

Article

Validation of Combined Indicator Using Joint Index Vector and Pain Score for Risk Weight Calculation of Incident Bone Fragility Fracture in Patients with Rheumatoid Arthritis

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Abstract

Background: Risk factors, including Joint Index Vector (JIV), a new disease activity indicator based on three-axis coordinates, and a pain score using a visual analog scale (PS-VAS), were evaluated for incident bone fragility fractures (inc-BFF) in patients with rheumatoid arthritis (RA) in a retrospective case–control study. **Methods:** RA patients who were followed for at least two consecutive years (RA) and a control group consisting of patients without RA but with similar background demographics (non-RA) were recruited and monitored. The prevalence of inc-BFF was compared between the two groups. Common potential risk factors in both groups and RA-specific factors within the RA group regarding inc-BFF were analyzed statistically. **Results:** A total of 278 patients were studied in each group. There was no significant difference in the prevalence of inc-BFF between the two groups. Presenting RA was not a major factor in developing inc-BFF. Higher Vz in the JIV, which reflects the difference in the involvement ratio between large and small joints, and higher PS-VAS showed significantly higher hazard ratios in a univariate model. $V_z > 0.01$, $PS-VAS \geq 25.5$, and simplified disease activity index ≥ 2.11 at follow-up, along with PS-VAS at baseline > 21.0 , are the key cutoff indices for RA-specific risk factors. When two of these factors were combined, the combination of Vz and PS-VAS at follow-up resulted in the highest hazard ratio (4.25; $p < 0.001$). **Conclusions:** These results suggest that combining Vz and PS-VAS is the key risk indicator for inc-BFF.

Keywords: bone fragility fracture; joint index vector; pain; rheumatoid arthritis



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1. Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that primarily targets articular cartilage and damages various tissues, including joints and bones. It is widely accepted that RA is a determinant of osteoporosis, and patients with RA are more likely to experience bone fragility fractures (BFFs) than non-RA patients [1]. The Fracture Assessment Tool (FRAX[®]), a worldwide research instrument that predicts the risk of osteoporotic fractures, estimates a 10-year probability through a questionnaire that includes RA in its calculation [2]. The risk of BFF due to RA is associated with chronic persistent inflammation, immobility, use of glucocorticoid steroids (GCSs), and other

medications [3], which increase bone fragility and fall risk, creating a negative link among multiple factors due to their overlapping effects [4]. However, little attention has been given to disease activity as a risk factor [5,6]. Now that biological disease-modifying anti-rheumatic drugs (bDMARDs) are common treatments and treat-to-target (T2T) strategies have become widespread [7], the impact of controlling disease activity on fracture risk warrants consideration. Achieving remission, as measured by a simplified disease activity index (SDAI) or clinical disease activity index (CDAI), has a significant advantage in preventing incident BFF because the T2T strategy effectively controls disease activity and reaches clinical remission; this minimizes adverse effects on bone metabolism and results in a lower incidence of BFF [8]. Previous studies have shown that bone mineral density does not decrease when clinical remission is achieved [9]; however, managing pain scores also helps prevent incident BFF in RA patients [10]. These findings suggest that controlling disease activity can have dual benefits—reducing pain and joint inflammation. Therefore, we hypothesized that pain severity and joint involvement could serve as useful indicators for predicting incident BFF. We verified the combined parameter, integrating pain level and joint involvement, as a risk factor for incident BFF.

2. Materials and Methods

2.1. Inclusion Criteria of RA Patients and Parameters Chosen with RA-Specific

Since August 2010, we have been treating RA according to the EULAR/ACR classification criteria [11] within the T2T framework [12]. Our main target is to achieve SDAI remission within six months of the first visit. We have been using fundamental methotrexate (MTX), added secondary biologic or targeted synthetic disease-modifying anti-rheumatic drugs (bDMARDs or tsDMARDs). Glucocorticoid steroids (GCSs) were not used as a last resort. A target was agreed upon by both the physician and the patient.

We recruited RA patients aged 50 or older and measured their bone mineral density (BMD) using dual-energy X-ray absorptiometry at the start of treatment. The primary outcome was incident BFF. Incident BFF includes fractures of the vertebral body, hip, shoulder, and wrist—so-called major osteoporotic fractures—and also includes pelvis, elbow, knee, and ankle fractures caused by bone fragility. Follow-up started at the time of BMD measurement (baseline) and continued until the first fracture occurred, or until the latest follow-up, death, loss to follow-up, or study completion. Kaplan–Meier survival curves were used to estimate incident BFF rates up to the last observation. We evaluated RA-specific potential risk factors for incident BFF, including disease duration, ACPA, RF, SDAI, and CDAI scores, HAQ-DI, and SHS at baseline. We also assessed mean SDAI and CDAI scores, remission rates, and pain scores measured by PS-VAS after baseline. These variables were analyzed using Cox regression, along with general risk factors such as age, sex, T-score from femoral neck BMD, prior BFF (pr-BFF), use of anti-osteoporotic drugs, and GCS administration before baseline—including the mean baseline dose and total dose after treatment. Additional potential risk factors, such as lifestyle-related diseases (LSDs), fall risk (Fall-ability), and cognitive impairment (C-I), were also considered. LSDs included comorbidities like type 2 diabetes mellitus (DM), COPD, hypertension, hyperlipidemia, heart failure, CKD $\geq$ Grade 3a, and insomnia. Fall-ability encompassed conditions such as musculoskeletal ambulation disability complex (MADS), osteoarthritis of the lower extremities (OA), joint contractures, joint contractures of the trunk or lower limbs (Contractures), disuse syndrome (Disuse), Parkinsonism, and neuromuscular disorders—diagnosed by specialists certified by relevant Japanese medical societies. All factors were first examined using univariate models, then with multivariate models for those showing significance.

We also included the Joint Index Vector (JIV) in the RA-specific candidate risk factors. JIV is a new index developed by Nishiyama to assess joint status in patients with RA [13].

This indicator evaluates joint involvement for swelling and tenderness across the entire extremities. It represents three-axis coordination using a three-dimensional axis, but no patient-related outcomes were included.

2.2. Introducing the JIV Measurement

JIV is determined by defining the 3-axis coordinates of XYZ.

The X coordinate is calculated as follows: The total number of swellings and tender joints in the proximal interphalangeal (PIP) and metacarpophalangeal (MCP) joints (small joints of the upper limbs; US), divided by the total number of these joints, determines the upper limb small joint index (JUS). The total number of swellings and tender joints in the wrist, elbow, shoulder, and sternoclavicular joints (large joints of the upper limbs; UL), divided by the total number of these joints, determines the upper limb large joint index (JUL). The X coordinate is the sum of JUS and JUL, called V_x . Therefore, V_x ranges from 0 to 4.

The Y coordinate is calculated as follows: The lower limb small joint index (JLS) is the total number of swelling and tenderness in the metatarsal–phalangeal (MTP) joints (small joints of the lower limbs; LS) divided by the total number of these joints. The lower limb large joint index (JLL) is the total number of swelling and tenderness in the dorsal foot, foot, knee, and hip joints (large joints of the lower limbs; LL) divided by the total number of these joints. The Y coordinate, V_y , is the sum of JLS and JLL. Therefore, V_y ranges from 0 to 4.

V_{xy} is defined using the X and Y coordinates, calculated as the number of vectors for the XY axes. Therefore, $V_{xy} = \sqrt{(X^2 + Y^2)}$ is described within the range of 0 to $4\sqrt{2}$.

The Z coordinate is calculated as the sum of JUL and JLL minus the sum of JUS and JLS. Therefore, Z values range from -4 to 4 . Additionally, as a three-dimensional object, the number of vectors on the XYZ axes is $V_{xyz} = \sqrt{(X^2 + Y^2 + Z^2)}$, which is also equal to $\sqrt{(V_{xy}^2 + V_z^2)}$, and is defined as V.

The calculation method for each coordinate of the three axes is referenced from Nishiyama's report [13].

2.3. Non-RA Patients Recruiting, General Parameters Picking Up, and Comparison Between the Groups

Patients with musculoskeletal diseases other than RA, such as spondyloarthritis, osteoarthritis, joint contracture, Parkinson's disease, and other conditions with high fall risk or other musculoskeletal issues, who matched common risk factors like sex, average age, mean bone mineral density in the hip and vertebral body, and others, were recruited as a control group. The study aimed to compare the incidence of BFF between RA and non-RA patients and to evaluate the potential role of BFF in RA. A Cox regression analysis of the common risk factors was performed to develop inc-BFF for both RA and non-RA groups, which were then combined. The study also compared hazard ratios using Kaplan–Meier survival analysis.

A ten-year BFF probability was calculated and compared between the two groups to assess the likelihood of developing RA. Candidate risk factors for the 10-year BFF were compared using the Mann–Whitney U test. We identified risk factors with significantly higher hazard ratios within 5% in univariate models and analyzed these factors with Cox regression in a multivariate model.

2.4. Determining the Cutoff Index of the Risk Factors and Evaluating the Candidate Risk Factors Separated by the Cutoff Index

Using Cox regression analysis in the RA group, we performed receiver operating characteristic (ROC) analysis to determine the cutoff index (COI) of significant factors using

a univariate model. If there was statistical significance in the RA-specific factors, one point was assigned when each value exceeded the COI. A Kaplan–Meier survival analysis (K-M) was conducted for each factor as a binary variable. Two of these factors were combined, and the point was recalculated to reflect both exceeding the COI (coded as one) and not exceeding it (coded as zero). K-M analysis was then repeated to evaluate the criteria for the combined factors.

2.5. Comparing Hazard Ratios Among the Non-RA and Strongest Hazard Ratio Groups in the Combined Criteria

The hazard ratios among the non-RA group were compared using a K-M analysis, and the two subgroups within the RA group that the COI separated showed the highest hazard ratio.

2.6. Statistical Procedures

All statistical procedures were conducted using StatMac:Plus® (Walnut Grove, CA, USA). Statistical significance was set at a 5% level.

2.7. Informed Consent Attainment

Anonymity was preserved for all patients and their families involved in this study. No names or addresses that could identify these individuals were disclosed. Informed consent was obtained from all patients and relevant parties (such as the parent or legal guardian) for publication.

2.8. Ethical Consideration

This study has been approved by the ethics committee of the institute where it was conducted.

3. Results

3.1. Demographic and Clinical Characteristics and the General and RA-Specific Candidate Risk Factors in the RA and Non-RA Group—Comparison Between the RA and Non-RA Group

In each group, there were a total of 278 patients: 86% women in RA and 86.3% in non-RA. The mean age was 74.1 ± 10.7 years in RA and 75.0 ± 10.8 years in non-RA, while BMI was 22.6 ± 4.2 in RA and 23.5 ± 4.1 in non-RA. The follow-up period averaged 85.1 ± 26.2 months in RA and 85.0 ± 25.8 months in non-RA. The incidence of BFF was 44 out of 278 (15.8%) in RA and 46 out of 278 (16.5%) in non-RA. The incidence of LSDs was 225 out of 278 (80.9%) in RA and 211 out of 278 (75.9%) in non-RA. The incidence of hyper fall-ability was 176 out of 278 (63.3%) in RA and 193 out of 278 (69.4%) in non-RA. Cognitive impairment occurred in 26 out of 278 (9.4%) in RA and 23 out of 278 (8.3%) in non-RA. There were no patients who experienced death during the follow-up period in both the RA and non-RA groups. Other parameters showed no significant differences between the two groups (Table 1). There was no significant difference in BFF incidence between the RA and non-RA groups (Figure 1). However, the 10-year BFF rates were 27.04% and 16.15%, respectively, and the GCS administration rate was 48.2% in the RA group and 6.5% in the non-RA group ($p < 0.001$) (Table 1).

Table 1. Baseline and follow-up characteristics of patients in the RA and the non-RA groups.

	RA Group (<i>n</i> = 278)	Non-RA Group (<i>n</i> = 278)	<i>p</i> -Value
women, %	86.0	86.3	0.985
Age, years	74.1 (10.7)	75.0 (10.8)	0.119
BMI, kg/m ²	22.6 (4.2)	23.5 (4.1)	0.187
follow-up period, months	85.1 (26.2)	85.0 (25.8)	0.974
incident BFF, %	15.8	16.5	0.833
10-year MOF, %	27.0 (18.4)	16.1 (10.7)	<0.001
Lifestyle-related diseases, %	80.9	75.9	0.131
type2 DM, %	23.4	28.4	0.170
COPD, %	10.4	7.6	0.238
hypertension, %	57.2	54.3	0.526
hyperlipidemia, %	34.2	34.2	0.976
chronic heart failure, %	20.9	19.4	0.690
CKD ≥ Grade3a, %	49.5	49.6	0.955
insomnia, %	23.4	23.3	0.939
Fall-ability, %	63.3	69.4	0.115
MADS, %	15.8	21.9	0.064
osteoarthritis, %	55.4	60.1	0.288
Disuse, %	9.0	4.7	0.051
Contractures, %	13.6	10.1	0.190
Parkinsonism, %	2.5	2.2	0.798
cognitive impairment, %	9.4	8.3	0.649
T-score	−1.73 (1.17)	−1.71 (0.97)	0.805
pr-BFF, %	50.4	55.8	0.220
anti-osteoporotic drug †, %	61.2	58.6	0.581
GCS administration until baseline, %	55.8	13.3	0.034
GCS mean dosage ‡, mg/day	2.7 (3.4)	5.9 (7.7)	<0.001
GCS total dose ever ‡, mg	2460 (6481)	859 (4972)	<0.001
disease duration of RA, years	7.6 (8.8)		
ACPA titer at BL, U/mL	176.6 (478.9)		
RF titer at BL, IU/mL	93.2 (214.0)		
SDAI score at BL	5.67 (7.91)		
HAQ-DI at BL	0.548 (0.656)		
SHS at BL	60.3 (73.6)		
mean SDAI score after BL	4.39 (4.38)		
mean SDAI remission rate after BL, %	39.5 (32.5)		

The values are presented as mean (SD) unless indicated otherwise. † anti-osteoporotic drugs included selective estrogen receptor modulators, bisphosphonates, denosumab, teriparatide, and romosozumab. ‡ As prednisone dose equivalent. Abbreviations: BMI, body mass index; BFF, bone fragility fracture; MOF, major osteoporotic fractures; DM, diabetes mellitus; COPD, chronic obstructive pulmonary diseases; CKD, chronic kidney dysfunction; MADS, musculoskeletal ambulation disfunction complex; GCS, glucocorticoid steroids; ACPA, anti-cyclic citrullinated polypeptide antibodies; BL, baseline; RF, rheumatoid factor; SDAI, simplified disease activity score, HAQ-DI, Health Assessment Questionnaire Disability Index; SHS, Sharp/van der Heijde score.

3.2. Evaluation of the Candidate Risk Factors in the RA and the Non-RA Group

Factors with significantly higher hazard ratios in univariate models within the RA group included the presence of pr-BFF, higher mean Vz after baseline, presence of LSD, presence of Fall-ability, presence of C-I, higher mean SDAI score after baseline, higher mean PS-VAS after baseline, higher PS-VAS at baseline, and higher ACPA titer, listed in order of increasing hazard ratio. Among these, the presence of pr-BFF, higher mean PS-VAS after baseline, and higher ACPA titer also showed significantly higher hazard ratios in the multivariate model (Table 2).

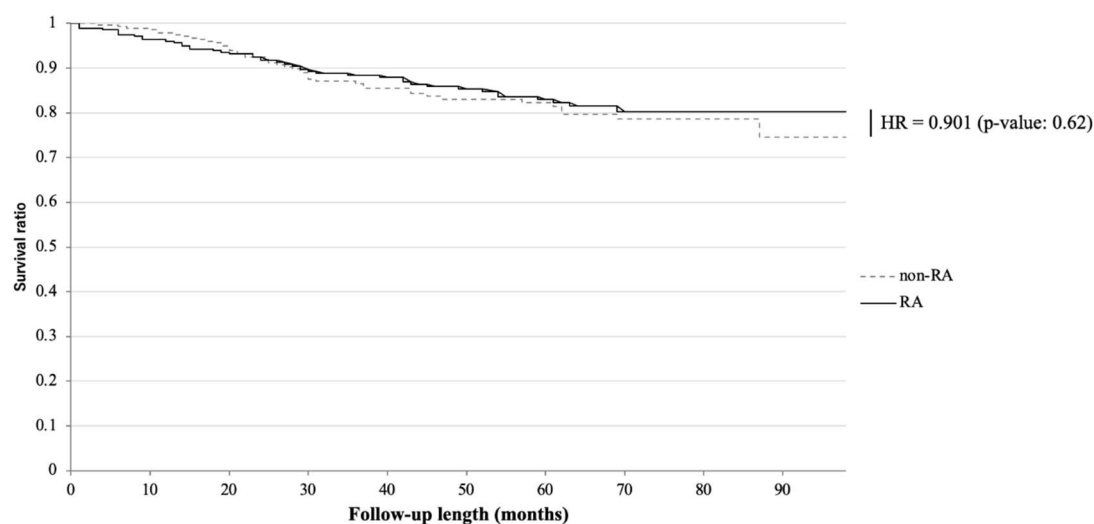


Figure 1. Kaplan–Meier survival curve of incident bone fragility fractures concerning having rheumatoid arthritis. There was no significant difference in the hazard ratio between the RA and the non-RA groups.

Table 2. Results of a Cox regression analysis of incident BFF for the general and RA-specific candidate risk factors in the RA group.

Candidate Risk Factors	Univariate Model		Multivariate Model	
	Hazard Ratio (95% CI)	<i>p</i> -Value	Hazard Ratio (95% CI)	<i>p</i> -Value
General				
female	6.42 (0.88–46.70)	0.07		
older age	1.01 (0.99–1.04)	0.33		
lower T-score	0.83 (0.66–1.05)	0.12		
prevalent bone fragility fractures	5.85 (2.60–13.12)	<0.001	5.01 (1.97–12.71)	<0.001
lifestyle-related diseases	4.83 (1.17–19.95)	<0.05	2.99 (0.40–22.52)	0.29
Fall-ability	2.75 (1.28–5.91)	<0.01	1.46 (0.61–3.51)	0.40
cognitive impairment	2.23 (1.04–4.80)	<0.05	0.71 (0.25–1.97)	0.51
anti-osteoporotic drug administration	0.92 (0.50–1.72)	0.8		
GCS administration	1.71 (0.94–3.09)	0.08		
higher serum albumin level at baseline	0.6 (0.26–1.40)	0.24		
higher mean serum albumin level after baseline	0.52 (0.23–1.17)	0.12		
higher PNI at baseline	0.97 (0.93–1.01)	0.2		
higher mean PNI after baseline	0.97 (0.93–1.01)	0.12		

Table 2. Cont.

Candidate Risk Factors	Univariate Model		Multivariate Model	
	Hazard Ratio (95% CI)	p-Value	Hazard Ratio (95% CI)	p-Value
RA specific				
longer disease duration of RA	0.98 (0.94–1.02)	0.31		
higher ACPA titer	1.00 (1.00–1.00)	<0.01	1.0007 (1.00–1.00)	<0.01
higher RF titer	0.83 (0.66–1.05)	0.12		
higher SDAI score at baseline	1.02 (0.99–1.05)	0.27		
higher HAQ-DI at baseline	1.43 (0.95–2.17)	0.09		
higher SHS score at baseline	1 (0.996–1.004)	0.7		
higher PS-VAS at baseline	1.01 (1.00–1.02)	<0.05	1.00 (0.98–1.02)	0.94
higher Vx at baseline	1.36 (0.39–4.73)	0.63		
higher Vy at baseline	1.24 (0.46–3.35)	0.67		
higher Vxy at baseline	1.13 (0.48–2.66)	0.78		
higher Vz at baseline	2.39 (0.79–7.12)	12		
higher mean SDAI score after baseline	1.05 (1.00–1.10)	<0.05	0.99 (0.91–1.08)	0.99
higher mean HAQ-DI after baseline	1.36 (0.87–2.11)	0.17		
higher mean PS-VAS after baseline	1.02 (1.01–1.04)	<0.001	1.03 (1.00–1.05)	<0.05
higher mean Vx after baseline	2.22 (0.35–14.09)	0.4		
higher mean Vy after baseline	1.67 (0.25–11.28)	0.6		
higher mean Vxy after baseline	1.66 (0.42–6.54)	0.47		
higher mean Vz after baseline	5.22 (1.01–33.30)	<0.05	2.21 (0.12–39.62)	0.59

Factors with statistical significance within 5% with the multivariate model are shown in bold style. Abbreviations: RA, rheumatoid arthritis; GCS, glucocorticoid administration; PNI, prognostic nutritional index; ACPA, anti-cyclic citrullinated polypeptide antibodies; RF, rheumatoid factor; SDAI, simplified disease activity score, HAQ-DI, Health Assessment Questionnaire Disability Index; SHS, Sharp/van der Heijde score; Vx, coordinate on X-axis in the Joint Index Vector; Vy, coordinate on Y-axis in the Joint Index Vector; Vxy, coordinate on X- and Y axis in the Joint Index Vector; Vz, coordinate on Z-axis in the Joint Index Vector.

When limited to the general factors, pr-BFF was the only significant factor in developing an inc-BFF in both the RA and the group get-together with the multivariate model. In contrast, no factor had a significantly higher hazard ratio in the non-RA group, even though pr-BFF showed a significantly higher hazard ratio with the univariate model (Table 3).

Table 3. Cox regression analysis results of the general candidate risk factor for the incidence of bone fragility fractures in the RA and non-RA groups.

RA Group (N = 278)				
Candidate Risk Factors	Univariate Model		Multivariate Model	
	Hazard Ratio (95% CI)	p-Value	Hazard Ratio (95% CI)	p-Value
General Factor				
female	6.42 (0.88–46.70)	0.07		
older age	1.01 (0.99–1.04)	0.33		
lower T-score	0.83 (0.66–1.05)	0.12		
prevalent bone fragility fractures	5.85 (2.60–13.12)	<0.001	4.72 (2.06–10.79)	<0.001
lifestyle-related diseases	4.83 (1.17–19.95)	<0.05	2.83 (0.67–12.06)	0.16
Fall-ability	2.75 (1.28–5.91)	<0.01	1.73 (0.78–3.84)	0.4
cognitive impairment	2.23 (1.04–4.80)	<0.05	1.16 (0.53–2.56)	0.71
anti-osteoporotic drug administration	0.92 (0.50–1.72)	0.8		
GCS administration	1.71 (0.94–3.09)	0.08		
non-RA group (N = 278)				
General factor				
female	0.99 (0.42–2.34)	0.98		
older age	1.01 (0.98–1.04)	0.39		
lower T-score	1.15 (0.91–1.45)	0.24		
prevalent bone fragility fractures	2.76 (1.40–5.45)	<0.01	2.1 (0.98–4.50)	0.06
lifestyle-related diseases	2.87 (1.13–7.30)	<0.05	1.64 (0.57–4.69)	0.36
Fall-ability	1.99 (0.93–4.26)	0.08		
cognitive impairment	2.68 (1.29–5.56)	<0.01	2.04 (0.97–4.29)	0.06
anti-osteoporotic drug administration	1.75 (0.97–3.16)	0.07		
GCS administration	0.92 (0.36–2.32)	0.85		
Together (N = 556)				
General factor				
presenting RA	0.9 (0.60–1.36)	0.62		
female	1.76 (0.82–3.82)	0.15		
older age	1.01 (0.99–1.04)	0.19		

Table 3. Cont.

Candidate Risk Factors	RA Group (N = 278)			
	Univariate Model		Multivariate Model	
	Hazard Ratio (95% CI)	p-Value	Hazard Ratio (95% CI)	p-Value
lower T-score	1.18 (1.00–1.39)	0.06		
prevalent bone fragility fractures	3.93 (2.34–6.59)	<0.001	2.94 (1.69–5.12)	<0.001
lifestyle-related diseases	3.26 (1.58–6.74)	<0.001	1.7 (0.79–3.68)	0.18
Fall-ability	2.39 (2.39–4.10)	<0.01	1.72 (0.99–3.01)	0.06
cognitive impairment	2.46 (1.45–4.17)	<0.001	1.49 (0.86–2.57)	0.15
anti-osteoporotic drug administration	1.74 (1.05–2.90)	<0.05	1.14 (0.68–1.94)	0.62
GCS administration	1.32 (0.84–2.08)	0.23		

Abbreviations: RA, rheumatoid arthritis; non-RA, other diseases than RA; GCS, glucocorticoid steroids.

3.3. Determining the COI of the Risk Factors and Hazard Ratios According to the COI

The ROC results showed that the significant COI of the overall risk factors was positively associated with the presence of pr-BFF, LSD, and Fall-ability. Significant RA-specific factors included > 21.0 and ≥ 25.5 for PS-VAS at baseline and the mean after baseline, ≥ 2.11 for mean SDAI after baseline, and > 0.01 for mean Vz after baseline.

In the K-M, a significantly higher hazard ratio was observed with the presence of pr-BFF, LSD, Fall-ability, and C-I in the general factors, and PS-VAS at baseline and post-baseline, SDAI after baseline, and Vz after baseline in the RA-specific factors (Table 4).

Table 4. The results of ROC and Kaplan–Meier survival analysis.

ROC				Kaplan–Meier		
Factor	COI	AUC (95%CI)	p-Value	Prevalence (+/-)	Hazard Ratio (95%CI)	p-Value
pr-BFF	present	0.700 (0.637–0.764)	<0.001	26.4%/5.1%	5.83 (3.22–10.53)	<0.001
LSD	present	0.586 (0.545–0.627)	<0.001	18.7%/3.8%	4.82 (2.26–10.30)	<0.05
Fall	present	0.610 (0.544–0.676)	<0.001	20.5%/7.8%	2.75 (1.49–5.05)	<0.01
CI	present	0.552 (0.492–0.613)	0.09	30.8%/14.3%	2.23 (0.80–6.23)	<0.05
ACPA	> 0.9	0.551 (0.451–0.652)	0.32	21.2%/7.1%	3.07 (1.39–6.80)	0.05
PS-VAS@BL	> 21.0	0.601 (0.508–0.695)	<0.05	22.7%/11.3%	2.09 (1.14–3.83)	<0.05
PS-VAS@FU	≥ 25.5	0.658 (0.568–0.748)	<0.001	26.1%/8.6%	3.36 (1.83–6.16)	<0.001
SDAI@FU	≥ 2.11	0.654 (0.568–0.739)	<0.001	21.0%/5.4%	4.06 (2.18–7.56)	<0.01
Vz@FU	> 0.01	0.604 (0.515–0.693)	<0.05	22.9%/7.1%	3.33 (1.83–6.05)	<0.01

Abbreviations: ROC, receiver operating characteristic; COI, cutoff index; AUC, area under the curve; 95%CI, confidence interval within 95%; pr-BFF, prevalent bone fragility fracture; LSD, lifestyle-related diseases; Fall, hyper fall-ability; CI, cognitive impairment; ACPA, anti-citrullinated polypeptide antibodies; PS-VAS, pain score using a visual analog scale; @BL, at baseline; @FU, during follow-up; SDAI, simplified disease activity index; Vz, Vz in the Joint Index Vector.

3.4. Kaplan–Meier Survival Analysis After Re-Set of the Factor Combined with Significant RA-Specific Factors

The combining patterns were PS-VAS at baseline and after baseline, PS-VAS at baseline and SDAI after baseline, PS-VAS at baseline and Vz after baseline, PS-VAS after baseline and SDAI after baseline, PS-VAS after baseline and Vz after baseline, and SDAI after baseline

and Vz after baseline. After combining, the results of the K-M analysis showed significantly higher hazard ratios for the pairs: PS-VAS after baseline and Vz after baseline, PS-VAS after baseline and SDAI after baseline, SDAI after baseline and Vz after baseline, PS-VAS at baseline and Vz after baseline, PS-VAS at baseline and SDAI after baseline, and PS-VAS at baseline and after baseline, respectively, ranked by high hazard ratio (Table 5).

Table 5. Results of Kaplan–Meier survival analysis after combining the RA-specific factors.

Combining Factors	Kaplan–Meier		
	Prevalence (+/–)	Hazard Ratio (95%CI)	p-Value
PS-VAS at baseline and PS-VAS after baseline	26.9%/11.5%	2.48 (1.27–4.83)	<0.01
PS-VAS at baseline and SDAI after baseline	26.1%/10.8%	2.49 (1.32–4.67)	<0.01
PS-VAS at baseline and Vz after baseline	33.3%/11.4%	3.10 (1.50–6.38)	<0.001
PS-VAS after baseline and SDAI after baseline	28.6%/8.1%	3.87 (2.09–7.17)	<0.001
PS-VAS after baseline and Vz after baseline	35.7%/9.5%	4.25 (2.12–8.53)	<0.001
SDAI after baseline and Vz after baseline	26.6%/7.5%	3.71 (2.05–6.71)	<0.001

Abbreviations: 95%CI, confidence interval within 95%; PS-VAS, pain score using a visual analog scale; SDAI, simplified disease activity index; Vz, Vz in the Joint Index Vector.

3.5. Comparing Hazard Ratios Among the Non-RA and Strongest Hazard Ratio Groups in the Combined Criteria

In the combined criteria, PS-VAS after baseline and Vz after baseline showed the highest hazard ratios. The Kaplan–Meier results indicated that the group exceeding the COI in PS-VAS and Vz after baseline had a significantly higher hazard ratio than the non-RA group, while the group not exceeding the COI in either measure had a significantly lower hazard ratio than the non-RA group (Figure 2).

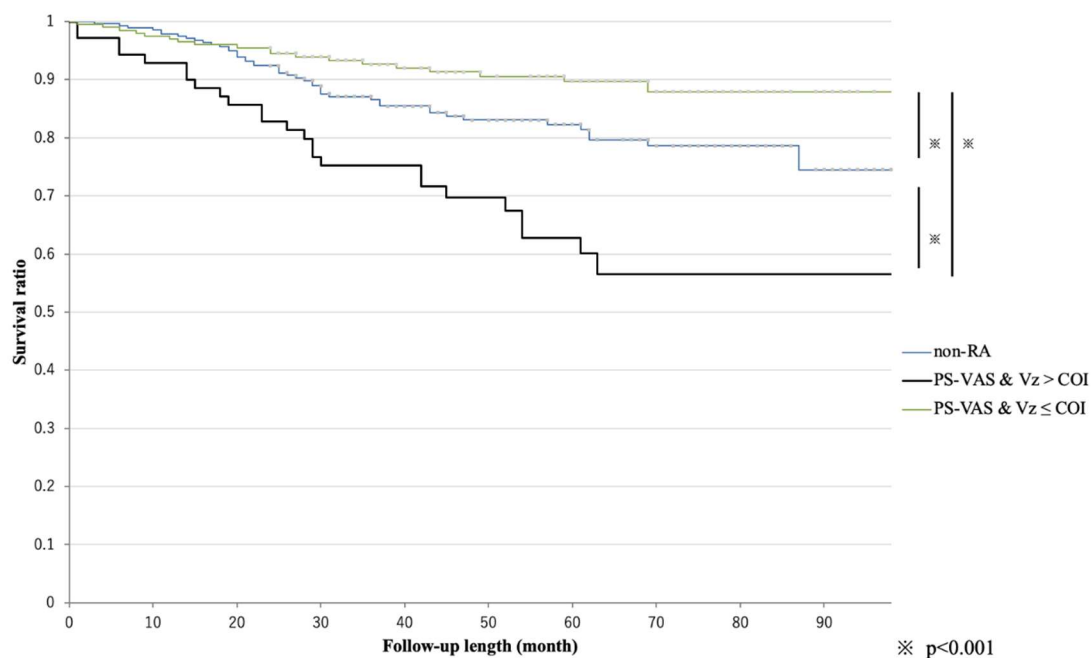


Figure 2. Kaplan–Meier survival curve of incident bone fragility fracture concerning having rheumatoid arthritis and whether PS-VAS and Vz exceed the cutoff index. The group in the RA who showed excesses of the cutoff index in PS-VAS and Vz showed a significantly higher Hazard ratio than the non-RA group, and the group who showed no excesses of the cutoff index showed a significantly lower hazard ratio than the non-RA group.

4. Discussion

BFF is one of the most serious complications in older people. The one-year survival rate of patients with femoral neck fractures is half that of patients without fractures at the same age [14]. In patients with RA, osteoporotic fractures are the third most significant cause of mortality after pulmonary and cardiac disease [15]. The risk of fragility fractures due to decreased bone strength includes RA. Bone density and bone quality are of great concern in terms of bone strength [16]. The association between lifestyle-related diseases, such as type 2 diabetes, and bone quality deterioration results from impaired collagen cross-linking caused by persistent inflammation [17]. In RA, a similar mechanism contributes to bone quality deterioration. Additionally, advanced joint deformity due to RA reduces exercise opportunities and leads to muscle atrophy and weakness. Consequently, fall risk is increased. Furthermore, long-term use of GCS also contributes to increased bone fragility [18]. Our BFF incidence rate in the RA group was comparable to the rates reported in a recent meta-analysis of patients with RA (15.31 per 1000 person-years [95% CI 10.43 to 22.47]) [19]. However, it was somewhat lower than the 10-year BFF, despite the fact that the non-RA group's 10-year BFF was similar. This divergence may result from better disease activity control. Many factors that weaken RA involve chronic, persistent inflammation. The risk associated with RA-specific actual fracture frequency was more significant for disease activity and ACPA titer, indicating that other risks were less substantial compared to those related to pr-BFF.

pr-BFF is the most significant risk factor for fragility fracture incidence [20–23]. In this study, the presence of pr-BFF showed a considerably higher hazard ratio in a Cox regression analysis and a higher Hazard ratio in a Kaplan–Meier survival analysis, especially in the RA group. The non-RA group exhibited a significantly higher hazard ratio of pr-BFF using a univariate model, even though no statistical significance was observed in a multivariate model. However, this may be due to a small number of cases.

It is known that ACPA is deeply involved in the onset of RA [24,25]. ACPA is also known to bind to vimentin on the surface of osteoclast membranes and activate osteoclasts [26]. The results of this study suggest that ACPA titers are linked to a higher risk of developing fragility fractures [27]. ACPA raises the risk of fragility fractures through the blood concentration gradient, gradually but significantly. These findings also suggest a possible link that ACPA is an independent risk factor for incident BFF. However, as previously reported, its impact is less strong than disease activity [28,29]. GCS did not significantly contribute to the development of BFF in this study. It was more important to achieve clinical remission.

Controlling disease activity in RA is essential for preventing fragility fractures. There is no difference in fracture incidence between patients with RA and those without it, but the risk increases in patients with RA when SDAI remission is difficult to achieve or cannot be sustained above a certain level during remission [8].

However, when a multivariate model was applied to the study dataset, the risk weight was statistically significant for the pain degree but not for the disease activity index score. It has already been reported that the pain score is an essential risk indicator for incident BFF in RA. The patient's global assessment is included as one of the components in DAS28, CDAI, SDAI, etc., which are significant indicators of RA disease activity. It is already recognized that there is a strong correlation with the pain score [30]. It was also reported that the probability of preventing incident BFF increases if SDAI or CDAI remission continues [8]. Considering this, it is suggested that the risk of incident BFF can be reduced if the pain score is well controlled. However, the pain score alone cannot fully express disease activity, and an indicator that reflects joint disease is needed. The reference here is the JIV.

The JIV is an index that reflects only the degree of joint disease in three-dimensional coordinates, enabling instant visualization of the severity of joint disease in RA patients. V_x and V_y represent the joint involvement rates of the upper and lower limbs, respectively, while V_{xy} can be seen as the overall joint morbidity rate, calculated as the average of the two. However, V_{xy} was not a significant risk factor for incident BFF, whereas V_z had a significantly higher hazard ratio. V_z indicates the dominance of large joints over small joints; the higher the V_z , the more large joints are affected. Therefore, as a potential risk factor for incident BFF, the prominence of large joint involvement over small joints appears more relevant than the proportion of joints affected.

Cox regression analysis with the multivariate model showed that PS-VAS had a significantly higher hazard ratio, whereas V_z was not significant. However, by assigning points to each of PS-VAS and V_z using the COI obtained from the ROC as the cutoff and summing these points into an index, a hazard ratio comparable to pr-BFF was achieved. Furthermore, the combined indicator demonstrated the strongest hazard ratio after resetting in the K-M analysis.

There was no significant difference in the hazard ratio when comparing the RA and non-RA groups. However, the group that combined PS-VAS and V_z had a significantly higher hazard ratio, surpassing the COI of the non-RA group. These findings suggest that controlling disease activity is vital for preventing incident BFF. Disease activity can be measured using SDAI or in combination with JIV and pain score.

The limitations of current studies include being single-center retrospective studies with small sample sizes and lacking analysis of each disease in LSD or Fall-ability. However, it is noteworthy that the combined indicator calculated with V_z in the JIV and PS-VAS, separated by the COI of each parameter, provides strong evidence for a high-risk weight of incident BFF comparable to the presence of pr-BFF. These findings will assist rheumatologists in considering osteoporosis treatment for patients with RA.

5. Conclusions

The frequency of incident BFF was compared between the RA and non-RA groups. There was no statistically significant difference; however, V_z in the JIV > 0.01 , PS-VAS ≥ 25.5 , and SDAI ≥ 2.11 showed significantly higher hazard ratios in the RA group. The hazard ratio was maximized when combining V_z and PS-VAS. These could serve as predictive markers for incident BFF.

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