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Original article

Musculoskeletal ambulation disability symptom complex as a risk factor of incident bone fragility fracture

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ABSTRACT

Objectives: Influence of presenting musculoskeletal ambulation disability symptom complex (MADS) on occurrence of bone fragility fracture (BFF) is investigated with retrospective cohort study.
Methods: A total of 931 subjects joined in the study. Subjects were selected as bone fragility risk positive in the fracture assessment tool questionnaire. Their assumed risk factors were harvested from the medical records and X-ray pictures. They were followed up at least 8 years consecutively, and occurrence of incident BFF was set as primary endpoint. Each assumed risk factor including MADS was evaluated using Cox regression analysis. Subjects were divided into 2 groups according to presence of MADS (G-MADS and G-noMADS). Adjusted hazard ratios between the 2 groups was evaluated using Cox regression analysis. The statistical procedures were performed before and after propensity score matching (PSM) procedures in order to make parallel with assumed risk factors.
Results: Statistically significant risk factors within 5% were prevalent vertebral body fracture, disuse, MADS, cognitive disorder, hypertension, contracture, Parkinsonism, being female sex, hyperlipidemia, insomnia, T-score in the femoral neck ≤ -2.3, chronic kidney disease $\geq$ stage 2, chronic obstructive pulmonary diseases, glucocorticoid steroid administrated, and osteoarthritis in order of the adjusted hazard ratios (from highest to lowest). Adjusted hazard ratios between G-MADS and G-noMADS were 2.70 and 1.83 for before and after PSM, respectively.
Conclusions: MADS demonstrated as a significant risk factor of BFF occurrence. In treating osteoporosis, fall risk should be aware of as well as bone fragility risk.

1. Introduction

The problem of bone fragility fracture (BFF) is a very important challenge for advanced nations facing the aging society [1]. Overcoming BFF and reducing their incidence are one of the major pressing missions for medical care, and reducing their frequency is a goal that society as a whole must tackle [2,3]. Hagino [4] proposed to name BFF more impressively and intuitively, and suggested that especially the proximal femoral fracture should be named “bone stroke”, similar to imaged brain strokes, and advocates that it is a disease with a high mortality rate along with stroke and requires public recognition.

Classically, older age, postmenopausal woman, existence of prevalent fracture, and low bone mass have been proposed as risk factors for BFF [5]. BFF has 2 main backgrounds. One is bone fragility. In the 1990s and early in this century, low bone mass was a main focus as a risk factor of bone fragility; therefore, bone mineral density measured on dual-energy X-ray absorptiometry (DXA) was regarded as an important check item in the Guideline for the Prevention and Treatment of Osteoporosis in Japan [6]. However, bone microstructural deterioration with cross-linked collagenous fibers has been evoked as a major risk factor in recent decades by reports that enhanced the BFF risk by presenting lifestyle-related diseases (LSD) [7–12]. Besides LSD, bone fragility owing to chronic

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inflammation [13], oxidative stress [14], inappropriate drug administration such as glucocorticoid steroids (GCS) [15], sleeping pills, psychotropic drugs [16], disuse [17], osteoarthritis (OA) [18], joint contracture [19], and genetic abnormality [20].

On the other hand, another essential background of the BFF; thus, the fall-ability, which has been considered a more overt risk of fracture since 1960, has been relatively mildly focused on compared with bone fragility [21,22]. Musculoskeletal ambulation disability symptom complex (MADS) is a disease concept proposed by the Japanese Orthopaedic Association in 2008, and is diagnosed when 11 underlying diseases or medical histories are matched with laboratory test results that measure lower extremity muscle strength and gait ability. MADS is a disease concept originally developed to screen patients who are concerned about the deterioration of their walking condition in view of the fact that this is an important factor for them to be in a nursing condition in the future [23–25]. It was originally designed to suggest an increased risk of falls in a straightforward manner, and it is easy to speculate that MADS is a risk for developing bone fragility fractures. However, to the best of our knowledge, there is no report describing the results of an investigation into the risk of BFF associated with MADS in clinical practice, and it remains unclear to what extent the risk of BFF is associated with MADS is. The purpose of this study is to assess the risk of BFF with MADS in a retrospective cohort study in clinical practice with parallel comparison with other risk factors and to rank the risk.

2. Methods

2.1. Patient recruiting and methods of information collecting

Patients who matched the Fracture Risk Assessment Tool (FRAX®) listed items such as prevalent bone fragility fracture, current smoking habit, GCS administration history, RA history, secondary osteoporosis, alcohol habit, and low bone mineral density (BMD) such as T-score ≤ -2.5 in either the lumbar spine and femoral neck, and who suffered from LSDs such as type 2 diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), hypertension (HT), hyperlipidemia (HL), chronic kidney disease $\geq$ stage 2 (estimated glomerular filtration rate, eGFR <60 mL/min/1.74 m^2), and insomnia, were recruited from patients who consulted our institute from April 2010 to August 2012.

They were measured with BMD in the lumbar spine and the femoral neck with dual-energy X-ray absorptiometry (DXA), and X-ray images of the lumbar spine at the same time were performed. DXA measurements were made with the DPX® Bravo ME9309 Bone Densitometer (GE Healthcare, Chicago, IL, USA). The coefficients of variations were 1.1% at lumbar spine and 0.9% at femoral neck. These measurement times were set as baseline. These patients' T-scores that shows as dissociation of the BMD compared to the mean BMD in healthy 30-year-olds of the same sex with standard deviation was presented in the study. Therefore, what we evaluated as a risk factor was T-score minimum value in the lumbar spine and in the femoral neck (Tscore_LS and Tscore_FN: continuous number).

At the same time, their X-ray images of vertebrae and proximal femur were taken. Prevalent vertebral body fracture (pr-VF) was assessed using the semiquantitative score (SQ) developed by Genant et al [26]. The SQ classifies VF from Grade-0 to Grade-3. In this study, pr-VF was determined as Grade-1 or more was set for a risk factor (Y/N: binary number). Proximal femoral fracture was assessed on radiographs, and other non-vertebral fractures were assessed using information from interviews and medical records. Prevalent non-vertebral fracture (pr-NVF) including hip fracture (Y/N: binary number) was set as a risk factor. Hip fracture information was obtained from the X-ray images and the other pr-NVFs were harvested from interviews.

In addition to X-ray and DXA assessment, patients were interviewed, and their medical records were used as background risk factors. The patient's sex (male/female: binary number) and age classified by 10-year increments from the patient's fifth decade of life (age; 50–90: continuous number), and the presence of DM (Y/N: binary number), COPD (Y/N: binary number), insomnia (Y/N: binary number), HT (Y/N: binary number), HL (Y/N: binary number), cognitive disorders that include mild cognitive impairment (Y/N: binary number), MADS (Y/N: binary number), presence of OA in the lower limb joint (Y/N: binary number), joint contracture in the trunk or lower limbs (Y/N: binary number), disuse syndrome (Y/N: binary number), Parkinsonism and neuromuscular diseases (Y/N: binary number), or body mass index (BMI: continuous number), and chronic kidney disease (CKD) stage (stages 0–5: stepwise number) calculated from the eGFR using serum creatinine levels, were identified as risk factors at baseline. Administration of GCS (Y/N: binary number), diagnosis and treatment of RA (Y/N: binary number), and lifestyle choices such as current smoking habit (Y/N: binary number), alcohol habit (Y/N: binary number) that may correlate with BFF at baseline were harvested from the medical records. Information on family history of proximal femoral fractures could not be obtained because it depended on the patient's memory and was too uncertain. Informed consent was obtained from all individual participants included in the study.

2.2. Diagnosis of MADS

MADS was diagnosed in accordance with the diagnosis criteria of MADS [27]; patients who had one or more diseases or pathological situations as follows; vertebral body fracture, spinal deformities, fracture of lower extremities, OA of the lower limb joint, spinal canal stenosis, neuromuscular diseases, RA and other chronic arthritis, amputation of the lower extremities, disuse in the locomotive system after being bed ridden for a long term, frequent falls, and matched rank J or A in ADL independency classification and assessment criteria of locomotive function as follows; less than 15 seconds of 'one-leg standing time' or 11 seconds or more with '3 meter timed up and go test'.

2.3. Pre-study statistical evaluation of risk factors

The patients were followed up continuously for more than 8 years from baseline. In the course of follow-up, the occurrence of BFF (incident BFF) was set as the primary end point. The time span from baseline to the primary end point was used for the statistical calculation. The correlations of incident BFF occurrence during follow-up and each risk factor were evaluated using a Cox regression analysis with a Kaplan–Meier survival curve for each risk factor. For the continuous or stepwise values such as age, Tscore_LS, Tscore_FN, BMI, and CKD were evaluated with a receiver operating characteristic (ROC) analysis. The cutoff index (COI) was determined for each risk factor, and the factors that demonstrated statistical significance within an area under the curve (AUC) of 5% were analyzed to determine the statistical significance. After determination of COI, these risk factors were analyzed as a same manner.

2.4. Patient group classification and statistical evaluation

Patients were divided into 2 groups in accordance with the presence of MADS (G-MADS and G-noMADS). Clinical characteristics in the 2 groups were compared using Mann-Whitney *U* test. A Cox regression analysis with a Kaplan–Meier survival curve for the presence of MADS was performed. First, they were compared with

crude data, and then compared with these after propensity score matching technique was used in the 2 groups. This procedure is performed in order to paralleling the risk factors that was significantly different between the 2 groups using crude data, of which the P-value in the Cox regression analysis demonstrated within 5%.

Flow chart of this study is shown in Fig. 1.

2.5. Software used in the statistical procedures

All statistical analyses were performed using StatPlus:mac® (AnalystSoft, Inc., Walnut, CA, USA).

3. Results

3.1. Patient characteristics

A total of 931 patients were included in the study. In these patients, 125 males and 806 females were included. Their mean age at baseline was 78.6 years old and ranged from 54 to 93 years. pr-VF and pr-NVF counted 581 and 100, and prevalent BFF counted 621. Current smoking and alcohol habits counted 34 and 33. DM, COPD, insomnia, HT, HL, cognitive disorder, and MADS counted were 202, 91, 197, 468, 247, 146, and 197, respectively. Mean eGFR calculated with creatinine was 65.6 (mL/min/1.72 m^2), and CKD grade distribution was 90, 485, 223, 92, 34, and 7 for Stage-0, Stage-1, Stage-2, Stage-3, Stage-4, and Stage-5, respectively. Thus, presence of CKD (eGFR< 90 mL/min/1.73 m^2) were counted as 356. Mean Tscore_LS and Tscore_FN were −2.29 and −2.05, respectively. GCS administration were counted as 168 (Table 1).

3.2. Pre-study evaluation of risk factors

Of the parameters with continuous and stepwise number, those that demonstrated statistical significance within 5% of the COIs were Tscore_FN, BMI, and CKD stage, which were −2.3, 25.0, and stage 2, respectively. Age and Tscore_LS did not demonstrate any statistical significance. Including these factors, the risk factors that significantly correlated with the occurrence of an incident BFF in the Cox regression analysis were pr-VF, Disuse, MADS, CD, HT, Contracture, Parkinsonism, female sex, HL, insomnia, Tscore_FN $\leq$ −2.3, CKD $\geq$ stage 2, COPD, GCS, and OA, with the adjusted hazard ratios (from highest to lowest) of these risk factors in the Kaplan–Meier survival curve were 2.80, 2.78, 2.70, 2.56, 2.42, 2.40, 2.12, 2.09, 1.82, 1.75, 1.71, 1.66, 1.64, 1.57, and 1.53, respectively (Table 2).

3.3. Evaluation of MADS using a Cox regression analysis

Background diseases in the G-MADS group distributed were 147 with vertebral body fracture, 43 with spinal deformity, 24 with fracture of the lower extremities, 128 with osteoarthritis in the lower limb joint, 37 with spinal canal stenosis, 4 with neuromuscular diseases, 44 with rheumatoid arthritis, 0 with amputation of the lower extremities, 42 with disuse of locomotive system, and 16 with frequent fall (Table 3).

With crude data, risk ratio of the G-MADS for an incident BFF for 96 months were 2.70 (95% CI, 1.96–3.73) compared to that of the G-noMADS. (Fig. 2A). After propensity score matching, risk ratio of the G-MADS was 1.83 (95% CI, 1.18–2.85) compared to that of the G-noMADS with the P-value of 6.5×10^{-3} (Fig. 2B). Demographic characteristics of the 2 groups before and after propensity score matching are shown in Table 4.

4. Discussion

Osteoporosis is caused by various pathogeneses. BFF risk is not increased only by decreased bone mineral density, but also by degeneration of bone matrix [28], deterioration of bone remodeling cycle [29], insufficient signal transmission from osteocytes [30], and what should not be forgotten is the increase of fall tendency. Osteoporosis is defined as “a condition of generalized skeletal fragility in which bone strength is sufficiently weak for fractures to occur with minimal trauma” [31]. Thus, not only bone fragility but also falling down should be considered as a BFF risk. Therefore, it is necessary to consider physical conditions that increase the risk of inappropriate falls as a risk of BFF in the real clinical setting.

The purpose of this study was to determine the most important risk in clinical practice among various BFF risks. In our retrospective cohort study, long-term incidence of BFF was followed with more than 8 years of follow-up. The results suggest that MADS is a strong risk for BFF. The hazard ratio in the crude data was approximately 2.7 times higher in the G-MADS group than in the G-noMADS group. However, in the crude data, there was a large difference in the patient background between the G-MADS group and the G-noMADS group. Because confounding factors were strongly suspected in the present data, the propensity score matching technique was used to level the patient background between the 2 groups. Subsequent data also showed a significantly higher hazard ratio in the G-MADS group, approximately 1.8-fold than the G-noMADS group.

This study evaluated MADS as a risk of BFF. Therefore, the specific diseases and conditions that cause MADS have not been

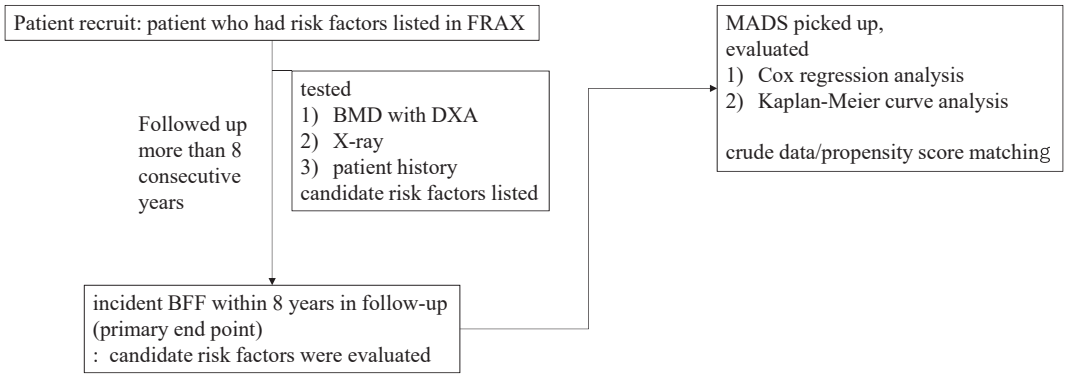

Fig. 1. Flow chart of this study. FRAX, Fracture Risk Assessment Tool; BMD, bone mineral density; BFF, bone fragility fracture; MADS, musculoskeletal ambulation disability symptom complex.

Table 1
Patient's demographic characteristics at baseline.

Cases	931
Sex (male:female, female%)	125:806, 86.6%
Age (yr, mean, SD) (number of 50s, 60s, 70s, 80s, 90s in age)	78.6, 10.7 (51, 124, 246, 389, 121)
Prevalent VF (%)	581 (62.4%)
VF grade (0, 1, 2, 3)	350, 182, 213, 186
Prevalent NVF (%)	100 (10.7%)
Prevalent BFF (%)	621 (66.7%)
Current smoking (%)	34 (3.3%)
Alcohol habit (%)	33 (3.5%)
Type 2 DM (%)	202 (21.7%)
COPD (%)	91 (9.8%)
Insomnia (%)	197 (21.2%)
Hypertension (%)	468 (50.3%)
eGFR (mean, S.D.)	65.6, 20.4
CKD stage (0, 1, 2, 3, 4, 5)	90, 485, 223, 92, 34, 7
CKD (%)	356 (38.2%)
Cognitive disorder (%)	146 (15.7%)
MADS (%)	197 (21.2%)
RA (%)	284 (30.5%)
OA (%)	528 (56.7%)
Disuse (%)	65 (7.0%)
Contracture (%)	91 (9.8%)
Parkinsonism (%)	25 (2.7%)
BMD_LS (mean, SD)	0.826, 0.205
Tscore_LS (mean, SD)	−2.29, 1.69
BMD_FN (mean, SD)	0.658, 0.144
Tscore_FN (mean, SD)	−2.05, 1.16
GCS administrated (%)	168 (18.0%)
OPD administrated (%)	572 (61.4%)
Vitamin D supplemented (%)	547 (58.8%)
BMI (mean, SD)	22.5, 3.9

SD, standard deviation; VF, vertebral body fracture; NVF, non-vertebral body fracture; BFF, bone fragility fracture; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; MADS, musculoskeletal ambulation disability symptom complex; RA, rheumatoid arthritis; OA, osteoarthritis; BMD, bone mineral density; LS, lumbar spine; FN, femoral neck; GCS, glucocorticoid steroid; OPD, anti-osteoporotic drug; BMI, body mass index.Units: BMD, g/cm2; eGFR, mL/min/1.73 m^2.

studied in detail. Some patients with G-noMADS also have a causative disease of MADS, however these patients did not meet the diagnostic criteria in the locomotive function test. Nevertheless, the propensity score matching was performed because there were more confounding factors such as LSD between G-MADS and G-noMADS.

Table 2
Risk ratios of risk factors.

Risk factor	Risk ratio (95% CI)
pr-VF	2.80 (1.88–4.17)
Disuse	2.78 (1.80–4.30)
MADS	2.70 (1.96–3.73)
CD	2.56 (1.82–3.62)
HT	2.42 (1.72–3.41)
Contracture	2.40 (1.61–3.58)
Parkinsonism	2.12 (1.04–4.33)
Being female	2.09 (1.13–3.86)
HL	1.82 (1.32–2.52)
Insomnia	1.75 (1.25–2.47)
Tscore_FN ≤ -2.3	1.71 (1.22–2.31)
CKD $\geq$ Stage 2	1.66 (1.13–2.42)
COPD	1.64 (1.02–2.62)
GCS	1.57 (1.10–2.28)
OA	1.53 (1.10–2.14)

pr-VF, prevalent vertebral body fracture; MADS, musculoskeletal ambulation disorder symptom complex; CD, cognitive disorders; HT, hypertension; HL, hyperlipidemia; T-score ≤ -2.3, T-score in the femoral neck no more than -2.3; CKD $\geq$ Stage 2, chronic kidney disease with Stage 2 or higher; COPD, chronic obstructive pulmonary diseases; GCS, glucocorticoid steroid administrated; OA, osteoarthritis.

From the results of this study, factors associated with increased fall-ability, such as joint contracture and MADS, appeared to be more significant risk factors than those associated with bone fragility, such as low bone density and LSD. Although the intervention effect of therapeutic drugs for osteoporosis was not investigated, in this observational study, although the incidence of BFF was significantly higher in the G-MADS group than in the G-noMADS group in terms of the rate of administration of therapeutic drugs for osteoporosis, and it is expected that therapeutic intervention with an emphasis on exercise function can be expected to have a preventive effect on BFF development than therapeutic intervention with an emphasis on bone strength. Based on the above, it may be important to provide exercise guidance or rehabilitation intervention to improve fall-ability as well as drug

Table 3
Background diseases in the G-MADS group.

Diseases and conditions	N
Total cases	197
Vertebral body fracture	147
Spinal deformities	43
Fracture of the lower extremities	24
Osteoarthritis in the lower limb joint	128
Spinal canal stenosis	37
Neuromuscular diseases	4
Rheumatoid arthritis	44
Amputation of the lower extremities	0
Disuse of locomotive system	42
Frequent fall	16

G-MADS, Group with musculoskeletal ambulation disorder symptom complex.

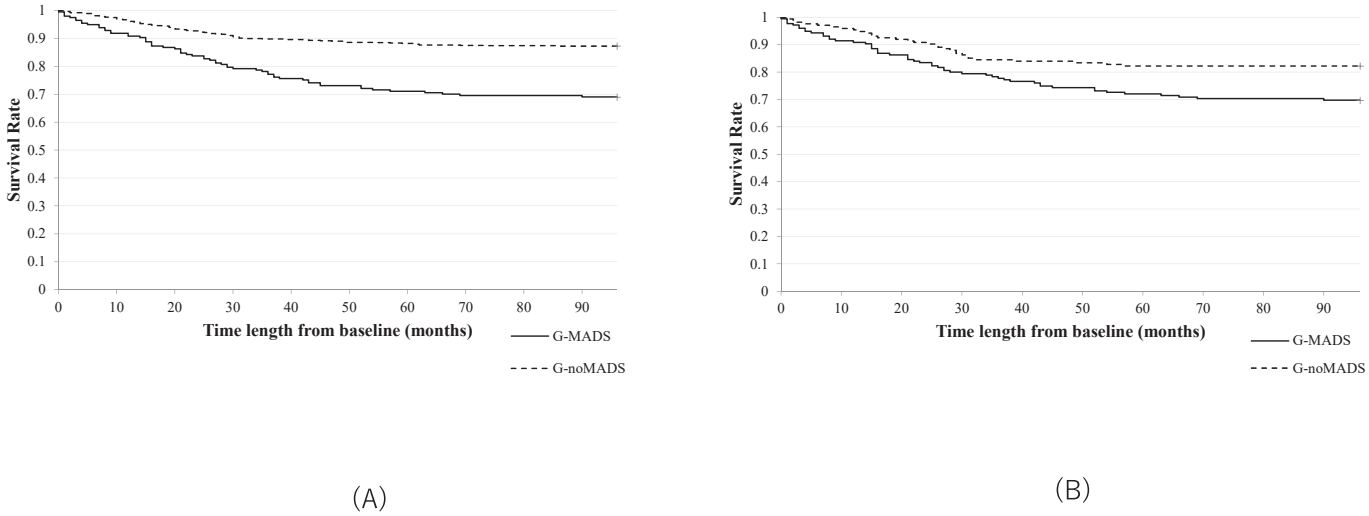

Fig. 2. Kaplan-Meier survival curve for G-MADS/G-noMADS groups. (A). Crude data. Adjusted hazard ratio in the G-MADS group was 2.70 (95%CI: 1.96–3.73) compared to G-noMADS. (B). After propensity score matching procedures. Adjusted hazard ratio in the G-MADS was 1.83 (95% CI, 1.18–2.85) compared to G-noMADS. MADS, musculoskeletal ambulation disability symptom complex.

Table 4
Demographic characteristics in the G-MADS and G-noMADS groups before and after propensity score matching procedure.

	Before PSM (crude data)			After PSM		
	G-MADS	G-noMADS	P-value	G-MADS	G-noMADS	P-value
n	197	734		175	175	
Female (%)	166 (84.3)	636 (87.4)	0.12	148 (84.6)	154 (87.9)	0.15
Age (yr, mean ± SD)	81.9 ± 8.5	77.7 ± 10.9	< **0.001**	82.0 ± 8.4	81.1 ± 8.4	0.14
Prevalent VF (%)	147 (74.6)	425 (9.7)	< **0.001**	132 (75.3)	117 (69.6)	0.09
Prevalent NVF (%)	29 (14.7)	71 (9.7)	< **0.05**	25 (14.3)	27 (15.4)	0.75
Current smoking (%)	9 (4.6)	16 (2.2)	< **0.05**	8 (4.4)	10 (5.7)	0.32
Alcohol (%)	4 (2.0)	10 (1.4)	0.25	4 (2.3)	4 (2.3)	1.00
DM (%)	69 (35.0)	135 (18.4)	< **0.001**	61 (34.8)	71 (40.7)	0.11
COPD (%)	34 (17.3)	45 (6.1)	< **0.001**	30 (17.0)	33 (18.9)	0.32
Insomnia (%)	79 (40.1)	118 (16.1)	< **0.001**	76 (43.4)	86 (49.1)	0.18
HT (%)	155 (78.7)	313 (42.6)	< **0.001**	136 (77.7)	138 (78.9)	0.39
HL (%)	74 (37.6)	173 (23.6)	< **0.001**	67 (38.3)	66 (37.7)	0.67
CKD ≥ Stage 2 (%)	85 (43.1)	272 (37.1)	0.13	80 (45.7)	74 (42.3)	0.45
CD (%)	73 (37.1)	73 (9.9)	< **0.001**	64 (36.6)	69 (39.4)	0.35
RA (%)	44 (22.3)	240 (32.7)	< **0.01**	39 (22.3)	38 (21.7)	0.80
OA (%)	129 (65.5)	399 (54.4)	< **0.01**	115 (65.7)	109 (62.3)	0.31
Disuse (%)	42 (21.3)	23 (3.1)	< **0.001**	27 (15.4)	18 (10.3)	0.11
Contracture (%)	37 (18.8)	54 (7.4)	< **0.001**	31 (17.7)	24 (13.7)	0.13
Parkinsonism (%)	17 (8.6)	8 (1.1)	< **0.001**	10 (5.7)	7 (4.0)	0.23
T-score in the LS < −2.5 (%)	105 (53.3)	335 (45.6)	0.08	89 (50.9)	87 (49.7)	0.83
T-score in the FN < −2.5 (%)	99 (50.3)	243 (33.1)	< **0.001**	85 (48.6)	82 (46.9)	0.83
GCS administrated (%)	40 (20.3)	128 (17.4)	0.18	37 (21.1)	46 (26.3)	0.12
OPD administrated (%)	69 (35.0)	143 (19.5)	< **0.001**	62 (35.4)	50 (28.6)	0.08
VD supplemented (%)	112 (56.9)	435 (59.3)	0.26	102 (58.3)	116 (66.3)	0.06
BMI (mean ± S.D.)	21.6 ± 3.2	22.7 ± 4.0	0.09	21.6 ± 3.3	21.6 ± 4.2	0.39

PSM, propensity score matching; G-MADS, Group with musculoskeletal ambulation disorder symptom complex. G-noMADS, Group without musculoskeletal ambulation disorder symptom complex. VF, vertebral body fracture; NVF, non-vertebral body fracture; DM, diabetes mellitus; COPD, chronic obstructive pulmonary diseases; HT, hypertension; HL, hyperlipidemia; CKD, chronic kidney disease; CD, cognitive disorders; RA, rheumatoid arthritis; OA, osteoarthritis; LS, lumbar spine; FN, femoral neck; GCS, glucocorticoid steroid; OPD, anti-osteoporosis drug; VD, vitamin-D; BMI, body mass index. Chi-square test for binary numbers and Mann-Whitney *U* test for mean age and BMI. Bold style are demonstrated as P-value within 5%.

therapy to improve bone fragility in the treatment of osteoporosis, and it is considered necessary to provide comprehensive treatment to prevent bone fragility fractures.

The study data raised one concern. A considerable number of overlapping cases were present with the presence of MADS and BFF. A post-hoc Cox regression analysis was then performed using data after excluding cases with the presence of epidemic BFF. As a result, the presence of MADS had a relatively high risk ratio (95% CI, 0.70–4.27) of 1.73, which was not significant. However, this may occur because there were only 46 cases of MADS versus 28 cases of incident BFF.

It cannot be denied that there are many limitations in the present study. It is a single-institution study, an observational study and not an intervention study, so it is not possible to evaluate the effects of drug intervention or rehabilitation intervention, and it is not possible to evaluate the rise and fall of MADS because the evaluation in the baseline is the standard. Moreover, this study did not consider the effect of exercise and rehabilitation after baseline.

5. Conclusions

MADS is a strong risk factor for the development of BFF. The results of this study may serve as one of the fracture prediction model.

CRediT author statement

Ichiro Yoshii: Conceptualization, Formal analysis, Writing – Original draft, Writing – Review & editing. **Tatsumi Chijiwa**: Methodology. **Naoya Sawada**: Investigation, Resources. **Shohei Kokei**: Validation, Data curation.

Conflicts of interest

The authors declare no competing interests.

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