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ORIGINAL ARTICLE

The role of bone mineral density in therapeutic decision-making using the Fracture Risk Assessment Tool (FRAX): a sub-study of the Taiwan OsteoPorosis Survey (TOPS)

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Abstract

Summary Fracture Risk Assessment Tool (FRAX)–based intervention threshold (IT) is widely applied for treatment decision-making; however, an IT based on FRAX without the measurement of bone mass density (BMD) has not been validated. The study demonstrated that estimates of fracture risk by FRAX without BMD were higher than those by FRAX with BMD in women with old age.

Introduction BMD is an integral component for bone strength assessment, but age-specific impacts of BMD on fracture risk assessment and therapeutic decision-making remained unclear. We aimed to investigate whether using BMD measurement changed the interpretation of the FRAX-based fracture probability assessment and treatment decision.

Methodology The database was provided by the Taiwanese Osteoporosis Association (TOA) which conducted a nationwide survey of BMD. We calculated the 10-year major and hip fracture probabilities using the FRAX for each participant, either with (FRAX + BMD) or without BMD (FRAX − BMD). Age-specific individual intervention thresholds (IITs) were established using the FRAX-based fracture risk, equivalent to a woman with a prior fracture. Participants whose FRAX scores of major fracture were greater than or equal to their IITs were deemed suitable for therapeutic intervention.

Results A total of 14,007 postmenopausal women were enrolled. Compared with FRAX + BMD, FRAX − BMD predicted lower FRAX scores in major and hip fractures in subjects aged 40–60 years; however, FRAX − BMD estimated higher risks for those aged 61–90 years. The therapeutic decision using FRAX − BMD was concordant to that using FRAX + BMD in 90.5% of the subjects, especially in the younger age group (40–70 years). FRAX − BMD identified more treatment candidates (7.7–16.4%) among those aged 71–90 years.

Conclusions The FRAX scores are influenced by age, irrespective of the consideration of BMD. FRAX − BMD is able to identify more subjects for therapeutic intervention in the elderly population. We should reconsider the role of BMD at different ages for therapeutic decision-making.

Keywords bone mineral density · osteoporosis · fragility fracture · intervention threshold

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Introduction

The fracture risk assessment (FRAX) tool was developed in 2008 to estimate the 10-year probability of hip fracture and major osteoporotic fracture, including clinical spine, forearm, hip, or shoulder fracture [1]. Its performance has been validated in different population-based prospective cohort studies [2, 3]. The FRAX score is calculated by entering the clinical risk factors (CRFs), and input of femoral neck (FN) bone mineral density (BMD) in the tool is optional. FRAX-derived fracture probability is predominantly assessed by country-specific database based on FN BMD; If FN BMD is not available, body mass index (BMI)–based database would be applied alternatively by system to estimate fracture risk [1]. The inclusion of FN BMD could enhance estimation and improve the sensitivity of fracture prediction [4]. However, FRAX without the BMD data has also provided valuable and comparable predictive ability in clinical studies, as evidenced by the Japanese Population-based Osteoporosis Study (JPOS) and the Canadian Multicenter Osteoporosis (CaMos) Cohort Study [3, 5]. In a population-based prospective cohort study, only 21% of total fractures were attributed to low BMD in women [6]. In a clinical trial aimed to determine the impacts of baseline characteristics on the fracture prevention, the authors failed to identify the relationship between the fragility fracture and baseline BMD, raising the question if BMD measurement at baseline is necessary for fracture risk assessment [7]. Since dual-energy X-ray absorptiometry (DXA) is not available for BMD measurement in some regions, FRAX score without BMD has been tested in several investigations and is demonstrated to have a prediction value comparable with that of FRAX with BMD in most cases, particularly in younger populations [3, 8, 9]. Therefore, some studies have recommended DXA screening for osteoporosis in women aged ≥ 65 years [10, 11]. However, the exact differences in fracture risk prediction using the FRAX score with and without BMD in subjects of different ages have not been sufficiently investigated.

In addition to fracture risk prediction, another important application of FRAX is the identification of high-risk candidates eligible for pharmacological treatment. The International Osteoporosis Foundation (IOF) and the National Osteoporosis Guideline Group (NOGG) recommend the case-finding strategy for the intervention threshold (IT), a FRAX-based fracture probability equivalent to that of women with prior fragility fractures without information of BMD and other CRFs [12]. FRAX-based IT is more sensitive for identifying women with a higher fracture risk than BMD-based IT, irrespective of the age [13, 14]. Medical interventions are recommended in patients whose calculated FRAX fracture risk is greater than or equal to their IT. Although this case-screening method is widely accepted in various countries, including the UK, Canada, Poland, Romania, Turkey, and Latin American countries [12, 15–20], evidence for the use of FRAX without BMD for identifying eligible treatment candidates is inadequate. Thus, we aimed to validate the predictive value of the FRAX model without BMD in patients of different ages and identifying subjects eligible for osteoporosis treatment based on their IT.

Materials and methods

Study design and materials

The specific method used in the Taiwan OsteoPorosis Survey (TOPS) has been described in a previous publication [21]. In brief, TOPS was conducted by the Taiwanese Osteoporosis Association (TOA) from January 2008 to December 2011. A health service bus equipped with a dual-energy X-ray absorptiometry machine (DXA; Hologic Explorer, Hologic Inc., Waltham, MA, USA) visited 105 different community locations in Taiwan. This bus included licensed nursing practitioners and an International Society for Clinical Densitometry (ISCD)–certified technologist. All the participants were requested to complete the questionnaire, including the section on CRFs of fragility fracture, in the Taiwanese version of FRAX [22]. Osteoporosis was defined based on World Health Organization (WHO) definition, that BMD at either one of lumbar spine, hip, or distal forearm lies 2.5 standard deviations or more below the average value of Caucasian women aged 20–29 years from the National Health and Nutrition Examination Surveys (NHANES) [23, 24].

After completing the questionnaire, a technologist measured the subjects' BMD at the lumbar vertebra (L1–4), hip, and FN in grams per square centimeter. The exclusion criteria were as follows: (1) age > 90 years or < 40 years, (2) refusal to undergo or failure in the DXA examination, or (3) incomplete questionnaire survey or inability to participate in a health interview. The 10-year probabilities of major and hip fractures were calculated using FRAX by entering the CRFs with/without the input of FN BMD. The output of fracture estimation was quoted as FRAX + BMD (with BMD input) or FRAX − BMD (without BMD input).

Individual intervention threshold

Different case-finding strategies have been developed for patients with a high fracture risk. The FRAX-based IT, first developed by the NOGG, defined the threshold as fracture risk equivalent to that in those with prior fragility fractures [25]. Intervention is considered for those whose major fracture probability calculated using FRAX is higher than the threshold. These thresholds are age-specific and are conventionally calculated based on the assumption of a mean BMI of 24–26 kg/m^2 as per previous studies [12, 16, 20]. According to the Taiwan Health Promotion Administration, a BMI ≥ 24 kg/m^2 indicates overweight, while a BMI of 18.5 to < 24 kg/m^2 indicates normal weight [26]. FRAX largely depends on the patient age and body weight; therefore, overestimation of body weight may lead to inaccurate estimation of the treatment threshold. In order to reduce bias and obtain accurate results, we built the IIT for each participant by replacing the mean BMI value of 24 kg/m^2 with the individual BMI values. IIT was calculated with FRAX that considers patient age, individual BMI, and assumption of previous fracture history. Treatment was advised for participants whose calculated major osteoporotic fracture risk was higher than the IIT (Fig. 1). If the FRAX model, with and without BMD input, gave the same treatment decision, it was regarded as "similar decision-making" (both FRAX + BMD and FRAX − BMD ≥ IIT, or both FRAX + BMD and FRAX − BMD < IIT). If the FRAX + BMD but not the FRAX − BMD approach supported the treatment decision, we defined it as "FRAX − BMD under-treatment" (FRAX + BMD ≥ IIT, FRAX − BMD < IIT). In contrast, if FRAX − BMD suggested treatment, but FRAX + BMD did not, we defined it as "FRAX − BMD overtreatment" (FRAX + BMD ≤ IIT, FRAX − BMD ≥ IIT).

Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows version 20.0 (IBM Corp., Armonk, NY, USA). The results for the continuous variables were expressed as mean ± standard deviation values unless otherwise stated. We used a paired t test to detect the differences between FRAX + BMD and FRAX − BMD in terms of major or hip fractures. The strength of the correlation was defined as perfect ($r = 1$), strong ($1 > r \geq 0.7$), moderate ($0.7 > r \geq 0.4$), weak ($0.4 > r > 0$), or none ($r = 0$), indicating no correlation [27]. All the tests were two-tailed, and p value < 0.05 was considered to indicate statistical significance.

Results

A total of 18,992 participants were screened, and finally, we enrolled 14,007 female participants after excluding subjects with invalid age and missing data on body weight, body height, and FN BMD (Supplementary Fig. 1). The demographic characteristics of all and age-stratified study subjects are summarized in Table 1. The mean age of the study population was 64.4 ± 10.5 years, and their mean BMI was 24.1 ± 3.4 kg/m^2. Based on the WHO definition, the prevalence of osteoporosis was 40.8% in women > 50 years, slightly higher than that in an earlier official survey, reporting a national prevalence of 38.3% in Taiwan [28]. There were consistent and upward trends in the prevalence of osteoporosis and previous fracture rate as age increased. Participants in the younger age group had a higher tendency for glucocorticoid exposure (7.4–14.2% in those aged < 60 years) than the elderly. We did not find a specific correlation between age and the prevalence of rheumatoid arthritis or secondary osteoporosis-associated diseases.

The 10-year probability of major and hip fractures calculated using either the FRAX + BMD or the FRAX − BMD model is summarized in Figs. 2 and 3, respectively. The Pearson correlation coefficients between the FRAX + BMD and FRAX − BMD models were 0.80 for major fractures and 0.71 for hip fractures (both had a strong correlation, $p < 0.001$). In subjects aged < 61 years, the major fracture probability using FRAX − BMD was lower than that using FRAX + BMD, and a subtle variance existed between the two (at ages 40–45, 45–50, 51–55, and 56–60 years; p = 0.08, 0.03, < 0.001, and < 0.001, respectively). At age > 61 years, the major fracture probability as per FRAX − BMD was higher than that as per FRAX + BMD (all $p < 0.001$). Furthermore, the difference in the probability using the two methods increased progressively as patient age increased to > 61 years. The 10-year probability of hip fracture calculated using both models showed similar patterns, as depicted in Fig. 3. The

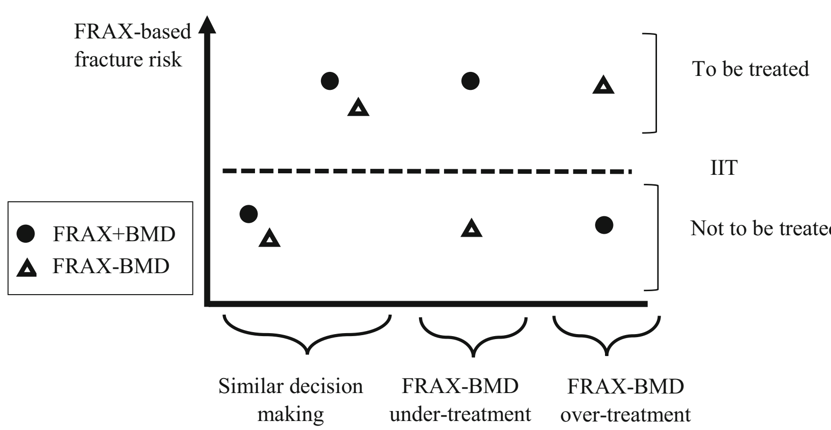


Fig. 1. Treatment strategy based on fracture risk assessed by FRAX in comparison with individual intervention threshold (IIT)

Table 1 Demographic data of the study population

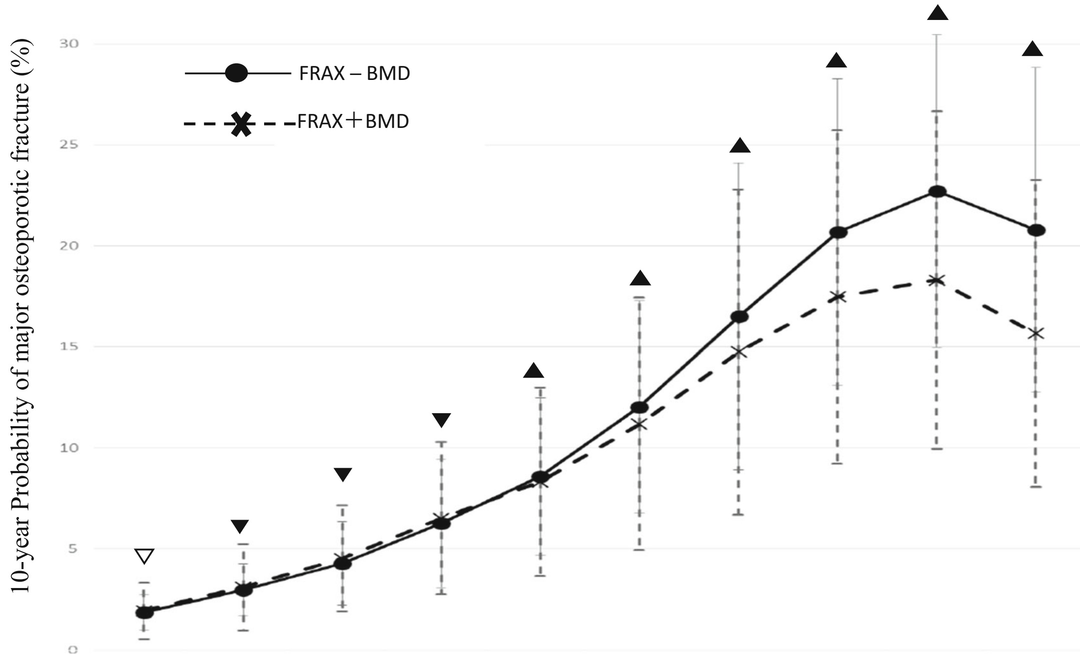
Variables	Total	40~45	46~50	51~55	56~60	61~65	66~70	71~75	76~80	81~85	86~90
Participants, *N* (%)	14007 (100)	451 (3.2)	863 (6.2)	1711 (12.2)	2365 (16.9)	2102 (15.0)	2304 (16.4)	1892 (13.5)	1395 (10.0)	698 (5.0)	226 (1.6)
Age (years)	64.4 ± 10.5	42.9 ± 1.7	48.4 ± 1.4	53.2 ± 1.4	58.1 ± 1.4	63.0 ± 1.5	68.0 ± 1.4	72.9 ± 1.4	77.8 ± 1.4	82.6 ± 1.4	87.6 ± 1.4
Body weight (kg)	57.2 ± 9.3	57.2 ± 9.0	57.6 ± 9.6	57.5 ± 8.9	57.9 ± 9.3	58.3 ± 9.2	58.0 ± 9.1	57.2 ± 9.4	55.1 ± 8.9	53.5 ± 9.2	51.2 ± 10.4
Height (cm)	154.2 ± 6.0	158.6 ± 5.4	157.2 ± 5.2	156.3 ± 5.3	155.6 ± 5.3	154.8 ± 5.4	153.7 ± 5.5	152.2 ± 5.8	151.3 ± 5.8	150.3 ± 6.3	148.9 ± 7.4
Body mass index (kg/m^2)	24.1 ± 3.4	22.7 ± 3.3	23.3 ± 3.8	23.5 ± 3.5	23.9 ± 3.6	24.3 ± 3.6	24.5 ± 3.7	24.7 ± 3.7	24.1 ± 3.6	23.7 ± 3.7	23.0 ± 3.9
Femoral neck BMD (g/cm^2)	0.666 ± 0.124	0.790 ± 0.111	0.761 ± 0.117	0.725 ± 0.116	0.692 ± 0.109	0.680 ± 0.106	0.650 ± 0.105	0.620 ± 0.109	0.587 ± 0.103	0.562 ± 0.108	0.544 ± 0.150
Femoral neck *T* score	− 1.7 ± 1.1	− 0.6 ± 0.9	− 0. ± 1.0	− 1.1 ± 1.0	− 1.4 ± 0.9	− 1.5 ± 0.9	− 1.7 ± 0.9	− 2.0 ± 0.9	− 2.3 ± 0.9	− 2. ± 0.9	− 2.6 ± 1.3
Osteoporosis[a], *N* (%)	5182/12693(40.8)	NA	NA	308(18.0)	635(26.8)	702(33.4)	983(42.7)	1029(54.4)	867(62.2)	493(70.6)	165(73.0)
Risk factors in FRAX tool[b]											
Parent fractured hip	960/9970 (9.6)	18/283 (6.4)	62/612 (10.1)	143/1193 (12.0)	208/1609 (12.9)	157/1468 (10.7)	160/1661 (9.6)	118/1379 (8.6)	57/1033 (5.5)	27/551 (4.9)	10/181 (5.5)
Previous fracture	820/13211 (6.2)	6/305 (2.0)	15/708 (2.1)	35/1567 (2.2)	78/2271 (3.4)	84/2034 (4.1)	150/2240 (6.7)	176/1840 (9.6)	146/1349 (10.8)	83/677 (12.3)	47/220 (21.4)
Glucocorticoids	685/9979 (6.9)	40/282 (14.2)	69/610 (11.3)	114/1192 (9.6)	120/1610 (7.4)	89/1470 (6.1)	96/1664 (5.8)	77/1385 (5.6)	43/1035 (4.2)	31/551 (5.6)	6/180 (3.3)
Rheumatoid arthritis	729/9967 (7.3)	16/281 (5.7)	61/612 (10.0)	112/1189 (9.4)	126/1609 (7.8)	97/1469 (6.6)	111/1659 (6.7)	86/1381 (6.2)	65/1037 (6.3)	41/550 (7.5)	11/180 (6.1)
Secondary osteoporosis[c]	2393/14007 (17.1)	73/451 (16.2)	158/863 (18.3)	183/1711 (10.7)	412/2365 (17.4)	364/2102 (17.3)	401/2304 (17.4)	323/1892 (17.1)	243/1395 (17.4)	109/698 (15.6)	27/226 (11.9)
Current smoking	141/9994 (1.4)	12/282 (4.3)	11/612 (1.8)	24/1194 (2.0)	20/1612 (1.2)	17/1474 (1.1)	20/1664 (1.2)	16/1386 (1.2)	11/1037 (1.1)	4/552 (0.7)	6/181 (3.3)
Alcohol	72/9928 (0.7)	3/281 (1.1)	7/611 (1.1)	10/1192 (0.8)	12/1607 (0.7)	7/1467 (0.5)	12/1650 (0.7)	10/1378 (0.7)	7/1026 (0.7)	2/539 (0.4)	2/177 (1.1)

Continuous variables expressed as mean ± standard deviation. Categorical variables expressed as number (percentage %) or number/available data (percentage %)

[a] According to WHO definition, osteoporosis is defined as *T* score ≤ − 2.5, at either one of the 3 skeletal sites: lumbar spine, hip, or distal forearm. Percentage is calculated based on whole number in each age group. Osteoporosis for participants between 40 and 50 years is not available (NA) due to lack of *Z* score in some premenopausal patients of the original raw data

[b] Each item of risk factors is defined as annotation on the website of FRAX tool (https://www.shef.ac.uk/FRAX/tool.jsp?lang=en)

[c] Secondary osteoporosis–associated diseases include type I (insulin-dependent) diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (< 45 years), chronic malnutrition, or malabsorption and chronic liver disease



	40~45	46~50	51~55	56~60	61~65	66~70	71~75	76~80	81~85	86~90
Number	451	863	1711	2365	2102	2304	1892	1395	698	226
FRAX+BMD	1.9±1.4	3.1±2.1	4.5±2.6	6.5±3.8	8.3±4.7	11.2±6.2	14.8±8.1	17.5±8.2	18.3±8.3	15.7±7.6
FRAX–BMD	1.9±0.9	3.0±1.3	4.3±2.1	6.3±3.2	8.6±3.9	12.0±5.2	16.5±7.6	20.7±7.6	22.7±7.7	20.8±8.0
p-value	0.08	0.03	<0.001	<0.001	0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Correlation	0.713	0.622	0.741	0.731	0.677	0.613	0.602	0.573	0.598	0.643
p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

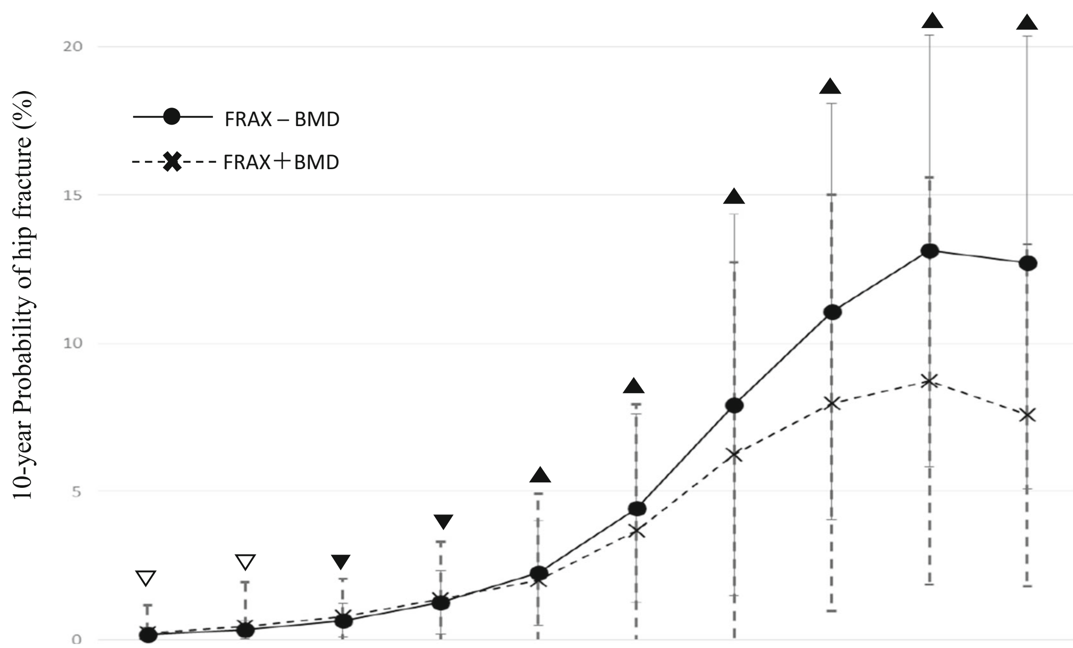
▲ FRAX–BMD > FRAX+BMD, with statistical significance by paired t-test. ▼ FRAX–BMD < FRAX+BMD, with statistical significance by paired t-test.
▽ FRAX–BMD < FRAX+BMD, without statistical significance. Each value on the plot is presented as mean ± 1 standard deviation.

Fig. 2 Ten-year major osteoporotic fracture probability of FRAX − BMD and FRAX + BMD at a different age

hip fracture probability assessed using FRAX − BMD was lower than that estimated using FRAX + BMD before the age of 61 years, and small differences existed in the probabilities using the two methods in subjects belonging to the following age groups: 40–45 years, 46–50 years, 51–55 years, and 56–60 years (p = 0.20, 0.07, < 0.001, and 0.01, respectively). However, the fracture probability predicted using FRAX − BMD was higher than that predicted using FRAX + BMD in those aged ≥ 61 years (all p < 0.001), with progressive increase in patient age.

Figure 4 displays the treatment prediction assessed using FRAX − BMD at a different age. In general, FRAX − BMD achieved 90.5% similarity in terms of treatment decision-making, while the treatment decision was discordant in 9.5% subjects, of which 5.2% were overtreated and 4.3% were under-treated. In those aged < 60 years, similar decisions were made for 92.4–93.8% subjects; however, for those aged ≥ 61 years, the rate of similar decisions declined from 91.6 to 82.3%, while the overtreatment rate increased from 3.8 to 16.4% as age increased. In Supplementary Table 1, we identified factors associated with concordant treatment recommendation in patients ≥ 61 years. Participants with higher FN BMD were disposed to concordant treatment recommendation, whereas patients with discordant management were characterized by higher BMI, previous history of parent fractured hip, previous fracture, rheumatoid arthritis, secondary osteoporosis, and exposure history of steroid and smoking. The average FRAX values for women with concordant and discordant treatment decision are summarized in Supplementary Table 2.

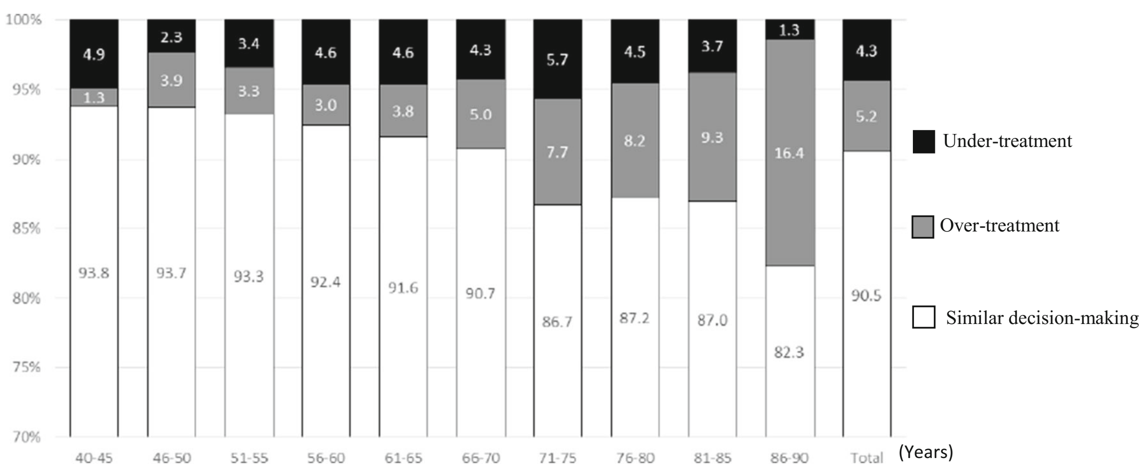
Fracture probability calculated using the FRAX has demonstrated a significant negative correlation with FN BMD in previous studies [4, 29]. Figure 5 confirms the correlation observed between the probabilities calculated using FN BMD and FRAX in the present study. Probabilities using both FRAX − BMD and FRAX + BMD displayed negative correlations with the FN T score; however, we found a minimal difference in the probabilities calculated using FRAX − BMD and FRAX + BMD if the FN T score was > − 2.5. In contrast, a widening discrepancy with FRAX − BMD over FRAX + BMD developed when the FN T score was < − 2.5 in major and hip fracture risk calculation (Fig. 5a and b).



	40~45	46~50	51~55	56~60	61~65	66~70	71~75	76~80	81~85	86~90
Number	451	863	1711	2365	2102	2304	1892	1395	698	226
FRAX+BMD	0.2±0.9	0.4±1.5	0.8±1.3	1.4±1.9	2.0±2.9	3.7±4.3	6.3±6.5	8.0±7.0	8.7±6.9	7.6±5.8
FRAX–BMD	0.2±0.2	0.4±0.3	0.7±0.6	1.3±1.1	2.3±1.8	4.5±3.2	7.9±6.4	11.1±7.0	13.1±7.3	12.7±7.6
p-value	0.20	0.07	<0.001	0.007	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Correlatiion	0.395	0.282	0.392	0.421	0.472	0.453	0.578	0.604	0.619	0.696
p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

▲ FRAX–BMD > FRAX+BMD, with statistical significance by paired t-test. ▼ FRAX–BMD < FRAX+BMD, with statistical significance by paired t-test.
▽ FRAX–BMD < FRAX+BMD, without statistical significance. Each value on the plot is presented as mean ± 1 standard deviation.

Fig. 3 Ten-year hip fracture probability of FRAX − BMD and FRAX + BMD at a different age



*Treatment decision is made if calculated FRAX fracture probability is greater than the individual intervention threshold. Identical decision-making means the agreement of FRAX mode, with or without BMD, to make the same decision to treat or not to treat (Both FRAX−BMD and FRAX+BMD >IIT, or FRAX−BMD and FRAX+BMD <IIT). Under-treatment represents FRAX−BMD fails to identify people whose calculated fracture risk is greater than IIT (FRAX+BMD >IIT> FRAX−BMD). Over-treatment represents FRAX−BMD suggests treatment, but FRAX+BMD does not (FRAX−BMD ≥ IIT, FRAX+BMD ≤ IIT).

Fig. 4 Age-specific treatment decision-making assessed by FRAX without BMD. *Treatment decision is made if calculated FRAX fracture probability is greater than the individual intervention threshold. Identical decision-making means the agreement of FRAX mode, with or without BMD, to make the same decision to treat or not to treat (both FRAX − BMD and FRAX + BMD > IIT, or FRAX − BMD and FRAX + BMD < IIT). Undertreatment represents FRAX − BMD fails to identify people whose calculated fracture risk is greater than IIT (FRAX + BMD > IIT > FRAX − BMD). Overtreatment represents that FRAX − BMD suggests treatment, but FRAX + BMD does not (FRAX – BMD ≥ IIT, FRAX + BMD ≤ IIT)

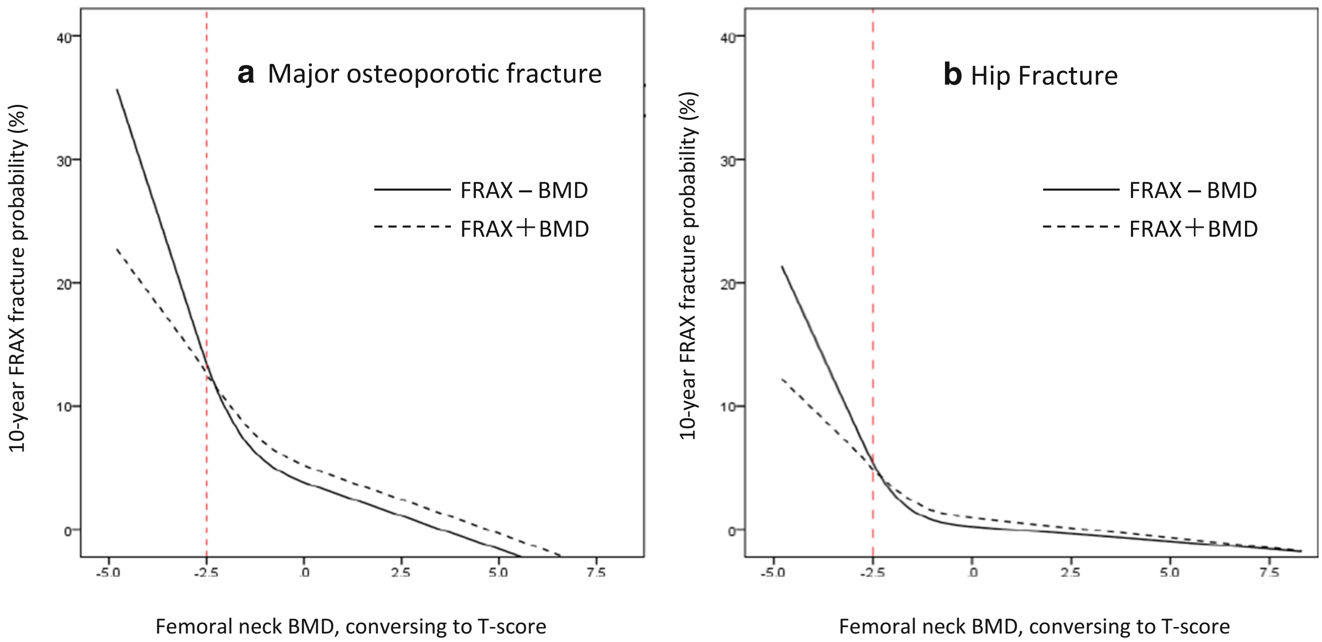


Fig. 5 FRAX with and without BMD in correlation with fracture probability at different value of femoral neck T-score

Discussion

The FRAX model with BMD and that without BMD showed a strong correlation, and our study demonstrated how BMD influenced the fracture probability and decision-making in subjects of different ages. In women aged < 61 years, compared with FRAX + BMD, FRAX − BMD was slightly lower in the major and hip fracture probabilities; however, FRAX − BMD estimated higher fracture risks with a rising disparity over FRAX + BMD in women aged ≥ 61 years. Thus, FRAX − BMD appears to be acceptable for identifying treatment candidates among subjects aged < 61 years because the concordance of the two models for treatment decision was > 92%.

FRAX − BMD was strongly correlated with FRAX + BMD in the prediction of major and hip fractures. This result was in agreement with previous reports. In a Brazilian study, Bastos-Silva et al. enrolled 402 postmenopausal women and showed a strong correlation (0.76) for major fractures and a moderate correlation (0.64) for hip fractures between the FRAX model with BMD and that without BMD [30]. Another Turkish study conducted by Olmez Sarikaya et al. showed a strong correlation for major fractures (0.84) and a moderate correlation for hip fractures (0.64) [8]. In a Korean cross-sectional study, Kim et al. used the database of the Korean National Health and Nutrition Examination Survey that included 1446 women aged 50–90 years to validate the predicted fracture probability of FRAX with and without the inclusion of BMD [31]. They found a similar performance of FRAX − BMD which underestimated and overestimated the fracture probabilities in subjects aged 50–69 years and 70–90 years, respectively, compared with FRAX + BMD. Another study conducted by Gadam et al. identified the treatment prediction values of FRAX − BMD based on the National Osteoporosis Foundation criteria; the treatment decisions were identical in 84% of the study population, especially the younger subjects, using either method [9]. These findings supported our observation that FRAX without BMD highly correlated with FRAX with BMD and expressed different prediction values in younger and older subjects. The present study further indicated that the difference in the probabilities calculated using FRAX − BMD and FRAX + BMD in subjects aged < 60 years was small and negligible; therefore, FRAX − BMD could replace FRAX + BMD for decision-making in subjects aged < 60 years.

The lower fracture probability derived from FRAX + BMD in the elderly subjects may be attributed to inaccurate BMD measurement or BMD overestimation resulting from misinterpretation on the DXA scan due to bone degeneration or sclerotic changes. Tenne et al. indicated that degenerative changes or scoliosis of the lumbar spine that were common, rapid-progressing conditions in the elderly may lead to the overestimation of the BMD values [32]. Compared with the lumbar spine BMD, which may be misjudged by concomitant degeneration, the hip is a more consistent site for BMD measurement that accurately reflects continuous bone loss with advancing age [32, 33]. FN BMD demonstrated better detection ability for osteoporosis and a strong relationship with prevalent vertebral fracture [34], providing evidence for the application in FRAX, wherein the inclusion of FN BMD is recommended.

The similarity of FRAX + BMD and FRAX − BMD in younger women and disparity in advancing age implicated the weight of BMD was different for FRAX calculation in young and old age patients. The FRAX model utilized a hazard function to predict fracture risk by Poisson regression, based on 4 models comprising hip fracture, with and without BMD, and major osteoporotic fractures, with and without BMD [1]. The presence of BMD in FRAX was reported to somewhat reduce the variation derived from BMI-based data [1]. As data shown in Fig. 5, adding BMD slightly increased the fracture risk for patients with "low bone mass" or "normal bone mass," but estimated lower fracture risk in patients with osteoporosis. In other words, applying FRAX + BMD in populations with higher prevalence of osteoporosis (old age population) may yield generally lower fracture scores, but less affected younger population with predominantly low bone mass or normal bone mass. In addition, the CRFs were less predictive for fracture in the presence of BMD in the FRAX model [1]. We should reconsider the interaction of BMD and other CRFs in the old population and adjust the impacts on fracture according to real world investigation.

The FRAX − BMD model captured more elderly people than the FRAX + BMD model did, identifying more patients for treatment. In the younger age group, although the fracture probability predicted using FRAX − BMD was slightly lower than that using FRAX + BMD, the difference was minimal and negligible. Thus, FRAX − BMD had a similar capacity as FRAX + BMD for identifying younger patients who required treatment. In sum, FRAX − BMD was a sensitive and straightforward case-finding strategy in the older population; however, further investigations are needed on the cost-effect and appropriate application of treatment.

Our research, limited by cross-sectional design, was unable to correlate the accurate fracture probability with FRAX − BMD or FRAX + BMD. From the prospective cohort of JPOS, the observed incident major fracture rate did not differ significantly between FRAX + BMD and FRAX − BMD (area under receiver operator curve [AUROC] of FRAX + BMD and FRAX − BMD were 0.69 vs. 0.67, respectively, $p = 0.121$) [3]. The CaMos cohort study presented similar results, that AUROC were 0.69 vs. 0.66 respectively for major fractures [5]. In a Spanish FRIDEX study, the AUROC of major fracture prediction by FRAX + BMD and FRAX − BMD was 0.716 vs. 0.693, respectively [35]. These prospective studies prove that FRAX − BMD provided comparable prediction as FRAX + BMD for fracture prediction.

The drawback of our study was that our questionnaire was administered by a study coordinator, not a physician. The definition of secondary osteoporosis in FRAX, in terms of chronic liver disease, was ambiguous. For example, hepatitis B infection was endemic in Taiwan (15–20%) [36], where most people were hepatitis B–inactive carriers, that is, positive for hepatitis B surface antigen but free from abnormal liver function or liver cirrhosis. The study coordinators may not have had enough information to differentiate disease status, such as cholestatic liver disease and end-stage cirrhosis, resulting in a high prevalence of secondary osteoporosis (17.1%) in our survey. In addition, there were other limitations of our study. First, this research was a cross-section study. Although the estimated fracture risks, either derived from FRAX with or without BMD, were closely correlated, we were unable to compare the actual fracture probability to the estimated fracture risk in women. Longitudinal study is required to validate the FRAX − BMD-based fracture probability in the elderly. Secondly, the study population did not include men; further research is required to apply the population of man in the case-finding strategy. Moreover, the bus made trips to different public outdoor spaces, offering DXA examinations. Those invited participants who were aware of their health status, followed a healthy lifestyle, or had chronic diseases would be more willing to take the examination. The prevalence of rheumatoid arthritis in women was 7.3%, much higher than the reported prevalence (0.16%) [37]. Besides, the mean age of menopause is 49.5 years in Taiwan [38]. We were unable to define osteoporosis in pre-menopausal women (40~50 years) in our study due to lack of *Z* score raw data. Finally, selection bias was possible in our survey because subjects with physical disabilities and limited outdoor activity or those with poor health awareness could not participate in the investigation. All the limitations mentioned earlier may have biased the study results.

Although FRAX (Taiwan version) has been available since 2011, it has not been tested for discrepancy of application for all age groups. The strength of the present study was that it was a large-scale, nationwide, real-world study conducted in Taiwan to examine the application FRAX with or without BMD in fracture risk assessment and treatment decision-making. Furthermore, to our knowledge, this is the first study to have used IIT in combination with FRAX for different age groups to understand the age-specific intervention and treatment requirements. These results could guide physicians in decision-making for fracture prevention in patients of different ages without BMD measurements.

Conclusions

FRAX without BMD displays an age-dependent influence on fracture risk prediction and treatment decision-making. FRAX − BMD and FRAX + BMD provide similar results for fracture risk evaluation and IIT-based treatment decision-making in young subjects; however, higer estimated fracture risk and overtreatment may occur in older participants. More of the elderly subjects would be recognized as therapeutic candidates based on the FRAX − BMD model. Interpretation of FRAX without BMD for fracture risk assessment and treatment should be personalized based on the age group.

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Compliance with ethical standards

Conflicts of interest None.

Ethical statement This study was approved by the institutional review board of the Chang Gung Memorial Hospital (102-1878B).

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