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ORIGINAL ARTICLE

Predictive factors of non-treatment and non-persistence to osteoporosis medication after fragility hip fractures at 3 years after discharge: a multicentre, prospective cohort study in the northern Kyushu district of Japan

Masaya Kanahori[1] · Yoshihiro Matsumoto[1] · Toshifumi Fujiwara[1] · Atsushi Kimura[1] · Tomoko Tsutsui[1] · Shinkichi Arisumi[1] · Akiko Oyamada[2] · Masanobu Ohishi[3] · Ko Ikuta[4] · Kuniyoshi Tsuchiya[5] · Naohisa Tayama[6] · Shinji Tomari[7] · Hisaaki Miyahara[8] · Takao Mae[9] · Toshihiko Hara[10] · Taichi Saito[11] · Takeshi Arizono[12] · Kozo Kaji[13] · Taro Mawatari[14] · Masami Fujiwara[15] · Minoru Takasaki[16] · Kunichika Shin[17] · Kenichi Ninomiya[18] · Kazutoshi Nakaie[19] · Yasuaki Antoku[20] · Yukihide Iwamoto[13] · Yasuharu Nakashima[1]

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Abstract

Summary We examined osteoporosis medication use and factors affecting persistence in 497 patients with fragility hip fractures. Only 25.5% of patients received continuous medication for 3 years, and 44.1% of patients received no treatment. Low Barthel index at discharge was a risk factor for both non-treatment and non-persistence to osteoporosis medication.

Purpose Fragility hip fractures (FHF) caused by osteoporosis decrease the quality of life and worsen life expectancy. Use of osteoporosis medication may be an efficient method in the prevention of secondary FHF. However, previous studies have reported low rates of osteoporosis medication and persistence after FHF. This study aimed to evaluate osteoporosis medication use and factors affecting persistence in patients with FHF in the northern Kyushu area of Japan.

Methods A total of 497 FHF patients aged ≥ 60 years with a 3-year follow-up were included. We prospectively collected data from questionnaires sent every 6 months regarding compliance with osteoporosis medication. We compared baseline characteristics among three groups: no treatment (NT), no persistence (NP), and persistence (P), and conducted multivariable regression models to determine covariates associated with non-treatment (NT vs. NP/P) and non-persistence (NP vs. P).

Results There were 219 (44.1%), 151 (30.4%), and 127 (25.5%) patients in the NT, NP, and P groups, respectively. Factors associated with non-treatment were male sex, chronic kidney disease, no previous osteoporosis treatment, and low Barthel index (BI) at discharge. The only factor associated with non-persistence was a low BI at discharge. Factors associated with a low BI at discharge were male sex, older age, trochanteric fracture, and surgical delay.

Conclusion Low BI at discharge is a risk factor for both non-treatment and non-persistence to osteoporosis medication. Therefore, appropriate interventions to improve BI may result in persistence to osteoporosis medication.

Keywords Barthel index · Fragility hip fractures · Osteoporosis · Osteoporosis medication

Introduction

Loss of bone strength due to osteoporosis can lead to fragility fractures. Among these fractures, fragility hip fractures (FHF) are known to decrease a patient's quality of life and worsen life expectancy [1]. Due to the rapidly ageing population in Japan, the prevalence of FHF continues to increase. Worldwide, the total number of FHF cases is estimated to reach 2.6 million in 2025 and 4.5 million in 2050, with the highest incidence expected in Asia [2, 3]. Importantly, FHF

Masaya Kanahori and Yoshihiro Matsumoto contributed equally to this work.

✉ Yoshihiro Matsumoto
ymatsu@ortho.med.kyushu-u.ac.jp

Extended author information available on the last page of the article

is one of the major causes for patients being bedridden in Japan [4], and FHF itself has been identified as a risk factor for fracture, independent of ageing, and bone loss [5, 6]. Therefore, targeting cases of FHF to prevent the vicious cycle of fragility fractures is considered a highly efficient method of treatment.

For the prevention of FHF, osteoporosis medications have been proven to be effective in randomised clinical trials [7]. The selection of appropriate osteoporosis medication and its continued long-term use may improve the clinical outcomes of FHF treatment. However, adherence rates are low in the real-world setting. In fact, several studies have reported low rates of osteoporosis medication use and low persistence to medication at the 1-year follow-up after FHF [8–10]. An international study in three countries—the USA, Korea, and Spain—reported unsatisfactory adherence among patients who were prescribed osteoporosis medications after FHF, with a rate of < 0.70 days of medication up to 1 year after fracture for all countries [9]. Furthermore, despite the increase in the number of FHF cases worldwide, some reports have indicated that adherence to osteoporosis medication has been worsening. For example, in a retrospective study on a cohort of approximately 100,000 residents from the USA, the use of osteoporosis medications within 12 months of hospitalisation for FHF decreased from 40.2% in 2002 to 20.5% in 2011 [11]. Discontinuation of osteoporosis medication is a major problem that not only results in a lack of expected drug efficacy but also leads to economic losses in health care [12].

Extraction of patients at high risk of non-treatment and non-persistence to osteoporosis medications may lead to improvement in the rate of osteoporosis medication use. Several reports have identified the characteristics of such patients, mostly in retrospective cohort studies using prescription databases [10, 13, 14]. One of the limitations of database-based studies is that some of the baseline characteristics affecting persistence to osteoporosis medication may not be obtained. In addition, there have been very few large-scale studies evaluating the persistence to osteoporosis medication in Japan [15]. In the present study, we report osteoporosis medication use as well as factors affecting non-treatment and non-persistence in the real-world setting, obtained from a 3-year follow-up of patients who developed FHF in the northern Kyushu area in Japan.

Patients and methods

Study design and participants

This was a multicentre, prospective, cohort study that included 497 patients aged ≥ 60 years who received treatment for primary FHF at our 17 affiliated hospitals in the northern Kyushu district of Japan between March 2013 and March 2016. FHF was defined as a fracture of the proximal femur caused by low-energy trauma. The exclusion criteria included high-energy trauma and pathological fractures. As described in our previous study [1, 16], to construct the FHF registry, the clinical data of eligible patients were submitted by each participating hospital to the data centre at the Kyushu University Hospital via the Clinical Research Internet Network (CRIN-Q) developed by the Kyushu University Hospital. Our 17 affiliated hospitals are all general hospitals with multiple departments and acute care that mainly provide surgical treatment for FHF. Based on data reported by the Ministry of Health, Labour and Welfare in Japan [17], there were 81 major hospitals in Fukuoka and Saga prefectures that performed surgery for FHF, and our 17 affiliated hospitals accounted for 21.0% of the total number of hospitals. As for the number of operations for FHF, our 17 affiliated hospitals performed 26.7% of the total number of operations at Fukuoka and Saga prefectures. Therefore, this cohort was considered to reflect data from approximately one-fourth of patients with FHF in the northern Kyushu district of Japan. We sent questionnaires every 6 months for up to 3 years after discharge to determine the patient's quality of life and medication status for osteoporosis. Death or secondary FHF was defined as the endpoint. All questionnaires were collected at the Kyushu University Hospital, and the data from questionnaires were managed at data centre as well as the clinical data. This study was reviewed and approved by the Institutional Review Board of the authors' affiliated institutions. Written informed consent was obtained from all patients before participation.

Data collection

The following data were collected on admission: sex, age, body mass index (BMI), drinking and smoking history, medical history, previous osteoporosis treatment, and previous fractures. As for previous osteoporosis treatment, if the patient received osteoporosis treatment at the time of injury, this was defined as ongoing treatment. If the patient had interrupted osteoporosis treatment at that time, we defined it as no previous osteoporosis treatment. The diagnosis of each comorbidity was made as indicated. Hypertension was defined as blood pressure of ≥ 140/90 mmHg. Diabetes mellitus was defined as fasting plasma glucose of ≥ 126 mg/dL, glucose level of ≥ 200 mg/dL in venous plasma in 2-h oral glucose tolerance test, random plasma glucose level of ≥ 200 mg/dL, and/or HbA1c of ≥ 6.5% and was not defined as HbA1c of ≥ 6.5% alone. Stroke was defined by history of acute stroke diagnosed using physical tests and brain scans. Chronic kidney disease (CKD) was diagnosed by a glomerular filtration rate of < 60 mL/min/1.73 m^2. Liver cirrhosis was diagnosed

by a combination of laboratory and imaging tests. Cardiac arrhythmia was diagnosed using electrocardiogram. Malignancy was defined as a previous diagnosis of malignancy, whether on treatment, at follow-up, or in remission. Connective tissue disease was diagnosed if the diagnostic criteria for each disease were met; for example, rheumatoid arthritis was diagnosed in accordance with the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis. Cardiac insufficiency was comprehensively diagnosed by history, physical examination findings, imaging studies, and biomarkers showing signs and symptoms of congestion and/or end-organ hypoperfusion. For the assessment of comorbidities, we calculated the Charlson comorbidity index (CCI) [18], the most widely used comorbidity index in the world, using the number of relevant comorbidities and a score derived from the age for each patient. In addition, the following data were collected as factors related to treatment and outcomes for FHF: bone mineral density (BMD), type of fracture, type of surgery, surgical delay, length of hospital stay (LOS), and place to discharge. For each data point, lumbar BMD was measured at the L2–L4 vertebrae and femoral BMD was measured at the femoral neck of the non-fractured hip using dual energy X-ray absorptiometry during hospitalisation for initial FHF treatment. BMD data were evaluated based on the young adult mean (YAM) value. Surgical delay was defined as the number of days from injury to surgery. LOS was defined as the number of days until discharge from the hospital for the initial treatment. A place to discharge referred to the discharge destination from the initial treatment hospital and was categorised as home, other medical institutions, or others. Other medical institutions included general hospitals, recovery hospitals, sanatoriums, and clinics. Others included nursing homes and transfers to other department for the treatment of comorbidities. We also calculated the Barthel index (BI) [19] at discharge for all patients. The BI is a common score of activities of daily living (ADL) used worldwide and has been shown to be suitable for assessing ADL after FHF [20]. Furthermore, medication status for osteoporosis after discharge was obtained from questionnaires collected every 6 months. Medication status was defined based on whether the patient received osteoporosis medication for 6 months, regardless of the type of preparation (injectable or oral). Data on death or secondary fracture was also obtained from questionnaires. Within 3 years of discharge, 107 patients (21.5%) died and 48 patients (9.7%) developed a secondary FHF, reaching the endpoint. At 3 years after discharge, questionnaires were still being administered to the remaining 342 patients (68.8%). Assuming that all questionnaires were to be collected from 497 patients for 3 years after discharge or until the endpoint, the total number of potential questionnaires was 2535. The total number of questionnaires collected was 2003, so the questionnaire collection rate was 79.0%. All 497 patients submitted at least one questionnaire; thus, all patients were included in the analysis.

We classified the 497 patients into three groups: no treatment (NT), no persistence (NP), and persistence (P), depending on the status of osteoporosis medication after discharge. The NT group included patients who did not receive any osteoporosis medication for 3 years after discharge or until the endpoint. In the NP group, patients were temporarily treated for 3 years or until the endpoint. Patients that had interrupted medication, even for 6 months, were included in the NP group. The P group included patients who started medication within 6 months after discharge and continued the medication for 3 years or until the endpoint. In case it was unknown whether the patient had been treated for 6 months because the questionnaire was not collected, continued treatment was defined as when the medication was continued in the preceding and following 6 months. When the questionnaires were not collected for 1 year, this was defined as not continued treatment.

In univariable and multivariable analyses, each variable was categorised as follows, according to the previous report [16]. Age was categorised as $60 \leq \text{age} < 75$ years, $75 \leq \text{age} < 85$ years, and age ≥ 85 years. BMI was categorised as $\text{BMI} < 18.5$ kg/m^2, $18.5 \leq \text{BMI} < 25$ kg/m^2, and $\text{BMI} \geq 25$ kg/m^2. CCI was classified as either ≤ 4 or ≥ 5 using the median as the cut-off value (CCI = 4). BMD was categorised as follows: normal, YAM $\geq 80\%$; osteopaenia, $70\% \leq \text{YAM} < 80\%$; and osteoporosis, YAM $< 70\%$. When BMD values from both locations were available and belonged to different categories, we adopted the worse value as the BMD measurement. Previous fractures were categorised as none, vertebral fractures (strongly correlated with fragility fractures), and others. Types of fractures were classified as either femoral neck fracture or trochanteric fracture. Type of surgery was classified as arthroplasty or internal fixation. Surgical delay was stratified every 2 days: < 2 days, $2 \leq$ and < 4 days, $4 \leq$ and < 6 days, and ≥ 6 days. LOS was categorised as LOS ≥ 35 days, $28 \leq \text{LOS} < 35$ days, $14 \leq \text{LOS} < 28$ days, and LOS < 14 days, because patients with hip fractures are generally treated at the hospital for 2–5 weeks in Japan. BI at discharge was categorised as BI ≥ 70, $30 \leq \text{BI} < 70$, and BI<30.

In addition, the reason for discontinuing or not receiving osteoporosis medication was obtained from questionnaires. The possible responses were as follows: 'never received osteoporosis medication after discharge', 'discontinued because of side effect', 'discontinued because it was a hassle to go to hospital', 'did not feel the necessity to receive osteoporosis medication', 'discontinued without noticing', and 'other reason'. Overall, 95 patients did not respond to this item even

though they were not receiving osteoporosis medication; thus, 275 patients completed this item. If a patient gave the same answer to the questionnaire at multiple time points, we counted it as one answer. If a patient gave different answers, we counted each answer. Thus, we calculated how many of the 275 respondents gave a specific answer.

Statistical analyses

We first described baseline patient characteristics in the NT, NP, and P groups. Mortality and secondary FHF rate in each group were also determined. We calculated means and standard deviations for continuous variables, absolute numbers and relative frequencies for categorical variables, and medians and interquartile ranges for non-normally distributed data.

Next, we compared the baseline characteristics of NT and NP/P patients to determine the factors affecting non-treatment. We also compared the baseline characteristics between the NP and P groups to identify factors associated with non-persistence. Differences between the two groups were statistically analysed using the Mann–Whitney *U* test for non-parametric continuous variables or Fisher's exact test for categorical variables, as appropriate. Then, we performed univariable analysis and conducted multivariable logistic regression models to determine which covariates were associated with non-treatment and non-persistence. Mortality and secondary FHF rates were not baseline characteristics; therefore, we excluded both from this analysis. In the multivariable analysis of non-treatment, factors significantly associated in the univariable analysis (sex, age, smoking history, CKD, CCI, previous osteoporosis treatment, surgical delay, and BI at discharge) were generally consistent with previous reports [10, 13, 14], and we performed multivariable analysis using these 8 factors with $p < 0.05$. Conversely, only one factor, BI at discharge, was significantly associated in the univariable analysis of non-persistence. Therefore, in multivariable analysis, we included two factors (CKD and CCI) with marginal significance ($p < 0.1$), and added two more factors (sex and age) that may be relevant to non-persistence according to previous studies [10, 13, 14]. In addition, we classified the 497 patients into two groups: low BI (BI < 30) and others (BI ≥ 30) at discharge. We compared the baseline characteristics between the groups and conducted multivariable regression models to determine which covariates were associated with low BI using the same method as above. The corresponding odds ratios (ORs) with 95% confidence intervals (CI) were estimated. Statistical significance was set at $p < 0.05$. All analyses were performed using JMP version 15.0 (SAS Institute Inc., Cary, NC, USA).

Results

Comparison of baseline characteristics of NT, NP, and P patients

There were 219 (44.1%), 151 (30.4%), and 127 (25.5%) patients in the NT, NP, and P groups, respectively. The baseline characteristics of the groups are summarised in Table 1. We then compared the baseline characteristics between NT and NP/P patients (Supplementary Table S1). The proportions of male patients and smokers were significantly higher in the NT than in the NP/P group (male: 31.5% vs. 13.7%, $p < 0.0001$, smokers: 24.2% vs. 15.8%, $p = 0.0225$). The mean age was significantly higher in the NT than in the NP/P group (83.2 years [SD: ± 7.9] vs. 81.3 years [SD: ± 7.8], $p = 0.0063$). Among the comorbidities, CKD was significantly more common in the NT group (13.2% vs. 5.8%, $p = 0.0045$). The value of CCI was significantly higher in the NT than in the NP/P group (5.0 vs. 4.0, $p = 0.0021$). Previous osteoporosis treatment was significantly less common in the NT than in the NP/P group (14.2% vs. 29.1%, $p < 0.0001$). Surgical delay was significantly longer in the NT than in the NP/P group (4.79 days vs. 4.08 days, $p = 0.0299$). The BI value at discharge was significantly lower in the NT than in the NP/P group (50.0 vs. 70.0, $p < 0.0001$). The mortality was significantly higher in the NT than in the NP/P group (37.4% vs. 9.0%, $p < 0.0001$). As for BMI, drinking habits, other comorbidities and previous fractures, BMD, type of fracture, type of surgery, LOS, place to discharge, and secondary FHF, there were no significant differences between the NT and NP/P patients. We also compared the baseline characteristics between NP and P patients (Supplementary Table S2). For all characteristics other than secondary FHF, there were no significant differences between NP and P patients. Only the secondary FHF was significantly higher in the P than in the NP group (15.7% vs. 5.3%, $p = 0.0048$).

Factors associated with non-treatment

Results of the multivariable analyses revealed the factors associated with non-treatment (Table 2). Male sex (OR: 2.21, 95% CI: 1.28–3.84, $p = 0.0046$), CKD (OR: 2.88, 95% CI: 1.36–6.08, $p = 0.0057$), no previous osteoporosis treatment (OR: 2.20, 95% CI: 1.35–3.58, $p = 0.0016$), and low BI at discharge (30 ≤ BI < 70: OR: 1.59, 95% CI: 1.02–2.47, $p = 0.0412$ and BI < 30: OR: 3.41, 95% CI: 1.92–6.06, $p < 0.0001$) were significantly associated with non-treatment.

Table 1 Baseline characteristics of never treated, no persistence, and persistence patients

	NT ($n=219$)	NP ($n=151$)	P ($n=127$)
Sex			
Female	150 (68.5)	126 (83.4)	114 (89.8)
Male	69 (31.5)	25 (16.6)	13 (10.2)
Age (years)	83.2 (7.9)	82.0 (7.7)	80.4 (8.0)
BMI (kg/m^2)	20.0 (3.2)	20.7 (3.4)	20.5 (3.5)
Alcohol (≥ 3 units/day)	18 (8.2)	7 (4.6)	7 (5.5)
Smoking	53 (24.2)	23 (15.2)	21 (16.5)
Principal comorbidities, *n* (%)			
Hypertension	104 (47.5)	75 (49.7)	54 (42.5)
Diabetes mellitus	41 (18.7)	34 (22.5)	20 (15.7)
Stroke	27 (12.3)	23 (15.2)	13 (10.2)
CKD	29 (13.2)	12 (7.9)	4 (3.1)
LC	10 (4.6)	6 (4.0)	7 (5.5)
Cardiac arrhythmia	12 (5.5)	5 (3.3)	6 (4.7)
Malignancy	30 (13.7)	17 (11.3)	18 (14.2)
CTD	16 (7.3)	9 (6.0)	11 (8.7)
Cardiac insufficiency	10 (4.6)	5 (3.3)	2 (1.6)
CCI	5.00 (4.0–6.0)	4.00 (4.0–5.0)	4.00 (4.0–5.0)
BMD (YAM, %)			
L-spine ($n=379$)[a]	($n=165$)	($n=116$)	($n=98$)
	73.0 (63.5–88.0)	69.0 (62.0–85.3)	73.0 (63.5–88.0)
Femoral neck ($n=451$)[b]	($n=200$)	($n=138$)	($n=113$)
	57.0 (50.0–69.8)	58.0 (50.0–68.0)	57.0 (50.0–69.8)
Previous osteoporosis treatment	31 (14.2)	40 (26.5)	41 (32.3)
Previous fracture, *n* (%)			
Vertebra	25 (11.4)	20 (13.2)	14 (11.0)
Distal radius	5 (2.3)	7 (4.6)	6 (4.7)
Proximal humerus	3 (1.4)	5 (3.3)	2 (1.6)
Others	17 (7.8)	10 (6.6)	17 (13.4)
Type of fracture, *n* (%)			
Femoral neck	125 (57.1)	85 (56.3)	72 (56.7)
Trochanteric	89 (40.6)	63 (41.7)	50 (39.4)
Sub-trochanteric	5 (2.3)	3 (2.0)	5 (3.9)
Type of surgery, *n* (%)	(Total = 219)	(Total = 149)[c]	(Total = 126)[d]
Arthroplasty	90 (41.1)	61 (40.9)	53 (42.1)
Nail	88 (40.2)	65 (43.6)	52 (41.3)
CHS	14 (6.4)	9 (6.0)	10 (7.9)
Hansson-pin/CCS	25 (11.4)	14 (9.4)	11 (8.7)
Others	2 (0.9)	0 (0.0)	0 (0.0)
Surgical delay (days)	($n=219$)	($n=150$)[e]	($n=127$)
	4.79 (2.6–8.1)	4.00 (2.3–6.2)	4.17 (2.1–6.3)
LOS (days)	22.0 (18.0–28.0)	22.0 (17.0–29.0)	23.0 (19.0–31.0)
BI at discharge	50.0 (25.0–80.0)	65.0 (40.0–90.0)	75.0 (50.0–90.0)
Place to discharge, *n* (%)			
Home	15 (6.8)	16 (10.6)	14 (11.0)
Other medical institution	190 (86.8)	127 (84.1)	110 (86.6)
Others	14 (6.4)	8 (5.3)	3 (2.4)
Mortality, *n* (%)	82 (37.4)	13 (8.6)	12 (9.4)
Secondary FHF, *n* (%)	20 (9.1)	8 (5.3)	20 (15.7)

NT, never treated; *NP*, no persistence; *P*, persistence; *BMI*, body mass index; *CKD*, chronic kidney disease; *LC*, liver cirrhosis; *CTD*, connective tissue disease; *CCI*, Charlson comorbidity index; *BMD*, bone mineral density; *YAM*, young adult mean; *CHS*, compression hip screw; *CCS*, cannulated cancellous screw; *LOS*, length of hospital stay; *BI*, Barthel index; *FHF*, fragility hip fracture

Unless specified otherwise, the results are presented as mean (SD) or median with interquartile range

[a]One hundred eighteen patients were measured only femoral BMD

[b]Forty-six patients were measured only lumbar BMD

[c]One patient was treated conservatively, and the other patient's data was missing

[d]One patient's data was missing

[e]One patient was treated conservatively

All data, except for the data marked with a note [a–e], had no missing data

Factors associated with non-persistence

Results of the multivariable analyses revealed the factors associated with non-persistence (Table 3). In contrast to non-treatment, only BI of < 30 (OR: 3.38, 95% CI: 1.33–8.57, $p = 0.0105$) was significantly associated with non-persistence. These results indicated that low BI at discharge was a risk factor for both non-treatment and non-persistence to osteoporosis medication.

Factors associated with low BI at discharge

Low BI at discharge was found to be a critical risk factor; we then decided to investigate which characteristic features of patients were associated with lower BI. Therefore, we classified the 497 patients into two groups: low BI (BI < 30) at discharge and other (BI ≥ 30), and compared the baseline characteristics between the two groups (Supplementary Table S3). The proportion of male patients was significantly higher in the low BI group (31.3% vs. 19.1%, $p = 0.0134$). We observed that low BI was associated with older age (86.5 years [SD: ± 6.5] vs. 81.0 years [SD: ± 7.9], $p < 0.0001$) and low BMI (19.8 kg/m^2 [SD: ± 3.2] vs. 20.5 kg/m^2 [SD: ± 3.4], $p = 0.0262$). The value of CCI was significantly higher in the low BI group (5.0 vs. 4.0, $p = 0.0045$). BMD in the femoral neck was lower in patients with low BI (53.0% vs. 61.0%, $p < 0.0001$). Low BI was associated with fracture type (femoral neck fracture: 42.4% vs. 60.3%, $p = 0.0015$) and surgery type (arthroplasty: 36.7% vs. 42.4%, $p = 0.0004$). Surgical delay was significantly longer in patients with low BI (5.69 days vs. 4.11 days, $p = 0.0074$). The place to discharge was also associated with low BI (home: 3.0% vs. 10.6%, $p = 0.0076$). Mortality was significantly higher in the low BI group (39.4% vs. 17.1%, $p < 0.0001$), and secondary FHF was significantly lower in the low BI group (2.0% vs. 11.6%, $p = 0.0021$).

Meanwhile, multivariable analysis showed that factors correlated with low BI at discharge were male sex (OR: 2.17, 95% CI: 1.26–3.74, $p = 0.0054$), older age (75 ≤ age < 85 years: OR: 4.43, 95% CI: 1.27–15.49, $p = 0.0199$, and age ≥ 85 years: OR: 10.68, 95% CI: 3.10–36.80, $p = 0.0002$), trochanteric fracture (OR: 1.99, 95% CI: 1.20–3.29, $p = 0.0072$), a surgical delay of ≥ 6 days (OR: 3.48, 95% CI: 1.61–7.51, $p = 0.0015$), and discharge to other place than home (OR: 5.14, 95% CI: 1.10–23.99, $p = 0.0372$) (Table 4).

Reasons for discontinuing or not receiving osteoporosis medication

The reasons for discontinuing or not receiving osteoporosis medications are summarised in Table 5. The most common specific answer was 'never received osteoporosis medication after discharge' provided by 183 of 275 patients (66.6%). 'Did not feel the necessity to receive osteoporosis medication' was the second most common reason as reported by 86 of 275 patients (31.3%). The other frequent answers included 'discontinued without noticing', 'discontinued because it was a hassle to go to the hospital', and 'discontinued because of side effect' with 51 (18.6%), 7 (2.6%), and 6 respondents (2.2%), respectively. In total, 103 patients (37.5%) answered 'other reason'. These results indicated that many patients in this population had not been recommended osteoporosis medication after FHF or had not been educated adequately about the necessity for treatment.

Discussion

In the present study, the status of osteoporosis treatment in a real-world setting for patients with FHF in the northern Kyushu area of Japan was evaluated.

Our findings showed that, surprisingly, 44% of patients did not receive any osteoporosis treatment. Factors associated with non-treatment were male sex, CKD, and low BI at discharge. As expected, history of no osteoporosis treatment was also associated with no current treatment. As for male sex, in general, osteoporosis in men is often neglected compared with that in women. A previous report showed that the rate of osteoporosis treatment after FHF was 4.5% in men compared with 27% in women [21]. Several reports have shown that osteoporosis-related complications were more common in men and that mortality rate associated with fractures was higher in men than in women [22, 23]; therefore, men should also receive appropriate treatment as women. Our study also found that CKD is a risk factor for non-treatment, with an OR of 2.88. Patients with an estimated GFR of < 60 mL/min have a greater than twofold risk of FHF compared with the general population [24]. Thus, physicians need to treat CKD-associated osteoporosis to prevent fractures, although care must be taken because of the limited range of drugs available for advanced stage of CKD.

Low BI at discharge was not only a risk factor for non-treatment but also the dominant factor for non-persistence to osteoporosis medication. We considered that a low BI may worsen patient comorbidities and frailty after discharge. These factors would have precluded adequate medical visits after treatment for FHF, resulting in an extremely low osteoporosis medication rate. Moreover, in our previous study, patients with low independence at discharge from the hospital after FHF treatment had a significantly lower survival rate after 1 year of fracture [16]. Therefore, after FHF treatment, active rehabilitation and improvement of the general conditions should be considered to increase the level of patient independence as much as possible. This approach

Table 2 Univariable analysis and multivariable logistic regression analysis for non-treatment

		Non-treatment (NT vs NP/P)			
		Univariate		Multivariate	
		Odds ratio (95% CI)[a]	*p* value	Odds ratio (95% CI)[a]	*p* value
Sex	Female	Reference		Reference	
	Male	2.91 (1.86–4.54)	<0.0001[b]	2.21 (1.28–3.84)	0.0046[b]
Age (years)	60–74	Reference		Reference	
	75–84	1.73 (1.01–2.97)	0.0471[b]	1.67 (0.93–3.00)	0.0882
	≧85	2.02 (1.18–3.45)	0.0105[b]	1.56 (0.84–2.89)	0.1612
BMI (kg/m^2)	12–18.4	1.22 (0.83–1.80)	0.3082		
	18.5–24.9	Reference			
	≧25	0.54 (0.27–1.07)	0.0785		
Alcohol (≧3 units/day)	No	Reference			
	Yes	1.69 (0.82–3.48)	0.1550		
Smoking	Never	Reference		Reference	
	Current/past	1.70 (1.09–2.65)	0.0201[b]	1.08 (0.62–1.90)	0.7859
CKD	No	Reference		Reference	
	Yes	2.50 (1.32–4.73)	0.0049[b]	2.88 (1.36–6.08)	0.0057[b]
CCI	<5	Reference		Reference	
	≧5	1.54 (1.08–2.21)	0.0169[b]	1.00 (0.66–1.53)	0.9997
BMD	Normal	Reference			
	Osteopenia	0.98 (0.45–2.14)	0.9524		
	Osteoporosis	0.79 (0.40–1.55)	0.4952		
Osteoporosis treatment	Never/ever	2.49 (1.57–3.95)	<0.0001[b]	2.20 (1.35–3.58)	0.0016[b]
	Yes	Reference		Reference	
Previous fracture	None	Reference			
	Vertebra	0.88 (0.50–1.53)	0.6410		
	Other	0.67 (0.38–1.18)	0.1651		
Type of fracture	Femoral neck	Reference			
	Trochanteric	0.98 (0.68–1.40)	0.8929		
Type of surgery	Arthroplasty	Reference			
	Internal fixation	1.01 (0.71–1.46)	0.9359		
Surgical delay (days)	<2	Reference		Reference	
	2–4	1.13 (0.66–1.94)	0.6491	0.99 (0.56–1.77)	0.9810
	4–6	1.01 (0.58–1.76)	0.9647	0.81 (0.45–1.47)	0.4902
	≧6	1.70 (1.02–2.84)	0.0436[b]	1.28 (0.74–2.23)	0.3810
LOS (days)	≧35	Reference			
	28–35	1.32 (0.68–2.58)	0.4161		
	14–28	1.22 (0.74–2.02)	0.4294		
	<14	1.86 (0.72–4.82)	0.2026		
BI at discharge	≧70	Reference		Reference	
	30–70	1.70 (1.13–2.56)	0.0104[b]	1.59 (1.02–2.47)	0.0412[b]
	<30	3.94 (2.37–6.53)	<0.0001[b]	3.41 (1.92–6.06)	<0.0001[b]
Place to discharge	Home	Reference			
	Other medical institution	1.60 (0.84–3.07)	0.1536		
	Others	2.55 (0.93–6.95)	0.0681		

NT, never treated; *NP*, no persistence; *P*, persistence; *BMI*, body mass index; *CKD*, chronic kidney disease; *CCI*, Charlson comorbidity index; *BMD*, bone mineral density; *LOS*, length of hospital stay; *BI*, Barthel index

[a]Odds ratios and corresponding 95% confidence intervals (CIs) were estimated using multivariable logistic regression models

[b]Statistically significant variables at $p < 0.05$

Table 3 Univariable analysis and multivariable logistic regression analysis for non-persistence

		Non-persistence (NP vs P)			
		Univariate		Multivariate	
		Odds ratio (95% CI)[a]	*p* value	Odds ratio (95% CI)[a]	*p* value
Sex	Female	Reference		Reference	
	Male	1.74 (0.85–3.56)	0.1298	1.83 (0.87–3.84)	0.1115
Age (years)	60–74	Reference		Reference	
	75–84	0.84 (0.44–1.59)	0.5854	0.73 (0.38–1.42)	0.3578
	≧85	1.57 (0.82–3.01)	0.1765	1.23 (0.60–2.51)	0.5699
BMI (kg/m^2)	12–18.4	0.89 (0.52–1.51)	0.6606		
	18.5–24.9	Reference			
	≧25	1.14 (0.53–2.48)	0.7388		
Alcohol (≧3 units/day)	No	Reference			
	Yes	0.83 (0.28–2.44)	0.7396		
Smoking	Never	Reference			
	Current/past	0.91 (0.48–1.73)	0.7668		
CKD	No	Reference		Reference	
	Yes	2.65 (0.83–8.45)	0.0982	2.19 (0.64–7.46)	0.2108
CCI	< 5	Reference		Reference	
	≧5	1.52 (0.94–2.47)	0.0884	1.17 (0.69–2.00)	0.5605
BMD	Normal	Reference			
	Osteopenia	0.60 (0.20–1.79)	0.3565		
	Osteoporosis	0.91 (0.35–2.36)	0.8539		
Osteoporosis treatment	Never/ever	1.32 (0.79–2.22)	0.2902		
	Yes	Reference			
Previous fracture	None	Reference			
	Vertebra	1.16 (0.56–2.43)	0.6876		
	Other	0.70 (0.35–1.39)	0.3048		
Type of fracture	Femoral neck	Reference			
	Trochanteric	1.02 (0.63–1.64)	0.9464		
Type of surgery	Arthroplasty	Reference			
	Internal fixation	1.05 (0.65–1.69)	0.8505		
Surgical delay (days)	< 2	Reference			
	2–4	1.50 (0.75–3.00)	0.2505		
	4–6	0.94 (0.47–1.88)	0.8593		
	≧6	1.17 (0.59–2.31)	0.6602		
LOS (days)	≧35	Reference			
	28–35	1.55 (0.64–3.77)	0.3310		
	14–28	1.29 (0.68–2.44)	0.4301		
	< 14	2.54 (0.59–10.99)	0.2135		
BI at discharge	≧70	Reference		Reference	
	30–70	1.01 (0.61–1.68)	0.9695	0.93 (0.54–1.59)	0.7895
	< 30	3.75 (1.53–9.17)	0.0038[b]	3.38 (1.33–8.57)	0.0105[b]
Place to discharge	Home	Reference			
	Other medical institution	1.01 (0.47–2.16)	0.9791		
	Others	2.33 (0.52–10.55)	0.2709		

NT, never treated; *NP*, no persistence; *P*, persistence; *BMI*, body mass index; *CKD*, chronic kidney disease; *CCI*, Charlson comorbidity index; *BMD*, bone mineral density; *LOS*, length of hospital stay; *BI*, Barthel index

[a]Odds ratios and corresponding 95% confidence intervals (CIs) were estimated using multivariable logistic regression models

[b]Statistically significant variables at $p < 0.05$

Table 4 Univariable analysis and multivariable logistic regression analysis for low Barthel index at discharge

		Low BI at discharge (BI < 30 vs BI ≧30)			
		Univariate		Multivariate	
		Odds ratio (95% CI)[a]	*p* value	Odds ratio (95% CI)[a]	*p* value
Sex	Female	Reference		Reference	
	Male	1.93 (1.18–3.16)	0.0088[b]	2.17 (1.26–3.74)	0.0054[b]
Age (years)	60–74	Reference		Reference	
	75–84	4.59 (1.36–15.50)	0.0140[b]	4.43 (1.27–15.49)	0.0199[b]
	≧85	11.82 (3.60–38.82)	< 0.0001[b]	10.68 (3.10–36.80)	0.0002[b]
BMI (kg/m^2)	12–18.4	1.41 (0.88–2.26)	0.1485		
	18.5–24.9	Reference			
	≧25	0.84 (0.36–2.00)	0.6998		
Alcohol (≧3 units/day)	No	Reference			
	Yes	0.56 (0.19–1.62)	0.2836		
Smoking	Never	Reference			
	Current/past	1.06 (0.61–1.83)	0.8476		
CCI	< 5	Reference		Reference	
	≧5	1.84 (1.18–2.87)	0.0074[b]	1.17 (0.71–1.91)	0.5371
BMD	Normal	Reference			
	Osteopenia	1.83 (0.56–6.02)	0.3174		
	Osteoporosis	2.21 (0.76–6.43)	0.1443		
Osteoporosis treatment	Never/ever	1.51 (0.85–2.68)	0.1556		
	Yes	Reference			
Previous fracture	None	Reference			
	Vertebra	1.37 (0.73–2.60)	0.3306		
	Other	0.70 (0.33–1.48)	0.3463		
Type of fracture	Femoral neck	Reference		Reference	
	Trochanteric	2.06 (1.32–3.22)	0.0015[b]	1.99 (1.20–3.29)	0.0072[b]
Type of surgery	Arthroplasty	Reference			
	Internal fixation	1.27 (0.80–2.00)	0.3064		
Surgical delay (days)	< 2	Reference		Reference	
	2–4	1.99 (0.93–4.27)	0.0758	2.08 (0.94–4.61)	0.0722
	4–6	1.47 (0.66–3.28)	0.3515	1.68 (0.72–3.90)	0.2317
	≧6	2.95 (1.44–6.05)	0.0032[b]	3.48 (1.61–7.51)	0.0015[b]
LOS (days)	≧35	Reference			
	28–35	0.71 (0.29–1.75)	0.4589		
	14–28	1.14 (0.61–2.11)	0.6881		
	< 14	1.25 (0.40–3.94)	0.6975		
Place to discharge	Home	Reference		Reference	
	Other medical institution	3.58 (1.08–11.83)	0.0363[b]	2.14 (0.61–7.54)	0.2375
	Others	7.87 (1.89–32.84)	0.0046[b]	5.14 (1.10–23.99)	0.0372[b]

BI, Barthel index; *BMI*, body mass index; *CKD*, chronic kidney disease; *CCI*, Charlson comorbidity index; *BMD*, bone mineral density; *LOS*, length of hospital stay

[a]Odds ratios and corresponding 95% confidence intervals (CIs) were estimated using multivariable logistic regression models

[b]Statistically significant variables at $p < 0.05$

may improve not only the survival rate but also the adherence rate to osteoporosis medication.

We also attempted to identify the risk factors for low BI after FHF. Older age was associated with low BI, which may be a consequence of sarcopaenia. It is interesting to note that male sex was a risk factor, but previous reports on sex differences in functional recovery after FHF have been conflicting and inconsistent [25]. Our study showed that low BI, at least at discharge, was more common in men. Trochanteric fracture was also a risk factor for low BI. Some

Table 5 Reasons for discontinuing or not receiving osteoporosis medication

Each item of questionnaire	Number of patients (%) (Total = 275)
Never received osteoporosis medication after discharge	183 (66.6)
Discontinued because of side effect	6 (2.2)
Discontinued because it was hassle to go to hospital	7 (2.6)
Did not feel the necessity to receive osteoporosis medication	86 (31.3)
Discontinued without noticing	51 (18.6)
Other reason	103 (37.5)

In total, 275 patients completed this part of the questionnaires. If a patient gave the same answer to the questionnaire at multiple time points, we defined it as one answer. If a patient gave different answers, we counted each answer

studies have reported that ADL scores for femoral neck fracture were higher than that for femoral trochanteric fracture at discharge, although there was no significant difference for ADL at 1 year [26, 27]. These results are consistent with our study results. Instability of the fracture site may contribute to lower ADL in patients with trochanteric fracture in the early postoperative period [28]. Discharge to another place was also associated with low BI. Although these patients had been living in a nursing home before FHF or were transferred to other departments for the treatment of comorbidities, a lower ADL was to be expected. Furthermore, surgical delay was found to be associated with low BI. Altogether, for patients with the aforementioned multiple risk factors, surgery should be performed as soon as possible to improve postoperative BI. Importantly, early surgery can improve not only postoperative BI but also adherence to osteoporosis medication after discharge.

On the other hand, once FHF patients were discharged, one way to improve adherence to osteoporosis medications is through a fracture liaison service (FLS), which involves a multidisciplinary team, including orthopaedic surgeons, primary care physicians, osteoporosis specialists, nurses, and care managers. The FLS can educate patients about the advantages and disadvantages of osteoporosis medications and encourage them to continue taking them. In this study, 31.3% of patients who provided a reason for discontinuing or not receiving osteoporosis medication responded that they did not feel the necessity to receive treatment, which suggests that patient education is extremely important. Another major advantage of FLS is the ability to assist with outpatient consultations. In addition, proactive assistance programs that send reminders to patients by phone, email, or letter may also be effective in improving adherence rates [29]. Improving medication adherence through these efforts may reduce the risk of secondary FHF [30].

There are several limitations to the current study. First, the follow-up rate was 79% because the adherence to medication was confirmed using questionnaires. This may have caused a selection bias, and thus, it is necessary to increase the follow-up rate by sending reminders. Another problem is that medication status was not accurately measured. In this study, the survey of medication status relied on self-reports by patients or their families, which may not always be accurate. It would have been more accurate if a prescription database [10] had been available, but we did not have access to such a database. As for the collected clinical data, a little variation in BMD may have occurred due to the lack of uniformity in measurement conditions across our 17 affiliated hospitals. However, since all 17 hospitals used the Hologic Horizon DXA System for measurement, there were no errors between models, and errors between the same models are considered to be very small. In addition, BI at discharge was a risk factor for both non-treatment and non-persistence to osteoporosis medication; thus, we considered investigating whether BI before FHF onset was also relevant, but we were unable to do so because of the lack of available data. It is unclear whether the same results were obtained in our cohort, but Gamboa et al. reported that low BI at admission in FHF patients was significantly correlated with non-adherence to oral bisphosphonate [31].

In conclusion, obtaining information on factors associated with non-treatment and non-persistence in osteoporosis treatment may allow healthcare providers to identify such patients in the early phase and conduct personalised interventions that would improve their management.

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Data availability Supplemental material for this article is available online.

Code availability Not applicable.

Declarations

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Conflicts of interest None.

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Authors and Affiliations

Masaya Kanahori[1] · Yoshihiro Matsumoto[1] · Toshifumi Fujiwara[1] · Atsushi Kimura[1] · Tomoko Tsutsui[1] · Shinkichi Arisumi[1] · Akiko Oyamada[2] · Masanobu Ohishi[3] · Ko Ikuta[4] · Kuniyoshi Tsuchiya[5] · Naohisa Tayama[6] · Shinji Tomari[7] · Hisaaki Miyahara[8] · Takao Mae[9] · Toshihiko Hara[10] · Taichi Saito[11] · Takeshi Arizono[12] · Kozo Kaji[13] · Taro Mawatari[14] · Masami Fujiwara[15] · Minoru Takasaki[16] · Kunichika Shin[17] · Kenichi Ninomiya[18] · Kazutoshi Nakaie[19] · Yasuaki Antoku[20] · Yukihide Iwamoto[13] · Yasuharu Nakashima[1]

1 Department of Orthopaedic Surgery, Graduate School of Medical Science, Kyushu University, Fukuoka, Japan

2 Department of Orthopaedic Surgery, Saga Handicapped Children's Hospital, Saga, Japan

3 Department of Orthopaedic Surgery, Chihaya Hospital, Fukuoka, Japan

4 Department of Orthopaedic Surgery, Karatsu Red Cross Hospital, Saga, Japan

5 Department of Orthopaedic Surgery, Japan Community Healthcare Organization, Kyushu Hospital, Fukuoka, Japan

6 Department of Orthopaedic Surgery, Steel Memorial Yawata Hospital, Fukuoka, Japan

7 Department of Orthopaedic Surgery, Japanese Red Cross Fukuoka Hospital, Fukuoka, Japan

8 Department of Orthopaedic Surgery, National Hospital Organization Kyushu Medical Centre, Fukuoka, Japan

9 Department of Orthopaedic Surgery, Saga-Ken Medical Centre Koseikan, Saga, Japan

10 Department of Orthopaedic Surgery, Aso Iizuka Hospital, Fukuoka, Japan

11 Department of Orthopaedic Surgery, Fukuoka City Hospital, Fukuoka, Japan

12 Department of Orthopaedic Surgery, Kyushu Central Hospital of the Mutual Aid Association of Public School Teachers, Fukuoka, Japan

13 Department of Orthopaedic Surgery, Kyushu Rosai Hospital, Fukuoka, Japan

14 Department of Orthopaedic Surgery, Hamanomachi Hospital, Fukuoka, Japan

15 Department of Orthopaedic Surgery, Sada Hospital, Fukuoka, Japan

16 Department of Orthopaedic Surgery, Harasanshin Hospital, Fukuoka, Japan

17 Department of Orthopaedic Surgery, Saiseikai Yahata General Hospital, Fukuoka, Japan

18 Department of Orthopaedic Surgery, Koga Hospital 21, Fukuoka, Japan

19 Department of Orthopaedic Surgery, National Hospital Organization Fukuoka-Higashi Medical Centre, Fukuoka, Japan

20 Faculty of Medicine, Hospital Informatic Centre, Oita University, Oita, Japan