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Fracture risk assessment tool (FRAX) and for the diagnosis of osteoporosis in Japanese middle-aged and elderly women: Chiba bone survey

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Abstract. Osteoporosis not only increases bone fracture risk but also affects survival in postmenopausal women. Although osteoporosis is diagnosed based on low bone mineral density (BMD) determined by dual energy X-ray absorptiometry (DXA), BMD measurement is sometimes difficult because DXA is not widely available in the community. The Fracture Risk Assessment tool (FRAX) can predict 10-year major osteoporotic fracture risk and hip fracture risk with or without femoral neck BMD. The FRAX has not been investigated adequately in community-dwelling Japanese women. We administered the FRAX tool in 13,421 Japanese women who underwent DXA-based forearm BMD measurement in Chiba Bone Survey, a population-based, multicenter, cross-sectional study of postmenopausal osteoporosis conducted in Chiba, Japan. Mean age was 57.77 ± 9.24 years. Mean forearm BMD was 87.94 ± 17.00% of young adult mean (YAM). Mean FRAX major osteoporotic fracture risk without femoral neck BMD was 7.06 ± 5.22%. BMD decreased and percentage of osteoporosis increased from age 55 onward. Age distribution of percentage of subjects with FRAX major osteoporotic fracture risk >15% was similar to that of percentage of osteoporosis subjects. We identified the cutoff value of FRAX major osteoporotic fracture risk for diagnosis of osteoporosis as 7.2%. With this cutoff, the positive likelihood ratio was over 1.0 at age 55 and above but accuracy was low. In conclusion, FRAX without femoral neck BMD reflects bone status, and may be useful to diagnose osteoporosis in Japanese women aged 55 and above, although the sensitivity was low for osteoporosis screening, especially in middle-aged women.

Key words: Osteoporosis, Bone mineral density, Fracture risk assessment tool, Major osteoporotic fracture risk, Hip fracture risk

OSTEOPOROSIS is defined as skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fractures [1]. Osteoporosis increases fracture risk, and fracture is related to disability. It is a very important problem especially for women, because long-term estrogen deficiency in postmenopausal women is an important cause of progression of osteoporosis [2]. Osteoporosis is usually diagnosed radiographically based on bone mineral density (BMD) determination by dual energy X-ray absorptiometry (DXA) [3]. However, measurement of BMD is sometimes difficult because of technical issues [4].

The Fracture Risk Assessment tool (FRAX) was developed by the World Health Organization to evaluate fracture risk in men and women [5]. It is based on patient samples and integrates the risks associated with clinical variables (age, gender, body mass index, history of previous fractures, family history of fracture, smoking, alcohol use, rheumatoid arthritis, and glucocorticoid use) with or without femoral neck BMD measured by DXA [5]. The FRAX tool has been studied in Europe, North America, South America, Asia and Australia [6]. FRAX algorithms output 10-year probabilities of major osteoporotic fracture and hip fracture. FRAX has acquired

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worldwide acceptance and is widely used in primary care because the tool is simple to use [6]. Although there were several reports of studies using FRAX in Japanese women [7, 8], the study populations of these studies were restricted and their characteristics, espscially at community level, were unclear.

FRAX was used for screening of osteoporosis in two reports [9, 10]. However, the subjects were postmenopausal or women older than 55 years. FRAX is used between 40 and 90 years old. It is unclear that FRAX is useful for diagnosing osteoporosis in women aged 40 years and above. Furthermore, the usefullness of FRAX to diagnose osteoporosis in Japanese women including premenopausal or younger ages has not been investigated. If FRAX without femoral neck BMD can be used to diagnose osteoporosis, the tool will be a major advantage from the clinical and economical points of view. In this study, we mainly investigated the usefulness of FRAX without femoral neck BMD in the diagnosis of osteoporosis in Japanese women aged 40 years and above who particpated in the Chiba Bone Survey.

Materials and Methods

Study population

In 2000, the Japanese government revised a law termed "Health and Medical Service Law for the Elderly" [11], in which local governments were recommended to conduct medical examinations for postmenopausal osteoporosis. Based on this law, Chiba City in cooperation with the Chiba City Medical Association started the Chiba Bone Survey from 2001 [12]. Two hundred and twenty clinics in Chiba participated in this multicenter, population-based, cross-sectional survey. A total of 277,745 women in the age groups of 40 and 50 years between 2001 and 2004, and at 40, 45, 50, 55, 60, 65, and 70 years between 2005 and 2009 (based on resident registrations) received notifications of medical examination for osteoporosis by post, and 69,837 (26.1%) of them participated in the examinations [12]. From this study population of the Chiba bone survey, we selected 13,421 women who underwent forearm BMD measurement using DXA. The study was approved by Chiba City Public Health Office, and the Ethics Committee of Sakura Hospital, School of Medicine, Toho University (S17016).

Outcome assessment

All participants underwent anthropometric measurements to calculate body mass index [BMI = weight (kg)/height $(m)^2$] and responded to a structured, nurse-assisted, self-administered questionnaire covering domains including patient characteristics, histories of fracture and disease, family history of fracture (especially hip fracture and kyphosis), and information on physical and sports activities, current smoking status, alcohol consumption, and history of dieting behavior. We classified all subjects as underweight (BMI < 18.5), non-obese (BMI 18.5–24.9), or obese (BMI > 25). Alcohol use was defined that amount of alcohol is over 3 units per day. Regular exercise was defined as any kind of physical activity 3 or more times per week. BMD was expressed as percentage of the average for a young adult (young adult mean, YAM: 20–44 years of age) at peak bone density. According to the diagnostic criteria for primary osteoporosis (2000 revision) [13], subjects were diagnosed by BMD as normal (BMD ≥ 80% of YAM), osteopenia (70% ≤ BMD < 80% of YAM) or osteoporosis (BMD < 70% of YAM).

Calculation of FRAX scores

FRAX scores are estimates of 10-year probabilities for major osteoporotic fracture (hip, clinical spine, wrist and humerus) and hip fracture. FRAX scores are based on risk factors of fracture, including age, gender, body mass index, previous fracture, family history of hip fracture, use of glucocorticoid, rheumatoid arthritis, secondary osteoporosis, current smoking status and alcohol use, and BMD of the femoral neck bone. FRAX scores can be estimated without femoral neck BMD. In the present study, BMD was measured at the forearm in all subjects. Therefore, we estimated FRAX scores without BMD. We examined the percentage of patients with FRAX major osteoporotic fracture risk higher than 15% (hereinafter abbreviated as FRAX > 15%). We selected FRAX > 15% as an outcome measure, because the Japanese guidelines for prevention and treatment of osteoporosis recommend initiation of pharmacological treatment in osteopenic subjects with FRAX > 15% and no fracture history [1].

Our main purpose of this study is to clarify FRAX can diagnose osteoporosis in Japanese women aged 40 and above.

Statistical analysis

Data are expressed as mean ± SD or numbers or percentage. For comparison between two groups, we used Dunnett's test for nominal variables and unpaired *t*-test for continuous variables. For comparison among 3 or

more groups, we used Tukey-Kramer honestly significant difference (HSD) test or χ^2 test for nominal variables. Sensitivity and specificity of FRAX major osteoporotic fracture risk for the diagnosis of osteoporosis were analyzed using the conventional receiver-operating-characteristic (ROC) curve. All analyses were performed using JMP computer software version 9.0 (SAS, Cary, NC, USA). *p* values less than 0.05 were considered significant.

Results

In this study, we analyzed 13,421 Japanese women aged between 40 and 70 years. The study population consisted of 8.6% at 40 years, 9.5% at 45 years, 9.6% at 50 years, 15.2% at 55 years, 20.1% at 60 years, 21.2% at 65 years, 15.8% at 70 years. Mean age was 57.77 ± 9.24 years, and mean BMI was 22.28 ± 3.20 kg/m^2. Menstruation was present in 27.1% of the subjects. A family history of hip fracture was found in 6.9%. Diabetes mellitus was observed in 3.7%, dyslipidemia in 12.5%, kidney disease in 2.4%, liver disease in 2.0%, and thyroid disease in 4.9%. Alcohol use was reported in 33.1%, and 7.5% were current smokers. Women doing regular exercises 3 or more times per week constituted 52.8%. The proportion of subjects with a history of unexpected fall within the recent 12 months was 4.5%, and that with any type of previous fracture was 22.0%. Mean forearm BMD was 87.94 ± 17.00% of YAM. According to the diagnostic criterion based on forearm BMD (<70% of YAM), 15.0% of the subjects had osteoporosis. Mean FRAX major osteoporotic fracture risk was 7.06 ± 5.22% and mean FRAX hip fracture risk was 1.31 ± 1.68%. FRAX > 15% was observed in 9.3% of the subjects (Table 1).

The mean BMD was relatively stable before menopause; 102.1 ± 10.0% at 40 years, 101.9 ± 9.8% at 45 years, and 100.6 ± 10.6% at 50 years (Fig. 1A). Thereafter, BMD decreased in an age-dependent manner; 91.7 ± 13.3% at 55 years, 83.8 ± 13.8% at 60 years, 79.6 ± 15.9% at 65 years, and 77.0 ± 18.0% at 70 years (Fig. 1A).

The percentage of subjects with osteoporosis is shown in Fig. 1B. There were only few subjects with osteoporosis at 40, 45, and 50 years (Fig. 1B). The percentage of subjects with osteoporosis increased drastically with age from age 55 onward (Fig. 1B).

All subjects were classified by BMD into normal (BMD ≥ 80% of YAM), osteopenia (70% ≤ BMD < 80% of YAM) and osteoporosis groups (BMD < 70% of YAM) according to the diagnostic criteria for primary osteoporosis (2000 revision) [13]. Mean age, percentage of previous fracture, percentage of FRAX > 15%, FRAX major osteoporotic fracture risk and FRAX hip fracture risk were the highest, while BMD was the lowest in the osteoporosis group (Table 2). BMD was significantly lower, and FRAX major osteoporotic fracture risk, FRAX hip fracture risk and percentage of FRAX > 15% were significantly higher in the osteopenia group than in the normal group. The percentages of subjects with previous fracture were the highest in osteoporosis group, and percentages of fracture at femoral neck and wrist were also the highest in osteoporosis group (Table 2). Previous fracture is necessary for calculating FRAX score, so we checked differences of characteristics in subjects with or without previous fracture among each group. Mean age, FRAX major osteoporotic fracture risk, hip fracture risk, and percentages of FRAX > 15% were the highest and BMD and BMI were lowest in osteoporosis group in subjects with or without previous bone fracture (data not shown). Percentages of menstruation were the highest in normal subjects and were significantly higher in osteopenia group than in osteoporosis group in subjects with or without previous fracture (data not shown). Other characteristics were almost same as analyzed in all subjects (data not shown). The proportion of subjects with menstruation was the highest in the normal group. Fig. 1B showed that percent of subjects with osteoporosis increased from age 55 years, and many of them were probably postmenopausal women. However, the proportion of women with menstruation was significantly higher in the osteoporosis group than in the osteopenia group (Table 2). The percentages of menstruation were significantly different among three groups, we analyzed subjects with or without menstruation among three groups. Characteristics of subjects without menstruation were same as all subjects. Otherwise, characteristics of subjects with menstruation were slightly different. There was no significantly different age, FRAX major osteoporotic fracture risk, and hip fracture risk between osteoporosis and osteopenia group. Other characteristics showed same tendency as all subjects (data not shown).

Fig. 2 shows the percentages of subjects with FRAX > 15%. None of the subjects at 40 and 50 years had FRAX > 15%. Only 1 subject at 45 years had FRAX > 15%, and she was classified as normal. The percentages of subjects with FRAX > 15% increased from age 55, and the increase was especially steep at 65 and 70 years. However, 71.9% subjects at 55 years had normal BMD.

Table 1 Background of subjects

Number	13,421
Age (40/45/50/55/60/65/70) (%)	8.6/9.5/9.6/15.2/20.1/21.2/15.8
Mean age (year)	57.8 ± 9.2
BMI (kg/m^2)	22.3 ± 3.2
Underweight/Non-obese/Obese (%)	8.3/74.7/17.0
Menstruation (%)	27.1
Delivery (%)	89.5
Family history of kyphosis (%)	19.1
Family history of hip fracture (%)	6.9
Diabetes mellitus (%)	3.7
Dyslipidemia (%)	12.5
Kidney disease (%)	2.4
Liver disease (%)	2.0
Thyroid disease (%)	4.9
Alcohol use (%)	33.1
Current smoker (%)	7.5
Regular exercise (%)	52.8
Recent history of fall (%)	4.5
Dieting (%)	4.1
Previous fracture (%)	22.0
BMD (% of YAM)	87.9 ± 17.0
Normal/Osteopenia/Osteoporosis (%)	67.5/17.5/15.0
FRAX major osteoporotic fracture risk (%)	7.1 ± 5.2
FRAX hip fracture risk (%)	1.3 ± 1.7
FRAX > 15% (%)	9.3

Data are expressed as mean ± SD or percentage. BMI: body mass index, BMD: bone mineral density, YAM: young adult mean, FRAX: fracture risk assessment tool. Underweight: BMI < 18.5 kg/m^2, Non-obese: 18.5 ≤ BMI < 25 kg/m^2, Obese: BMI ≥ 25 kg/m^2. Osteopenia: 80% > BMD ≥ 70% of YAM, Osteoporosis: BMD < 70% of YAM. FRAX > 15% denotes FRAX major osteoporotic fracture risk > 15%.

We already showed that there were fewer osteoporotic subjects at 50 years, but there was no osteoporotic subject with FRAX > 15% at 50 years. Subjects with osteoporosis were observed from age 55 and increased at 60, 65, and 70 years. The percentage of osteoporosis subjects was approximately 42% at 65 and 70 years. Surprisingly, approximately 30% of subjects at 65 and 70 years had normal BMD (Fig. 2). We analyzed differences of characteristics between subjects with normal and decreased BMD at 65 and 70 years. BMD was significantly higher in normal BMD subjects than in subjects with decreased BMD at 65 years, but other characteristics showed no significant difference between normal and decreased BMD subjects (data not shown). BMD and BMI were significantly higher and FRAX hip fracture risk was significantly lower in subjects with normal BMD than in subjects with decreased BMD at 70 years. Interestingly, FRAX major osteoporotic fracture risk was no significant difference between normal and decreased BMD subjects at 70 years (data not shown).

The relationship between FRAX major osteoporotic fracture risk and age in normal, osteopenia and osteopo-

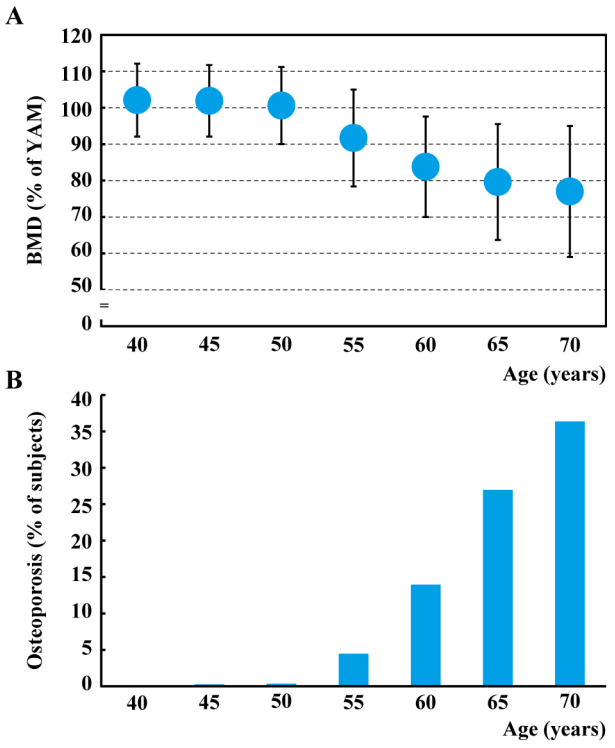

Fig. 1 A: Bone mineral density (BMD) according to age. Data are presented as mean ± SD. YAM: young adult mean. B: Percentage of subjects with osteoporosis by age.

rosis groups is shown in Fig. 3. Only 1 subject at 40 years had osteoporosis. There were no significantly differences in major osteoporotic fracture risk among three groups at 40, 45 and 50 years. FRAX score for major osteoporotic fracture was significantly higher in osteoporosis group than in the other two groups from age 55 onward (Fig. 3).

The relationship between FRAX hip fracture risk and age among three groups is shown in Fig. 4. At 40 years, mean FRAX hip fracture risk was the highest in the osteoporosis group, although only 1 subject at this age had osteoporosis. There were no differences among three groups at 40, 45 and 50 years. FRAX hip fracture risk was the highest in osteoporosis group from age 60 onward. FRAX hip fracture risk was significantly higher in osteopenia group than that in normal group age 55 onward, but there were no significant differences between osteopenia and osteoporosis groups (Fig. 4).

We attempted to use FRAX major osteoporotic fracture risk to diagnose osteoporosis in all subjects. The ROC curve shows the fraction of true-positive result (sensitivity) and false-positive result at the cutoff value of FRAX major osteoporotic fracture risk (Fig. 5). The cutoff value for FRAX major osteoporotic fracture risk that gave the maximal sensitivity and specificity was 7.2%. At this cutoff value, the sensitivity was 82%, the specificity was 63%, and the area under the ROC curve (AUC) was 0.789 (Fig. 5).

We previously mentioned that there are two reports to use FRAX for screening of osteoporosis [9, 10]. However, these two reports do not check accuracy of cutoff value to diagnose osteoporosis. So, we calculated positive likelihood ratio, negative likelihood ratio and accuracy at each age to diagnose osteoporosis using the cutoff value of 7.2% (Table 3). Positive likelihood ratio (PLR) was 0 and negative likelihood ratio (NLR) was 1.0 or higher at 40, 45 and 50 years. However, PLR was higher than 1.0 at 55, 60 and 65 years and 1.0 at 70 years, while NLR was less than 1.0 from age 55 onward (Table 3). These results indicate that the cutoff value for FRAX major osteoporotic fracture risk of 7.2% can be used to diagnose osteoporosis in women aged 55 and above. We checked the accuracy of the cutoff value to diagnose osteoporosis. Accuracy was over 99% at 40, 45 and 50 years. However, accuracy decreased from age 55 onward, and was lower than 40% at 65 and 70 years. There was 1 subject with osteoporosis at 40 years, 3 subjects at 45 years and 4 subjects at 50 years, but our cutoff value failed to diagnose osteoporosis in these subjects. This cutoff value diagnosed non-osteoporotic subjects at 40, 45 and 50 years.

Discussion

In the present study, BMD decreased and the percentage of subjects with osteoporosis increased in subjects aged 55 and above. When we compared among the normal, osteopenia and osteoporosis groups, BMD was the lowest while percentage of FRAX > 15%, FRAX major osteoporotic fracture risk and FRAX hip fracture risk were the highest in the osteoporosis group. Percentage of subjects with menstruation was significantly higher in the osteoporosis than in the osteopenia group. The percentage of subject with FRAX > 15% increased from age 55 onward, and this result was similar to the percentage of subjects with osteoporosis. FRAX major osteoporotic fracture risk and FRAX hip fracture risk were the highest in the osteoporosis group from age 55 onward. We analyzed the cutoff value of FRAX major osteoporotic fracture risk for the diagnosis of osteoporosis using the ROC curve, and found the cutoff value to be 7.2%. This cutoff

Table 2 Comparisons of characteristics among Normal, Osteopenia and Osteoporosis groups

	Normal group	Osteopenia group	Osteoporosis group	*p* value
Number	9,064	2,351	2,006	
Age (40/45/50/55/60/65/70) (%)	12.5/13.8/13.7/18.5/18.0/14.5/8.9	1.0/0.9/1.6/11.5/29.6/32.5/23.0	0.1/0.2/0.2/4.4/18.7/38.1/38.4	<0.0001[a]
Mean age (year)	54.8 ± 9.2	62.9 ± 5.8	65.5 ± 4.5	<0.0001[b,c,d]
BMI (kg/m^2)	22.4 ± 3.3	22.2 ± 3.0	21.7 ± 2.8	<0.0001[b,d]
Underweight/Non-obese/Obese (%)	7.7/74.0/18.3	8.0/75.8/16.2	11.3/76.8/11.9	<0.0001[a]
Menstruation (%)	38.4	5.8	11.4	<0.0001[b,c], <0.001[d]
Delivery (%)	88.4	92.2	91.2	<0.0001[c], <0.001[b]
Family history of kyphosis (%)	17.9	20.8	22.4	<0.0001[b], <0.005[c]
Family history of hip fracture (%)	5.6	8.8	10.5	<0.0001[b,c]
Diabetes mellitus (%)	3.1	4.5	5.3	<0.0001[b], <0.01[c]
Dyslipidemia (%)	10.4	16.6	16.8	<0.0001[b,c]
Kidney disease (%)	2.3	2.6	2.4	NS[b,c,d]
Liver disease (%)	1.8	2.0	3.0	<0.005[b]
Thyroid disease (%)	4.6	5.1	6.1	<0.05[b]
Alcohol use (%)	35.8	28.8	26.0	<0.0001[b,c]
Current smoker (%)	8.4	6.0	5.0	<0.0001[b], <0.0005[c]
Regular exercise (%)	49.3	57.9	62.4	<0.0001[b,c], <0.01[d]
Recent history of fall (%)	4.3	4.6	5.1	NS[b,c,d]
Dieting (%)	4.6	3.3	2.9	<0.005[b], <0.05[c]
Previous fracture (%)	19.4	23.9	31.8	<0.0001[b,c,d]
fracture site (%)				
femoral neck	2.2	2.3	4.7	<0.005[b], <0.05[d]
wrist	16.9	21.9	27.0	<0.0001[b], <0.05[c]
finger	12.9	8.9	7.5	<0.001[b], <0.05[c]
upper arm	7.0	6.9	8.3	NS[b,c,d]
BMD (% of YAM)	97.3 ± 11.2	74.6 ± 2.9	61.4 ± 6.8	<0.0001[b,c,d]
FRAX major osteoporotic fracture risk (%)	5.6 ± 4.5	9.2 ± 4.8	11.4 ± 5.6	<0.0001[b,c,d]
FRAX hip fracture risk (%)	0.9 ± 1.2	1.8 ± 1.7	2.7 ± 2.3	<0.0001[b,c,d]
FRAX > 15% (%)	4.7	13.4	25.4	<0.0001[b,c,d]

Data are expressed as mean ± SD or percentage. BMI: body mass index, BMD: bone mineral density, YAM: young adult mean, FRAX: fracture risk assessment tool. NS: not significant. Underweight: BMI < 18.5 kg/m^2, Non-obese: 18.5 ≤ BMI < 25 kg/m^2, Obese: BMI ≥ 25 kg/m^2. Osteopenia: 80% > BMD ≥ 70% of YAM, Osteoporosis: BMD < 70% of YAM. FRAX > 15% denotes FRAX major osteoporotic fracture risk > 15%. [a] χ^2 test, Tukey-Kramer honestly significant difference (HSD) test: [b] osteoporosis *vs.* normal, [c] osteopenia *vs.* normal, [d] osteoporosis *vs.* osteopenia.

value seems to be useful for the diagnosis of osteoporosis in subjects aged 55 and above, although accuracy was less than 80% in these age groups.

FRAX scores are 10-year probabilities of major osteoporotic fracture and hip fracture. Japanese criteria for initiation of pharmacological treatment for osteoporosis recommend pharmacological treatment in osteopenic persons with FRAX > 15% and no fracture history [1]. A

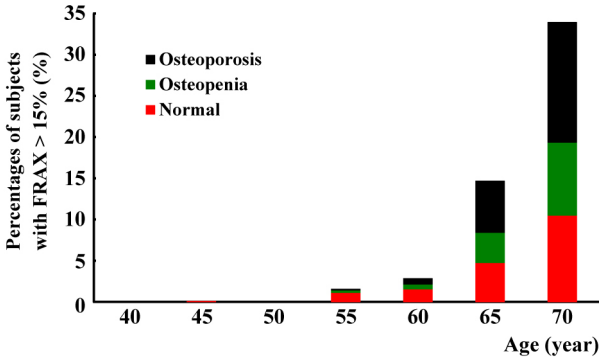

Fig. 2 Percentages of subjects with FRAX > 15% according to age. Black bar denotes osteoporosis group, green bar denotes osteopenia group, and red bar denotes normal group. FRAX > 15% denotes FRAX major osteoporotic fracture risk > 15%.

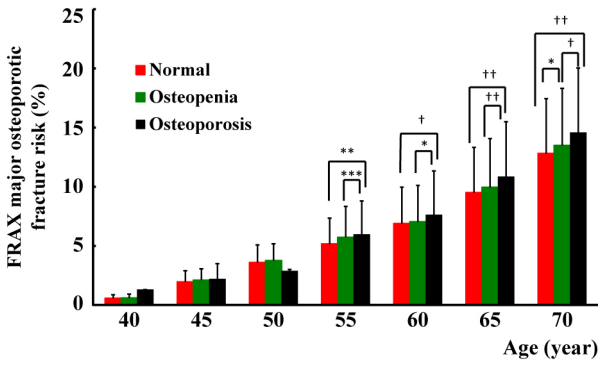

Fig. 3 Comparison of FRAX major osteoporotic fracture risk among three groups according to age. Black bar denotes osteoporosis group, green bar denotes osteopenia group, and red bar denotes normal group. Data are presented as mean ± SD. * $p < 0.05$, ** $p < 0.005$, *** $p < 0.001$, † $p < 0.0005$, †† $p < 0.0001$, Tukey-Kramer honestly significant difference (HSD) test.

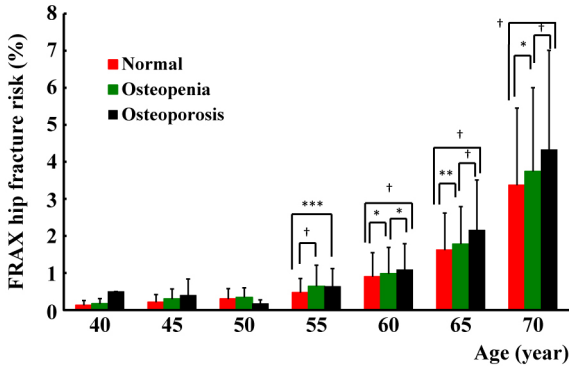

Fig. 4 Comparison of FRAX hip fracture risk among three groups according to age. Black bar denotes osteoporosis group, green bar denotes osteopenia group, and red bar denotes normal group. Data are presented as the mean ± SD. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.0005$, † $p < 0.0001$, Tukey-Kramer HSD test.

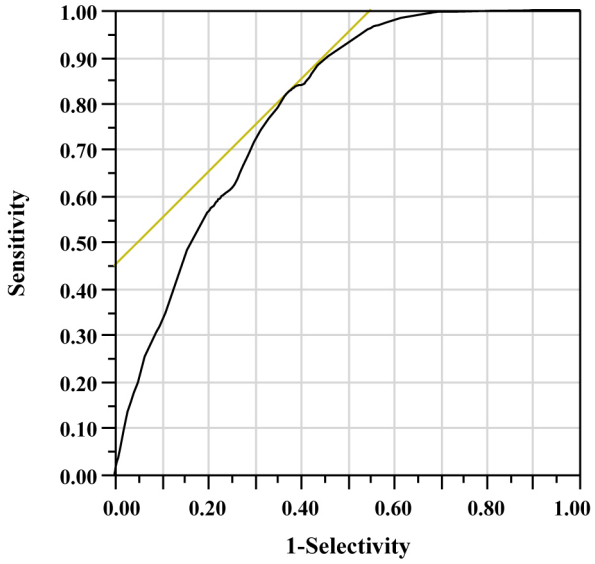

Fig. 5 Usefulness of FRAX major osteoporotic fracture risk for diagnosis of osteoporosis. The curve represents the receiver-operating-characteristic (ROC) curve for detecting osteoporosis. The area under the ROC (AUC) is the greatest (AUC; 0.789). Sensitivity and specificity are highest when the cutoff value for FRAX major osteoporotic fracture risk is 7.2% (sensitivity, 82%; specificity, 63%).

study in Chinese postmenopausal women identified the FRAX-based intervention threshold for osteoporosis to be 9.95% [14]. This intervention threshold was obtained from women including those with osteoporosis, while the FRAX > 15% in the Japanese criteria for treatment initiation is for osteopenic persons without fracture history. Therefore, the two thresholds have different clinical significance. Percentage of subjects with FRAX > 15% was the highest in the osteoporosis group, and age distribution of the percentage of subject with FRAX > 15% was similar to that of the percentage of subjects with osteoporosis. Furthermore, FRAX > 15% picked up non-osteoporosis subjects including normal subjects in this study. Sometimes subjects without osteoporosis need treatment for fracture risk or prevention of declining BMD; for example, when the subjects are using glucocorticoids. Although FRAX > 15% in Japanese criteria is

Table 3 Positive likelihood ratio, negative likelihood ratio and accuracy for each age

Age (years)	40	45	50	55	60	65	70
PLR	0	0	0	1.48	1.25	1.08	1.00
NLR	1.00	1.00	1.01	0.86	0.92	0.40	0
accuracy (%)	99.9	99.6	99.1	75.3	68.8	34.3	36.3

PLR; positive likelihood ratio, NLR; negative likelihood ratio.

for osteopenic subjects without fracture history, FRAX > 15% might have clinical relevance for the treatment of osteoporosis or osteopenia.

Both FRAX major osteoporotic fracture risk and hip fracture risk were the highest in the osteoporosis group and were significantly higher in the osteopenia group than in the normal group. Furthermore, FRAX scores distinguished subjects with osteoporosis from those without from age 55 onward in this study. FRAX scores increased with increase in age in this study, and is consistent with previous study in Japanese subjects [7]. The average FRAX major osteoporotic fracture risk and hip fracture risk were almost the same as the previous Japanese study [7]. However, these average scores appear to be lower than those reported in some European countries and slightly lower than in China [14, 15]. FRAX scores are known to differ among countries [6]. Our results of FRAX scores reflect bone status and showed the same trend as previous studies.

The cutoff value of FRAX major osteoporotic fracture risk for diagnosing osteoporosis was 7.2% in this study. A study in Japanese women showed that the cutoff value of FRAX major osteoporotic fracture risk for screening osteoporosis was 10.5% [9], with sensitivity, specificity and AUC of 60%, 67.5% and 0.64, respectively. In the present study, the sensitivity and AUC were higher while specificity was slightly lower than those in the previous study. The mean age in the previous study was 66.4 ± 7.6 years and was higher than in our study. Our result showed that FRAX major osteoporotic risk was higher at older ages than at younger age. This may be one reason why the cutoff values differed by over 3% between our study and the previous study. In the U.S. Preventive Services Task Force (USPSTF) report, the cutoff level of FRAX major osteoporotic fracture risk estimated without BMD for identifying osteoporosis at the femoral neck was 9.3% in postmenopausal women [10]. The sensitivity, specificity and AUC were 33.3%, 86.4% and 0.60 in the USPSTF report. Compared to our study, specificity in the USPSTF report was higher, whereas AUC was lower and sensitivity was considerably lower. Although the cutoff values differ among our study, a previous study in Japanese women and the USPSTF report, we consider that our cutoff value is reliable.

Our cutoff value 7.2% showed that FRAX may be useful to diagnose osteoporosis at 55 years and above, so we analyzed subjects only at 55 years and above. The cutoff value of FRAX major osteoporotic fracture risk to diagnose osteoporosis was 7.6% estimated by ROC curve. At this cutoff value, the sensitivity was 74%, the specificity was 54%, and the AUC was 0.697. PLR was over 1.0 and NLR was under 1.0 at each age, these results were almost same when we used cutoff value 7.2% (data not shown). Accuracy was slightly higher compared with cutoff value 7.2% at 65 years but was almost same between these two cutoff values at 55, 60, and 70 years. Although the cutoff value of FRAX major osteoporotic fracture risk for diagnosing osteoporosis in subjects aged 55 years and above was slightly higher than it in subjects aged 40 years and above, PLR, NLR, and accuracy were almost same. So, we decided that the cutoff value of FRAX major osteoporotic fracture risk for diagnosing osteoporosis is 7.2% in this study.

Calculation using our cutoff value of FRAX major osteoporotic fracture risk showed low negative likelihood ratios, with positive likelihood ratios higher than 1.0 at ages 55 and above and 0 at ages 50 and below. However, accuracy was less than 80% at ages 55 and above, and over 99% at ages 50 and below. Our cutoff value seems to be useful to diagnosis osteoporosis but not sufficiently accurate from age 55 onward. Furthermore, although there was 1 subject with osteoporosis at 40 years, 3 subjects at 45 years and 4 subjects at 50 years, our cutoff value could not diagnose these osteoporosis subjects. Accuracy was very high at ages 50 and below, but almost all the subjects were non-osteoporotic subjects with FRAX major osteoporotic fracture risk less than 7.2%. In the present study, FRAX scores were estimated without femoral neck BMD. Two studies indicate the clinical relevance of FRAX score estimated without

BMD. One study shows that FRAX without BMD identifies low bone mass by DXA [16]. Another study shows that both FRAX with femoral neck BMD and FRAX without BMD predict major osteoporotic and vertebral fractures [17]. A recent study reports that FRAX without BMD discriminates major osteoporotic fracture and hip fracture during 10 years to the similar degree as BMD measured by digital X-ray radiogrammetry (DXR), but is inferior to DXR-BMD in predicting femoral neck osteoporosis [18]. FRAX score with femoral neck BMD may be required to diagnose osteoporosis.

There are other osteoporosis risk assessment tools such as Simple Calculated Osteoporosis Risk Estimation tool (SCORE); Osteoporosis Risk Assessment Instrument (ORAI); Age, Body Size, No Estrogen (ABONE); and Osteoporosis Self-assessment Tool (OST) equation. All these assessment tools including FRAX have sensitivity less than 90% for detecting low BMD [19]. Similar to other assessment tools, FRAX has several limitations. For example, FRAX does not include the duration of exposure and dose responce to risk factors such as glucocorticoid use, smoking and alcohol [20, 21].

There are some limitations in the present study. First, only 26.1% (n = 69,837) of the study population in Chiba bone survey underwent medical examination for osteoporosis. From these subjects, we selected 13,421 who underwent BMD measurement by forearm DXA. Therefore, the subjects analyzed may not represent all middle-aged and elderly women in Japan. Second, we selected subjects who received BMD measurement at the forearm, and not at the femoral neck. In Chiba Bone Survey, there were 13,421 subjects who had forearm BMD measurements, and only 254 subjects who had femoral neck BMD measurements. We therefore selected subjects with BMD measured at the forearm in order to analyze a large number of subjects. If we had analyzed subjects who had femoral neck BMD data, the results would have been different. Third, we selected subjects with BMD measurement at forearm to analyze large number of subjects, but femoral neck BMD measurement is more accurate than forearm BMD measurement. We analyzed 254 subjects with BMD measurement at femoral neck. The cutoff value of FRAX major osteoporotic fracture risk to diagnose osteoporosis was 7.6% estimated by ROC curve. At this cutoff value, the sensitivity was 63%, the specificity was 53%, and the AUC was 0.578. PLR was over 1.0 and NLR was under 1.0 at 60 years and above. PLR was 0 at 55 years and below. Accuracy was almost same as subjects with BMD measurement at forearm but was 16.1% at 70 years. Although there were few differences between subjects with BMD measured at forearm and femoral neck, we considered that cutoff value and PLR were similar (data not shown). Fourth, FRAX did not have adequate accuracy to diagnose osteoporosis in this study. However, FRAX was originally developed to predict future bone fracture risk, not to diagnose osteoporosis. Although FRAX could not diagnose osteoporosis in this study, the originally purpose of FRAX; *i.e.*, to predict future bone fracture, should be examined in these subjects.

In conclusion, FRAX major osteoporotic fracture risk and hip fracture risk were able to distinguish between subjects with and those without osteoporosis in Japanese women aged 55 years and older. FRAX > 15% had clinical relevance for the treatment of osteopenia or osteoporosis. FRAX major osteoporotic fracture risk was statistically useful to diagnose osteoporosis, but accuracy was low. Therefore, FRAX major osteoporotic fracture risk without BMD reflects bone status and may be useful to diagnose osteoporosis in Japanese women aged 55 years and older, but caution should be exercised to use FRAX for screening of osteoporosis.

Authors' Contributions

RO contributed to analysis and interpretation of data, drafting of the manuscript, and statistical analysis. MO contributed to analysis and interpretation of data, critical revision of the manuscript for important intellectual content, and statistical analysis. SS contributed to interpretation of data, and critical revision of the manuscript for important intellectual content. TY contributed to interpretation of data, and critical revision of the manuscript for important intellectual content. HK contributed to interpretation of data, and critical revision of the manuscript for important intellectual content. TT contributed to interpretation of data, and critical revision of the manuscript for important intellectual content. IT contributed to study concept and design; acquisition, analysis and interpretation of data; critical revision of the manuscript for important intellectual content; and statistical analysis. All authors reviewed the manuscript and approved the final version submitted for publication.

Conflict of Interest

The authors declare that they have no conflict of interest.

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