-VAS at the baseline was no more than the COI and increased to more than the COI after the baseline; B to B, a patient group whose PS-VAS at the baseline was no more than the COI and kept on after the baseline. The incidence rate of BFF of the groups was compared statistically using the chi-square test.
C. Demographic characteristics in subgroups separated with the COI of the PS-VAS were compared using the Mann-Whitney *U*-test. The demographic characteristics of the subgroups separated from the other potent risk factors were compared using the Mann-Whitney *U*-test.
D. The number of incidents BFF positive or negative (incident BFF (+) and (−)) for the subgroups was counted in the study subjects. Sensitivity and specificity were calculated for a single potent risk factor and the combined condition of the factors.

2.5. Additional study for drug intervention

In the other additional study, the influence of drug intervention on incident BFF was investigated. The study subjects were separated with each drug, such as pain reliever, GCs, and biological disease-modifying anti-rheumatic drugs (bDMARDs). The intervention and incident BFF rates after the baseline between the subgroups for each drug were compared using the Mann-Whitney *U*-test.

2.6. Statistical procedures

All the statistical analyses were performed with StatPlus: Mac® (AnalystSoft, Inc., Walnut Glove, CA, USA). Statistical significance was set at $< 5\%$.

2.7. Ethics and consent

This study was approved by the Yoshii Clinic ethics committee (approval number: G-Cl-2022-2) following the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. In addition, anonymity was ensured for all patients and their families who participated in this study, and no names nor addresses were issued that could help identify these individuals. Informed consent was obtained from all individual participants included in the study.

3. Results

The flowchart of the study is shown in Fig. 1. A total of 239 patients were included in the study. RA's mean age and disease duration at baseline were 73.6 and 7.0 years, respectively. Forty-three had an incident BFF. Mean SDAI at the baseline and during the follow-up period were 5.59 and 4.47. In this population, the time at the baseline was not at the first consult but when some time passed from the first consult, resulting in such a low SDAI score at the baseline.

When patients were classified according to the presence of incident BFF, follow-up length, HAQ-DI, PS-VAS, pr-BFF, GCs administration, presence of LSDs, Fallability, and CI at baseline, change of SDAI score, PS-VAS, T-score in the FN, and eGFR_CysC during follow-up after baseline were significantly different between the 2 groups (Table 1). Fractures in the site for the prevalent and the incidental are shown in Table 2.

3.1. Cox regression analysis

Higher HAQ-DI, higher PS-VAS, higher ACPA titer, presence of pr-BFF, LSD, Fallability, CI at baseline, and SDAIRR during follow-up had significantly higher risk ratios using a univariate model. In these candidate factors, higher PS-VAS at baseline, higher ACPA titer, and presence of pr-BFF had significantly higher risk ratios using multivariate models (Table 3).

3.2. Receiver operation characteristics curve analysis

The presence of pr-BFF at baseline had 0.5 of the COI, and the area-under-the-curve (AUC) was 0.692 ($P < 0.001$), whereas PS-VAS at baseline had 21.0 of the COI, and the AUC was 0.616 ($P < 0.01$). ACPA titer showed no significant COI. Therefore, ACPA was rejected (Fig. 2).

3.3. Kaplan-Meier survival curve analysis and chi-square test

The hazard ratio of the presence of pr-BFF regarding the incident BFF was 5.21 times higher than not presenting pr-BFF in the Kaplan-Meier survival analysis ($P < 0.001$), whereas PS-VAS > 21.0 was 2.24 times higher than PS-VAS ≤ 21.0 ($P < 0.01$) (Fig. 3). The chi-square test revealed that 7 of 114 pr-BFF negative patients (6.1%) had incident BFF, whereas 36 of 125 pr-BFF positive patients (28.8%) had incident BFF. Therefore, sensitivity and specificity according to pr-BFF were 28.8% and 93.9%. On the other hand, 19 of 149 PS-VAS $\leq$21.0 patients (12.8%) had incident BFF, whereas 24 of 90 PS-VAS > 21.0 patients (26.7%) had incident BFF; therefore, sensitivity and specificity according to 21.0 mm of PS-VAS at the baseline were 26.7% and 87.2% (Table 4).

3.4. Additional tests in the subgroups

A. It was clarified that pr-BFF was the most potent risk factor, and the second was PS-VAS. In the subgroups of 125 pr-BFF positive patients, 14 of 73 in the PS-VAS ≤ 21 mm patients (19.2%) had incident BFF, whereas 22 of 52 in the PS-VAS > 21 mm patients (42.3%) had incident BFF, therefore sensitivity and specificity were 42.3% and 80.8%. In the subgroup of 114 pr-BFF negative patients, PS-VAS showed no statistically significant COI. Therefore, an additional test was not examined (Supplementary Table 1).
B. The COI of PS-VAS after the baseline was 24.6 ($P < 0.001$). The incidence rates were 31.3% (= 20/64), 26.5% (= 9/34), 12.0% (= 3/22), and 9.5% (= 11/116) for A to A, B to A, A to B, and B to B, respectively in the frequency order (Supplementary Table 2).
C. Many variables showed significant differences between the PS-VAS $>$ COI and PS-VAS $\leq$ COI. Likely as the PS-VAS, many variables showed significant differences between the pr-BFF (+) group and the pr-BFF (−) group (Supplementary Table 3).

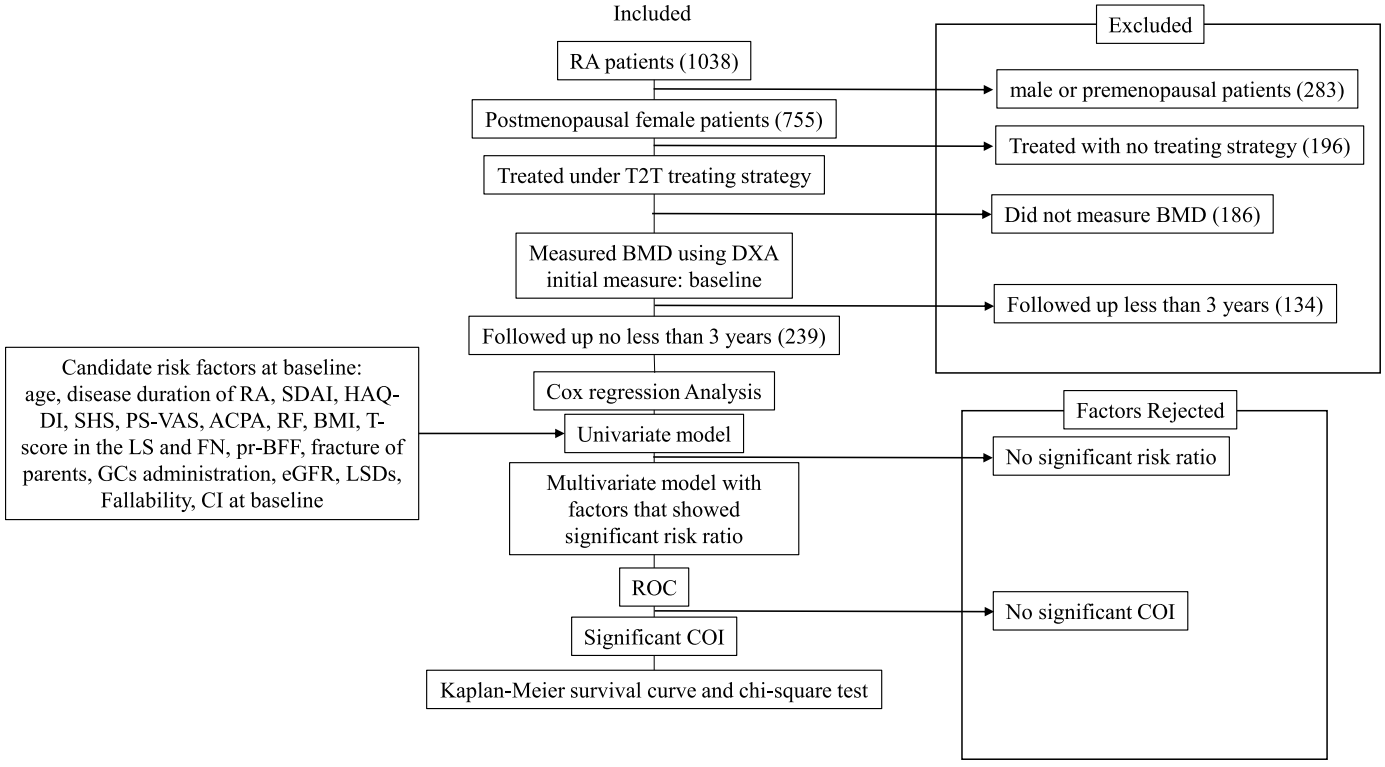

Fig. 1. Flowchart of the study. Numbers of subject are shown in parentheses Abbreviations: RA, rheumatoid arthritis; T2T, treat-to-target; BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; SDAI, simplified disease activity index; HAQ-DI, Health Assessment Questionnaire Disability Index; SHS, Sharp/van der Heijde score; PS-VAS, pain score using visual analog scale; ACPA, anti-citrullinated polypeptide antibodies; RF, rheumatoid factor; BMI, body mass index; LS, lumbar spine; FN, femoral neck; pr-BFF, prevalent bone fragility fracture; GCs, glucocorticoids; eGFR, estimated glomerular filtration rate; LSDs, lifestyle-related diseases; CI, cognitive impairment; ROC, receiver operation characteristics; COI, cut-off index.

Table 1
Demographic characteristics of the patients in all and for groups separated by development of incident BFF.

		Total (N = 239)	Incident BFF+ (N = 43)	P-value using MWU	Incident BFF- (N = 196)	P-value using BLR
At baseline	Age (yr)	73.6 (10.9)	75.7 (10.6)	0.13	73.1 (10.9)	0.17
	D.D. (yr)	6.95 (7.8)	6.13 (5.9)	0.99	7.13 (8.2)	0.43
	SDAI	5.59 (7.68)	6.62 (8.50)	0.07	5.36 (7.46)	0.37
	HAQ-DI	0.519 (0.652)	0.709 (0.650)	<0.05	0.476 (0.644)	<0.05
	SHS	61.3 (74.4)	69.3 (77.8)	0.18	59.5 (73.5)	0.45
	PS-VAS (mm)	22.8 (25.5)	32.5 (29.2)	<0.05	20.6 (24.1)	< 0.01
	ACPA (U/mL)	170.0 (490.5)	283.8 (874.6)	0.41	142.8 (333.5)	0.18
	RF (IU/mL	83.3 (166.2)	108.6 (142.6)	0.12	77.7 (170.4)	0.32
	BMI (kg/m^2)	22.7 (4.4)	20.1 (2.5)	0.39	22.9 (4.5)	0.38
	T-score (LS)	−2.1 (1.5)	−2.1 (1.5)	0.96	−2.1 (1.5)	0.85
	T-score (FN)	−1.8 (1.1)	−2.1 (1.3)	0.08	−1.8 (1.1)	0.14
	pr-BFF	125 (52.3%)	36 (83.7%)	<0.001	89 (45.4%)	< 0.001
	Fx of parents	8 (3.3%)	3 (7.0%)	0.41	5 (2.6%)	0.53
	OPDs administration	142 (59.4%)	31 (72.1%)	0.07	111 (56.6%)	0.06
	GCs administration	75 (31.4%)	19 (44.2%)	<0.05	56 (28.6%)	< 0.05
	eGFR (mL/min/1.73m^2)	65.6 (19.7)	56.9 (14.9)	0.26	66.9 (20.0)	0.25
	LSDs	190 (79.5%)	41 (95.3%)	<0.01	149 (76.0%)	< 0.05
	Fallability	154 (64.4%)	36 (83.7%)	<0.01	118 (60.2%)	< 0.01
	CI	24 (10.0%)	8 (18.6%)	<0.05	16 (8.2%)	< 0.05
During follow-up	Follow-up period, months	53.8 (21.8)	26.8 (18.7)	<0.001	59.7 (17.5)	< 0.001
	Mean SDAI	4.47 (4.52)	5.64 (3.95)	<0.01	4.21 (4.60)	0.07
	Mean HAQ-DI	0.528 (0.619)	0.669 (0.611)	<0.05	0.497 (0.617)	0.11
	Mean SHS	60.4 (73.2)	69.0 (74.9)	0.12	58.6 (73.0)	0.39
	Mean PS-VAS, mm	25.2 (18.1)	33.9 (19.5)	<0.001	23.3 (17.2)	< 0.001
	Mean T-score (LS)	−2.1 (1.4)	−2.3 (1.4)	0.95	−2.0 (1.4)	0.96
	Mean T-score (FN)	−2.0 (0.9)	−2.3 (1.0)	<0.05	−2.0 (1.0)	< 0.05
	Mean eGFR, mL/min/1.73m^2	61.0 (20.0)	52.2 (20.4)	0.09	62.9 (19.4)	< 0.01
	OPDs administration	45 (18.8%)	7 (16.3%)	0.63	38 (19.4%)	0.64

The values are presented as mean (SD) unless indicated otherwise.
P-values are presented in regard to incident BFF using binary logistic regression analysis.
OPD included selective estrogen receptor modulators, bisphosphonates, denosumab, teriparatide, and romosozumab.
MWU, Mann-Whitney *U*-test; BLR, binary logistic regression analysis; BFF, bone fragility fracture; D. D., disease duration of RA at baseline; SDAI, simplified disease activity index; HAQ-DI, Health Assessment Questionnaire Disability Index; SHS, Sharp/van der Heijde score; ACPA, anti-citrullinated polypeptide antibodies; RF, rheumatoid factor; BMI, body mass index; pr-BFF, prevalent bone fragility fracture; Fx, fracture; GCs, glucocorticoids; eGFR, estimated glomerular filtration rate; LSDs, lifestyle-related diseases; Fallability, hyper-fallability; CI, cognitive impairment; SDAIRR, SDAI remission rate; OPD, anti-osteoporotic drugs.

Table 2
Fractures sites (prevalent and incidental).

			Incidental MOF					
			(−)	(+)				
				VF	Hip	Wrist	Proximal humerus	Total
Prevalent MOF	(−)		107	2	3	2	0	114
	(+)	VF	78	12	20	1	1	112
		Overlapped	7	1	1	0	0	9
		Proximal femur	2	0	0	0	0	2
		Wrist	2	0	0	0	0	2
	Total		196	15	24	3	1	239

Overlapped: six vertebral and hip; one vertebral and wrist.
MOF, major osteoporotic fracture; VF, vertebral fracture.

D. The sensitivity and specificity were 28.8% and 93.9% in the presence of pr-BFF and 26.7% and 87.2% for PS-VAS separated by the COI, respectively. When the 2 indicators are combined, sensitivity and specificity become 42.3% and 88.8%, respectively (Supplementary Table 4).

3.5. Additional study for drug intervention

Mean PS-VAS after the baseline showed 26.0 and 22.1 for pain relievers, 25.8 and 24.7 for GCs, and 27.7 and 23.5 for bDMARDs in the drug-administrated and no-drug-administrated groups. There were no significant differences between the 2 groups. For the incidence rate of the BFFs, there showed 16.3% (= 31/190) and 24.5% (1 = 12/49) for a pain reliever, 22.3% (= 25/112) and 14.2% (= 18/127) for GCs, 26.5% (= 26/98) and 12.1% (= 17/141) for bDMARDs, in the patient group who were intervened and the patient group who were not intervened, respectively (Supplementary Table 5).

4. Discussion

The degree of pain in RA patients is one of the indicators of patient-related outcomes (PRO). It correlates with disease activity, especially PGA included in one of the components of SDAI or CDAI, and correlates with disease activity and functional capacity expressed as HAQ-DI [15]. These facts suggest that pain scores may be an appropriate indicator of PRO. In addition, we focused on the objective similarity of pain scores, reflecting the patient's mobility difficulties and disease activity. In other words, when the patient's pain is severe, the willingness to actively and passively move the body decreases, leading to a lack of movement, which creates a vicious cycle in which the patient is unable to move, and as a result, is more likely to fall [16] and incur fractures.

We need to be aware of the interaction between pain and activities of daily living. PS-VAS and HAQ-DI are correlated with each other and are likely to be confounding factors [17]. This suspicion is supported by the increase of the pain score point estimate and the HAQ score's complete

Table 3
Candidate risk factors and validation of the risk factors using a Cox regression analysis.

		Univariate model		Multivariate model		
		β-value (95%CI)	P-value	β-value (95%CI)	P-value	Risk ratios
At baseline	Older age	0.02 (−0.01–0.05)	0.16			
	D.D., (yr)	−0.02 (−0.06–0.03)	0.41			
	Higher SDAI	0.02 (−0.02–0.05)	0.30			
	Higher HAQ-DI	0.43 (0.02–0.83)	< 0.05	0.00 (−0.54–0.54)	1.00	1.00
	Higher SHS	0.00 (−0.00–0.00)	0.64			
	Higher PS-VAS	0.01 (0.00–0.02)	< 0.01	0.02 (0.00–0.04)	< 0.05	1.02
	Higher ACPA titer	0.00 (0.00–0.00)	< 0.05	0.00 (0.00–0.00)	< 0.01	1.00
	Higher RF titer	0.00 (−0.00–0.00)	0.20			
	Higher BMI	−0.18 (−0.59–0.23)	0.39			
	Higher T-score in the LS	−0.02 (−0.22–0.18)	0.84			
	Higher T-score in the FN	−0.21 (−0.49–0.07)	0.15			
	Presence of pr-BFF	1.65 (0.84–2.46)	< 0.001	1.38 (0.46–2.31)	< 0.01	3.98
	Presence of parents' fracture	0.38 (−0.09–0.86)	0.18			
	GCs administration	0.50 (−0.10–1.10)	0.10			
	Higher eGFR	−0.00 (−0.02–0.01)	0.36			
	Presence of LSDs	1.68 (0.26–3.10)	< 0.05	1.10 (−0.93–3.13)	0.29	3.00
	Presence of Fallability	1.11 (0.30–1.92)	< 0.01	0.55 (−0.39–1.50)	0.25	1.74
	Presence of CI	0.80 (0.03–0.39)	< 0.05	−0.35 (−1.39–0.68)	0.50	0.70
Change during follow-up from the baseline	Higher SDAI	0.01 (−0.05–0.06)	0.84			
	Higher HAQ-DI	0.15 (−0.77–1.07)	0.75			
	Higher SHS	0.00 (−0.00–0.00)	0.87			
	Higher PS-VAS	−0.09 (−0.68–0.50)	0.75			
	Higher T-score in the LS	−0.14 (−0.91–0.62)	0.71			
	Higher T-score in the FN	0.21 (−0.72–1.13)	0.66			
	Higher eGFR	−0.02 (−0.05–0.01)	0.20			
	OPDs administration	−0.20 (−1.01–0.61)	0.62			

The values are presented as mean (SD) unless indicated otherwise. P-values are presented in regard to incident BFF using binary logistic regression analysis OPD included selective estrogen receptor modulators, bisphosphonates, denosumab, teriparatide, and romosozumab. BFF, bone fragility fracture; D. D., disease duration of RA at baseline; SDAI, simplified disease activity index; HAQ-DI, Health Assessment Questionnaire Disability Index; SHS, Sharp/van der Heijde score; ACPA, anti-citrullinated polypeptide antibodies; RF, rheumatoid factor; BMI, body mass index; pr-BFF, prevalent bone fragility fracture; Fx, fracture; GCs, glucocorticoids; eGFR, estimated glomerular filtration rate; LSDs, lifestyle-related diseases; Fallability, hyper-fallability; CI, cognitive impairment; SDAIRR, SDAI remission rate; OPD, anti-osteoporotic drugs.

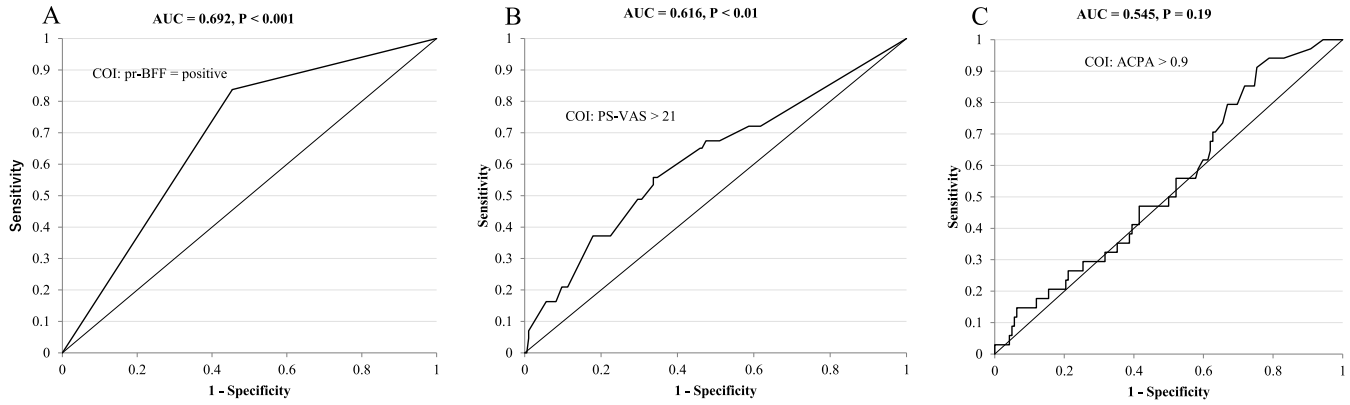

Fig. 2. Results of ROC analyses. A. For the presence of prevalent bone fragility fracture (pr-BFF). B. For pain score using a visual analog scale (PS-VAS). C. For anti-citrullinated polypeptide antibodies (ACPA) titer. AUC, area-under-the-curve; COI, cutoff index.

attenuation despite having a more robust beta coefficient in the univariate model. However, in the multivariate model, the significance of HAQ-DI disappeared, as shown in Table 2. This suggests that PS-VAS is a more significant risk factor than HAQ-DI for the appearance of incident BFF. Therefore, it is considered worth considering PS-VAS as an indicator for predicting the occurrence of incident BFF. As well as HAQ-DI, GCs administration, presence of LSDs, easy-to-fall ability, and cognitive impairment are known as potent risk factors, and these have a risk for confounding the results. However, these factors also showed no statistical significance using the multivariate model. Therefore, these factors were not independent risk factors in this population.

When the COI of pr-BFF and PS-VAS separated patients shown in the ROC study, the variable that showed significant differences by the Mann-Whitney *U*-test was very different (Supplementary Table 3). Factors that showed significant differences in pr-BFF were not significantly varied in PS-VAS at baseline except for the HAQ score. These results suggest that the presence of these 2 indicators, pr-BFF and PS-VAS, can be inferred to function effectively as complementary indicators. The presence of pr-BFF was significantly associated with many variables at baseline, and PS-VAS was significantly related to many variables during follow-up.

When criteria for meeting these 2 indicators simultaneously were established, the sensitivity and specificity of incidental BFF were 43.1% and 90.1%, respectively, with a hazard ratio 5.22 using Kaplan-Meier survival analysis ($P < 0.001$). The sensitivity increases from about 30% to 42.3% when the 2 criteria are combined, even though there is

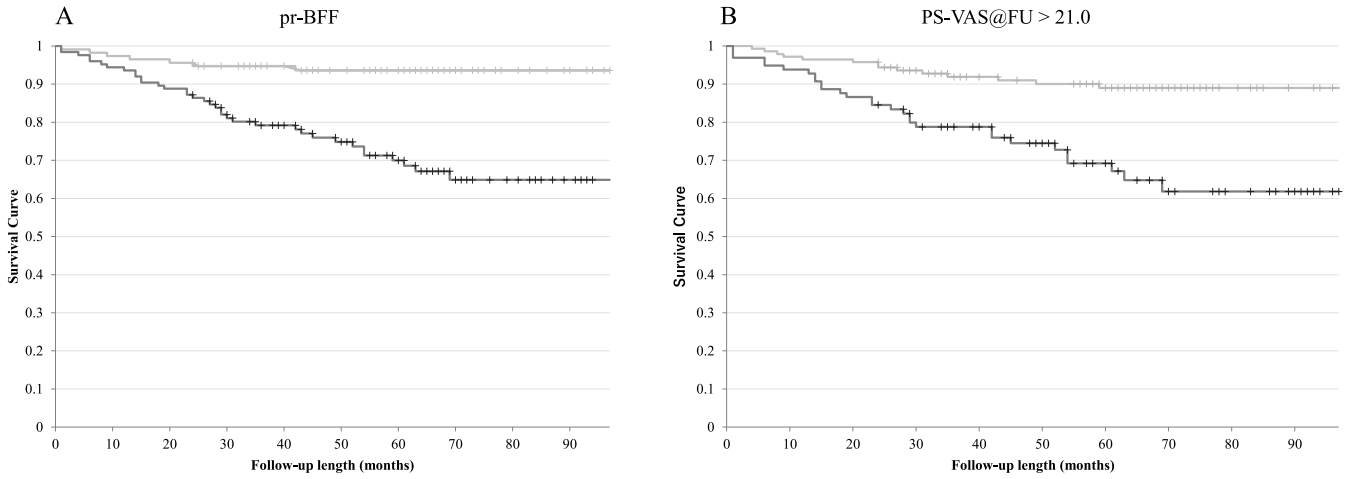

Fig. 3. Results of Kaplan-Meyer survival curve analysis. A: Results for presence of prevalent bone fragility fracture (pr-BFF). The hazard ratio of pr-BFF positive was 5.21 ($P < 0.001$). Survival curves show significant difference (a line above: pr-BFF negative, a line below: pr-BFF positive). B: Results for mean pain score with visual analog scale (PS-VAS) during follow-up (@FU). The hazard ratio of PS-VAS@FU > 21.0 was 2.24 ($P < 0.001$). Survival curves show significant difference (a line above: PS-VAS@FU ≤ 21.0, a line below: PS-VAS@FU > 21.0).

Table 4
Hazard ratios, sensitivities, and specificities of presenting pr-BFF and the PS-VAS >21 for the incident BFF.

	ROC	Kaplan-Meier survival curve		Chi-square test		
	COI	Hazard ratio	P-value	Incident BFF(−) in factor ≤ COI (specificity)	Incident BFF(+) in factor > COI (sensitivity)	P-value
pr-BFF	present (+)	5.21	< 0.001	107 in 114 (93.9%)	36 in 125 (28.8%)	< 0.001
PS-VAS	> 21	2.24	< 0.01	130 in 149 (87.2%)	24 in 90 (26.7%)	< 0.001

pr-BFF, prevalent bone fragility fracture; PS-VAS, pain score using visual analog scale; ROC, Receiver operation characteristics; COI, cut-off index.

little difference in specificity when isolated from COI. Still, the sensitivity is much higher. However, these high specificities suggest that PS-VAS is more likely to be an indicator of preventing incident BFFs than a risk factor. The absence of pr-BFF may also function more fundamentally as an indicator of guarantee for no fractures.

Pain degree after the baseline may be affected by drug interventions such as pain relievers, including non-steroid anti-inflammatory drugs and opioids, GCs, and bDMARDs after the baseline, and these factors might affect the incidence of the BFFs. As an additional test of this study, we compared the mean PS-VAS and incidence rate of BFF after the baseline in subgroups that separated with each drug intervention. Results showed that PS-VAS after the baseline showed no statistically significant difference by the drug intervention, and there were no significant differences between the 2 groups except for bDMARDs despite drug intervention plus subgroup showed significantly higher incident BFF rate. These results suggested that pain relievers do not affect pain degree in this population, and the intervention of these drugs does not affect the development of incident BFF. Thus, absolute PS-VAS is the more critical factor for the incidence of BFF than the move of the PS-VAS degree. Therefore, monitoring PS-VAS is considered essential for evaluating not only PRO but also as an indicator for predicting incident BFF.

This study has various limitations. One is that it is a single-center study, one is that the number of cases was too small, one is that patient selection is not randomized, one is that observation periods vary from patient to patient, and one is that ethnic issues are not considered. Many patients with low bone density may have biases regarding patient selection. Differences in observation periods may have been corrected by Cox regression analysis. In any case, the fact that patient pain is an indicator of fragility fractures is a new finding that needs careful consideration.

5. Conclusions

We studied how pain degree correlates with incidental BFF using a case-control study dataset and found that prevalent BFF and PS-VAS were significant risk factors for developing BFF under pr-BFF. PS-VAS is suggested to be an essential indicator for predicting BFF.

Data availability statement

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

CRediT author statement

Ichiro Yoshii: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing - original draft; Writing - review & editing. **Naoya Sawada**: Resources; Supervision; Validation; Writing – review & editing. **Tatsumi Chijiwa**: Resources; Supervision; Validation; Writing – review & editing.

Conflicts of interest

The authors declare no competing interests.

Acknowledgments

The authors thank Saori Tamura for the enthusiastic DXA and BMD measurements and Kaoru Kuwabara, Eri Morichika, and Aoi Yoshida for

their dedicated data collection. **ORCID** Ichiro Yoshii: 0000-0002-9123-4624. Naoya Sawada: 0000-0001-9551-3252. Tatsumi Chijiwa: 0000-0002-0567-0391.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.afos.2023.12.001.

References

[1] Hooyman JR, Melton 3rd LJ, Nelson AM, O'Fallon WM, Riggs BL. Fractures after rheumatoid arthritis. A population-based study. Arthritis Rheum 1984;27:1353–61.
[2] Lodder MC, de Jong Z, Kostense PJ, Molenaar ET, Staal K, Voskuyl AE, et al. Bone mineral density in patients with rheumatoid arthritis: relation between disease severity and low bone mineral density. Ann Rheum Dis 2004;63:1576–80.
[3] van Staa TP, Geusens P, Bijlsma JW, Leufkens HG, Cooper C. Clinical assessment of the long-term risk of fracture in patients with rheumatoid arthritis. Arthritis Rheum 2006;54:3104–12.
[4] Kim SY, Schneeweiss S, Liu J, Daniel GW, Chang CL, Garneau K, et al. Risk of osteoporotic fracture in a large population-based cohort of patients with rheumatoid arthritis. Arthritis Res Ther 2010;12:R154.
[5] van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Use of oral corticosteroids and risk of fractures. J Bone Miner Res 2000;15:993–1000.
[6] Kanis JA, Johansson H, Oden A, Johnell O, de Laet C, Melton III LJ, et al. A meta-analysis of prior corticosteroid use and fracture risk. J Bone Miner Res 2004;19:893–9.
[7] Cortet B, Guyot MH, Solau E, Pigny P, Dumoulin F, Flipo RM, et al. Factors influencing bone loss in rheumatoid arthritis: a longitudinal study. Clin Exp Rheumatol 2000;18:683–90.
[8] Furuya T, Inoue E, Hosoi T, Taniguchi A, Momohara S, Yamanaka H. Risk factors associated with the occurrence of hip fracture in Japanese patients with rheumatoid arthritis: a prospective observational cohort study. Osteoporos Int 2013;24:1257–65.
[9] Gosch M, Jeske M, Kammerlander C, Roth T. Osteoporosis and polypharmacy. Z Gerontol Geriatr 2012;45:450–4.
[10] El Maghraoui A, Rezqi A, Mounach A, Achemlal L, Bezza A, Ghozlani I. Prevalence and risk factors of vertebral fractures in women with rheumatoid arthritis using vertebral fracture assessment. Rheumatology 2010;49:1303–10.
[11] Yoshii I, Chijiwa T, Sawada N. Influence of pain score measured by a visual analog scale (PS-VAS) on the Health Assessment Questionnaire Disability Index and 28-joint Disease Activity Index with C-reactive protein in rheumatoid arthritis patients. Int J Rheum Dis 2018;21:1955–61.
[12] Cai Y, Leveille SG, Shi L, Chen P, You T. Chronic pain and risk of injurious falls in community-dwelling older adults. J Gerontol A Biol Sci Med Sci 2021;13(76):e179–e186.
[13] Smolen JS, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas D, Burmester G, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis 2010;69:631–7.
[14] Smolen JS, Landewé RBM, Bergstra SA, Kerschbaumer A, Sepriano A, Aletaha D, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. Ann Rheum Dis 2023;82:3–18.
[15] Studenic P, Smolen JS, Aletaha D. Near misses of ACR/EULAR criteria for remission: effects of patient global assessment in Boolean and index-based definitions. Ann Rheum Dis 2012;71:1702–5.
[16] Li W, Gamber M, Han J, Sun W, Yu T. The association between pain and fall among middle-aged and older Chinese. Pain Manag Nurs 2021;22:343–8.
[17] Yoshii I, Chijiwa T, Sawada N. Influence of pain score measured by a visual analog scale (PS-VAS) on the Health Assessment Questionnaire Disability Index and 28-joint Disease Activity Index with C-reactive protein in rheumatoid arthritis patients. Int J Rheum Dis 2018;21:1955–61.