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Age-dependent FRAX-based assessment and intervention thresholds for therapeutic decision making in osteoporosis in the Malaysian population

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Abstract

Summary Fracture risk stratification is crucial in countries with limited access to bone density measurement. 24.8% women were in the high-risk category while 30.4% were in the low-risk category. In the intermediate risk group, after recalculation of fracture risk with bone density, 38.3% required treatment. In more than half, treatment decisions can be made without bone density.

Purpose We aimed to examine the role of age-dependent intervention thresholds (ITs) applied to the Fracture Risk Assessment (FRAX) tool in therapeutic decision making for osteoporosis in the Malaysian population.

Methods Data were collated from 1380 treatment-naïve postmenopausal women aged 40–85 years who underwent bone mineral density (BMD) measurements for clinical reasons. Age-dependent ITs, for both major osteoporotic fracture (MOF) and hip fracture (HF), were calculated considering a woman with a BMI of 25 kg/m^2, aged between 40 and 85years, with a prior fragility fracture, sans other clinical risk factors. Those with fracture probabilities equal to or above upper assessment thresholds (UATs) were considered to have high fracture risk. Those below the lower assessment thresholds (LATs) were considered to have low fracture risk.

Results The ITs of MOF and HF ranged from 0.7 to 18% and 0.2 to 8%, between 40 and 85years. The LATs of MOF ranged from 0.3 to 11%, while those of HF ranged from 0.1 to 5.2%. The UATs of MOF and HF were 0.8 to 21.6% and 0.2 to 9.6%, respectively. In this study, 24.8% women were in the high-risk category while 30.4% were in the low-risk category. Of the 44.8% (n=618) in the intermediate risk group, after recalculation of fracture risk with BMD input, 38.3% (237/618) were above the ITs while the rest (n=381, 61.7%) were below the ITs. Judged by the Youden Index, 11.5% MOF probability which was associated with a sensitivity of 0.62 and specificity of 0.83 and 4.0% HF probability associated with a sensitivity of 0.63 and a specificity 0.82 were found to be the most appropriate fixed ITs in this analysis.

Conclusion Less than half of the study population (44.8%) required BMD for osteoporosis management when age-specific assessment thresholds were applied. Therefore, in more than half, therapeutic decisions can be made without BMD based on these assessment thresholds.

Keywords Intervention thresholds · Lower assessment thresholds · Upper assessment thresholds · FRAX · Osteoporosis · Bone mineral density · Malaysia

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Introduction

Malaysia, similar to other Asian countries, is expected to see a rapid rise in the prevalence of osteoporotic fractures, in tandem with an aging population [1] Osteoporosis is one of the most prevalent conditions associated with aging and a leading cause of disability [2]. The global prevalence of osteoporosis is reported to be highest in Asia reaching 24.3% [3]. Osteoporosis is a major risk factor for fracture in the

older population and lead to great social and economic burden [4]. Osteoporosis remains silent until complicated by an osteoporotic fracture [5]. It is reported that up to 30% of the hip fractures occurring world-wide arise from the Asian population [6]. The global annual number of hip fractures increased approximately by 25% from the year 1990 to year 2000, underscoring the importance of early detection and prevention of osteoporosis [7].

Dual-energy X-ray absorptiometry (DXA) is the most widely used and validated tool to assess bone mineral density (BMD) [8]. Although BMD is the major determinant of fracture risk, it alone does not account for the total risk and the incorporation of clinical risk factors is crucial in the accurate estimation of fracture risk and therapeutic decision making [9, 10]. There are several tools that are validated for fracture risk assessment including the Fracture Risk Assessment Tool (FRAX), Garvan and Q Fracture [11, 12]. The FRAX developed in 2008 is a computerized algorithm that is derived from global models of population-based cohorts incorporating demographic, anthropometric, and clinical risk factors and is the most widely used fracture risk assessment tool worldwide [13, 14]. The FRAX estimates 10-year probability of hip and major osteoporosis-related fractures incorporating information on clinical risk factors and BMD at the femoral neck [15]. Although, the inclusion of BMD enhances the performance characteristics of FRAX algorithm, many studies have shown that FRAX output without BMD input can be used in clinical decision making, reliably, especially in countries with limited DXA facilities [16]. Currently, 72 country-specific FRAX models including 14 from Asian countries are available [17] and these models have been developed based on country-specific fracture and mortality rates or from surrogate populations [18, 19].

An intervention threshold (IT) at which active interventions are recommended is pivotal in clinical decision making at individual level [20]. These thresholds vary between countries and ethnicities mainly due to the variations of fracture incidence and the availability of DXA and other health resources [21]. In Malaysia, the availability of DXA is limited to tertiary care centers in few major cities [22]. A large proportion of those who require screening for osteoporosis seek treatment at primary care centers which have either limited or no access to DXA facility. Country specific ITs will aid in streamlining patient care as well as the rational use of limited DXA facilities in the country. The Malaysian osteoporosis guidelines [23] recommend BMD measurement via DXA as gold standard for diagnosis of osteoporosis. Due to lack of prior local data, the Malaysian guidelines have adopted a standardized IT, with recommendation to initiate treatment with a 10-year fracture FRAX probability of ≥ 3% for HF or 20% for MOF, unless density scores fall into osteoporotic ranges or patient has sustained prior a fragility fracture.

The UK National Osteoporosis Guideline Group (NOGG) [24] recommend active treatment for women with fracture risk exceeding upper assessment thresholds calculated based on clinical risk factors alone. Furthermore, the NOGG demarcates those who do not require either active treatment or further testing based on the lower assessment thresholds. Only those who have fracture probabilities falling in between the lower and upper assessment thresholds are considered for the estimation of BMD by DXA in order to reassess fracture risk. This approach allows both the optimal utilization of limited DXA resources and making treatment decisions in primary care settings without undue delay. Countries such as Austria, Chile, and Sri Lanka have followed this method to define assessment and intervention thresholds in those countries [17, 25, 26].

Although in Malaysia there is no country specific FRAX model, Johansson et al [27] recently described a surrogate FRAX model for Malaysia using the ethnic-specific incidence of hip fracture in men and women living in Singapore, combined with the death risk in Malaysia, which could be used in the future to determine fracture probability within the Malaysian population and help guide decision making for osteoporosis treatment. Furthermore, Malaysia does not have ITs that suits the local population in order the make rational therapeutic decisions. These limitations have led to a considerable diversity in care given to patients with osteoporosis and those with high fracture risk. The development of ITs that suit the local population will help in building the confidence of clinicians and in making the patient management guidelines uniform across the country. Hence, this study was designed to determine different assessment and intervention thresholds for DXA derived fracture risks for the Malaysian population.

Methods

Study participants

The total number of participants included in this study was 1380. They were all postmenopausal women referred for BMD assessment and determination of fracture risk. While the majority were of Chinese ethnicity (62.3%), the proportions of Indians and Malays were 20.4% and 17.3% respectively. Mean (SD) age and BMI of study subjects were 65.4 (10) years and 24.7 (4.6) kg/m^2. The proportion of women with parental history of hip fracture, rheumatoid arthritis, and secondary causes of osteoporosis were 6.2%, 11.7%, and 2.8%, respectively. Furthermore, 12.5% were current users of oral corticosteroids. 2.6% were current smokers and 3.2% were current alcohol consumers. The mean BMD values for total spine and hip were 0.882 (0.21) gm/cm^2 and 0.676 (0.14) gm/cm^2 respectively. The

calculated FRAX score for MOF and HF were 10.5 (8.9) % and 4.5 (5.9) % without BMD and 11.0 (9.1) % and 4.5 (5.7) % with BMD incorporated.

Baseline demographics of the participants are shown in Table 1.

Table 1 Baseline demographics of participants

Characteristic	Number (%), or mean (±SD)
Total number of subjects	1380
Age (years)	65.4 (10.0)
Ethnicity	
Malay	239 (17.3)
Chinese	860 (62.3)
Indian	281 (20.4)
Body mass index (kg/m^2)	24.7 (4.6)
Previous fracture	
Yes	261 (18.9)
No	1119 (81.1)
Parent fractured hip	
Yes	85 (6.2)
No	1294 (93.8)
Current smoking	
Yes	36 (2.6)
No	1344 (97.4)
Glucocorticoids	
Yes	173 (12.5)
No	1207 (87.5)
Rheumatoid arthritis	
Yes	161 (11.7)
No	1219 (88.3)
Secondary osteoporosis	
Yes	38 (2.8)
No	1342 (97.2)
Alcohol intake	
Yes	44 (3.2)
No	1336 (96.8)
Bone mineral density (gm/cm^2)	
Total spine	0.882 (0.21)
Hip	0.676 (0.14)
FRAX score	
10-year probability of fracture (%)	
with BMD (FRAX+BMD)	
MOF	11.0 (9.1)
HF	4.5 (5.7)
w*ithout BMD (FRAX-BMD)*	
MOF	10.5 (8.9)
HF	4.5 (5.9)

DXA scanners

As DXA scanners are not widely available in Malaysia, these women were referred to the DXA facility in four major osteoporosis centers across Malaysia, in the Klang Valley (University Malaya Medical Centre, Puchong Medical Specialist Centre and Faculty of Medicine and Health Sciences, Universiti Putra Malaysia) and in the northern region of Malaysia in Penang (Hospital Pulau Pinang) for the assessment of BMD and fracture risk as a part of routine clinical evaluation for postmenopausal osteoporosis. The women referred to these centers were predominantly representative of urban Malaysians but also comprised of rural patients referred for assessment. The patients were reflective of the Malaysian ethnic populations, comprising of the three major ethnic groups the Malaysian-Malays, Chinese, and Indians.

DXA scanners used were GE-Lunar Prodigy DXA, GE-Lunar iDXA, Hologic Explorer DXA, and Hologic Discovery. Scanning and analysis in all four centers were performed by experienced and qualified radiographers using the standard protocols provided by the manufacturer. Center-specific medical research ethics approvals were obtained prior to the conduct of this project.

Statistical analysis

Determining intervention and assessment thresholds

Intervention thresholds (ITs) were determined by the method described initially by the National Osteoporosis Guideline Group (NOGG) [28], endorsed by the National Institute for Health and Care Excellence (NICE) in the UK [29] and adopted by other countries [30, 31] subsequently. This approach follows the argument that if a postmenopausal woman with a prior fragility fracture is qualified for interventions regardless of baseline BMD and other clinical risk factors, then a same age fracture free woman with the same fracture probability should also be treated in the similar manner. Based on this theory, the probabilities of major osteoporotic facture and hip fracture in the next 10 years were calculated for a woman with a BMI of 25 kg/m^2 with a prior fragility fracture in the absence of other clinical risk factors. The fracture probabilities calculated without BMD input for the age range of 40–85 years were considered the age-dependent ITs for this population.

Furthermore, two sets of assessment thresholds, lower and upper, were also calculated. Similar to ITs, lower assessment thresholds (LATs) were calculated, for the age range of 40 to 85, for a postmenopausal woman of BMI 25 kg/m^2 without any clinical risk factor. Those with fracture probabilities below these values (low risk zone) were considered to have a low fracture risk, hence do not require either BMD assessment or specific treatment. The upper assessment

thresholds (UATs) were set at 1.2 times the ITs estimated earlier. Those with fracture probabilities equal to or above these values (high risk zone) were considered to have high fracture risk hence qualify for specific treatment irrespective of baseline BMD. Only those with fracture probabilities in the intermediate zone, i.e., between the two assessment thresholds, were considered to require BMD input in order to recalculate fracture risk and decide on treatment requirement, based on ITs.

Application of the assessment and intervention thresholds to a group of treatment-naïve postmenopausal women

In the second stage, above assessment and intervention thresholds were applied to a group of treatment-naïve postmenopausal women who underwent DXA evaluation as a part of routine clinical assessment. Initially, they were allocated to three categories: high risk, low risk, and intermediate risk based on the fracture risk estimated with the Singaporean Malay, Chinese, and Indian FRAX algorithm, using clinical risk factors without BMD. Those in the intermediate group had fracture risks reassessed with the inclusion of BMD and they were reclassified high risk or low risk after applying the age-dependent ITs.

Determination of fixed intervention thresholds

In order to develop fixed ITs, 618 women who underwent DXA were classified into high risk (treatment requiring) and low risk (treatment not requiring) based on the age-dependent ITs described earlier. The receiver operating characteristic (ROC) analyses were performed with risk category (high or low) as the state variable and fracture probability, either MOF or HF, as the explanatory variable. The area under curve (AUC) was used to assess the performance of the models and the optimum cut-point was selected using two methods; the point that maximized the Youden function (Sensitivity + Specificity -1) and the point on the ROC curve that was closest-to-(0,1) corner in the ROC plane.

Results

Assessment and intervention thresholds

The total study population of 1380 participants was analyzed. The LATs of MOF ranged from 0.3 to 11.0% between 40 and 85 years while those of HF ranged from 0.1 to 5.2%. The corresponding values of UATs of MOF and HF were 0.8 to 21.6% and 0.24 to 9.6%, respectively. The ITs of MOF and HF ranged from 0.7 to 18.0% and 0.2 to 8.0% between 40 and 5 years. Table 2 stratifies the age dependent ATs and ITs.

Based on these thresholds, 24.8% women in the study group were in the high-risk category (above the UATs) while 30.4% were in the low-risk category (below the LATs). Of the 44.8% (n=618) in the intermediate- risk group, 38.3% (237/618) were above the ITs while the rest (n=381, 61.6%) were below the ITs. These findings are diagrammatically illustrated in Figs. 1 and 2.

Fixed intervention thresholds

In the ROC analyses, the AUC (SE) for MOF probabilities was 0.77 (0.013) while that of HF probabilities was 0.78 (0.013), $p<0.001$ for both. In selecting an appropriate fixed ITs, a considerable trade-off between sensitivity and specificity was observed between different cut-off values. Judged by the Youden Index, 11.5% for MOF probability which was

Table 2 Age-dependent assessment and intervention thresholds between 40 and 85 years

Age (years)	LAT MOFP (%)	LAT HFP (%)	UAT MOFP (%)	UAT HFP (%)	IT MOFP (%)	IT HFP (%)
40	0.3	0.1	0.8	0.24	0.7	0.2
45	0.6	0.1	1.6	0.24	1.3	0.2
50	1.2	0.1	3.1	0.48	2.6	0.4
55	2.2	0.3	5.8	1.1	4.8	0.9
60	4.1	0.7	10	2.4	8.4	2.0
65	6.7	1.4	15.6	4.3	13	3.6
70	9.1	2.4	20.4	6.0	17	5.0
75	10	3.4	21.6	7.4	18	6.2
80	11	4.7	21.6	8.6	18	7.2
85	11	5.2	21.6	9.6	18	8.0

LAT MOFP lower assessment thresholds, major osteoporotic fracture probability, *LAT HFP* lower assessment thresholds, hip fracture probability, *UAT MOFP* upper assessment thresholds, major osteoporotic fracture probability, *UAT HFP* upper assessment thresholds, hip fracture probability, *IT MOFP* intervention thresholds, major osteoporotic fracture probability, *IT HFP* intervention thresholds, hip fracture probability

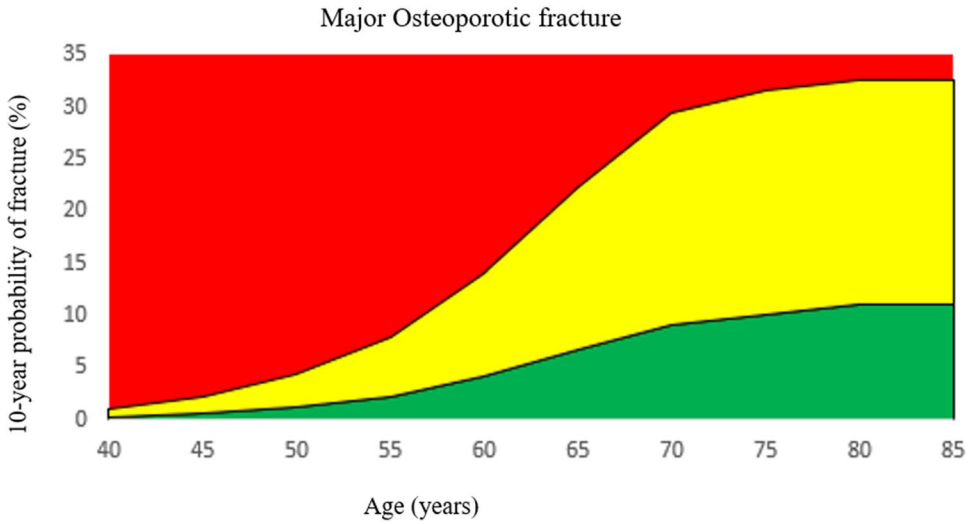

Fig. 1 Age-dependent assessment and intervention thresholds between 40 and 85 years for major osteoporotic fracture

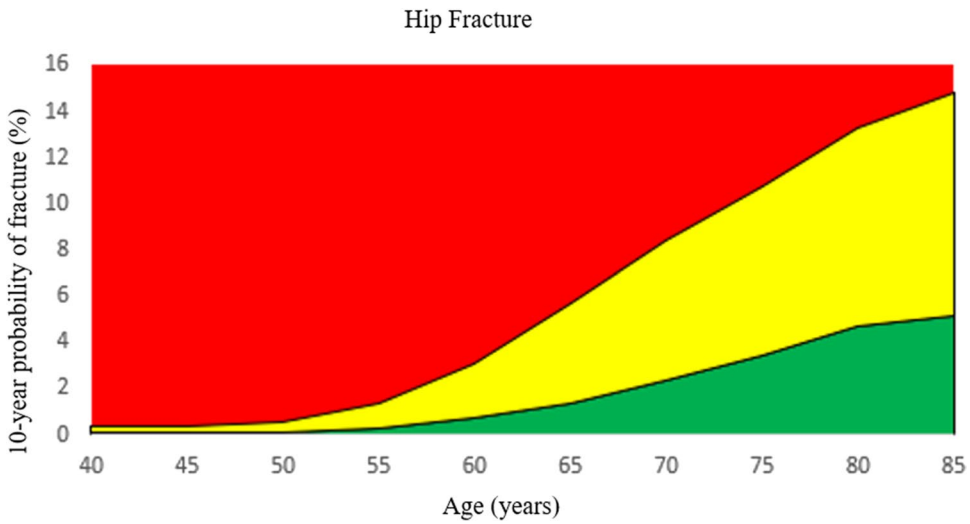

Fig. 2 Age-dependent assessment and intervention thresholds between 40 and 85 years for hip fracture

associated with a 0.62 and 0.83 sensitivity and specificity and 4% for HF probability which was associated with 0.63 and 0.82 sensitivity and specificity were found to be the most appropriate fixed ITs in this analysis. These thresholds were confirmed by examining the point on the ROC curve that was closest-to-(0,1) corner in the ROC.

Discussion

The risk categorization of patients without BMD to guide treatment decisions in osteoporosis is imperative in developing nations like Malaysia where BMD is not readily available. Our study helps streamline those in need of BMD for fracture risk estimations and can be used as a guide to direct treatment decisions where BMD facility is not available.

Previous studies have shown that assessment with FRAX without BMD gives approximate fracture risk prediction similar to FRAX with BMD. A sub-study of the Taiwan OsteoPorosis Survey (TOPS) [32] found the therapeutic decision making using FRAX without BMD to be concordant to that with BMD in 90.5% of the subjects. Similarly, Teeratakulpisarn et al [33] in their Thai cohort of 3545 participants found 83.8% concordance between FRAX with BMD and without BMD in recommending active treatment. Tamaki et al [34] did a 10-year follow-up of 815 women aged 40–74 years at the baseline, and found the predictive ability of FRAX without BMD was similar to that with BMD and it did not differ from the observed 10-year fracture rate used as an outcome. Despite these findings, there is an argument that the inclusion of BMD enhances the accuracy of FRAX based fracture risk predictions. Fraser et al [35] found FRAX with BMD to have better fracture discrimination than FRAX without BMD or BMD alone when compared to hard outcomes such as 10-year fracture outcomes.

According to the UK NOGG [24], interventions may be considered without a BMD information in women with prior fragility fracture and in women with high risk for osteoporotic fracture determined using FRAX. Women with fracture risk between the LAT and UAT should be considered for BMD estimations using DXA to re-assess their fracture probabilities with BMD input. In our study, in nearly 55% of the study sample, the decision to intervene could be made without BMD input (24.8 % women in high-risk category and 30.4 % women in low-risk category). In our analysis, the proportion of women who required BMD assessment to make treatment decision is slightly higher (44.8%) than that reported by Kariakos et al. [36] in the UK. They found that only 32% of women required BMD testing when the current NOGG age-dependent assessment thresholds were applied. In an Indian study, Nagendra et al [37] found that 32.3 % of patients (both men and women) required BMD testing to initiate or defer treatment while in a recent Sri Lankan study [31], the proportion of women who required BMD for further assessment was 68.6 %. Leslie et al [38] used a cohort of 36,730 women and 2873 men, aged 50 years or more, drawn from the Manitoba Bone Density Program database to assess the fracture risk without BMD. Similar to our study, they found the maximum benefit of including BMD in the risk assessment was greatest among those initially at moderate risk. In our study, among the 44.8 % in the intermediate risk group who were re-stratified after including BMD, 38.3% were above ITs and required treatment while 61.6% were below the ITs and did not require treatment.

Age is an independent risk factor for fracture and the 10-year MOFP and HFP progressively increase with age. Hence it is intuitive that age-specific ITs are more appropriate than fixed ITs when making treatment decisions. Age-dependent ITs, first developed by NOGG, are based on the rationale that if a woman with a prior fragility fracture is eligible for treatment, then, at any given age, a man or woman without a fracture but with the same fracture probability should also be eligible. For instance, in our study, IT for MOF for an 85-year-old woman was 25 times higher than that for a 40-year-old woman. Likewise, IT for HF for an 85-year-old woman were 40 times higher compared to that of a 40-year-old woman.

Early detection and intervention to prevent osteoporosis and fractures are key components in the management of osteoporosis. Approaches that target only those with prior fragility fractures or patients with BMD defined osteoporosis for treatment may not be the optimal approach. Based on our study findings, applying the newly derived ATs and ITs to guide osteoporosis management is a reliable option. This will help clinicians with limited or no access to DXA to make treatment decisions for a substantial proportion of patients without undue delay and also allow those with DXA facility to optimize services by streamlining patients.

The ideal set of ITs that suit a country, whether age dependent or fixed, should be decided after considering many factors as they both have inherent advantages and limitations. While age-dependent ITs lead to overtreatment of young and under treatment of old people, the vice versa is true for fixed ITs. Of these drawbacks, the under treatment of old people who have a high absolute fracture risk is a major concern. Furthermore, validation and cost effectiveness of these ITs need to be determined and the views of clinicians should be sought prior to implementation. The final decision on the type of ITs that suit the country, however, should be decided by those responsible for developing patient management guidelines and healthcare authorities.

Determining uniform ITs that suit all ethnic groups in a multi-ethnic country can be a daunting task. This requires ethnicity specific data on fracture incidence and the prevalence of clinical risk factors in the community. Analyses of the current study were done considering the Malaysian-Chinese ethnicity and until ethnicity-specific ITs are developed, we propose to apply these ITs for all other ethnic groups in Malaysia. At the fixed ITs described in the current analysis, the ages of women (with BMI of 25 kg/m^2 and without clinical risk factors) who qualify for specific treatment are 77, 73, and 75years for Malay, Chinese, and Indian ethnicities, respectively. This minor discrepancy disappears when glucocorticoid use is incorporated to risk profile (corresponding ages are 65, 66, and 66 for Malay, Chinese, and Indian ethnicities, respectively). Hence, we feel that clinicians in Malaysia could consider applying these ITs regardless of the ethnicity of their patients.

The strength of our study is the large number of subjects included and they belonged to a multi-ethnic background that reflects the Malaysian population. The data were collated from multiple centers located in different parts of the country. To our knowledge, this is the first study in Malaysia with age-specific ITs validated for our own population.

The study is limited by the fact that the DXA machines used at different centers varied and the operator dependent bias cannot be ruled out as the study was carried out at multi-centers. Future studies with a uniformed use of DXA scanners are warranted to overcome this limitation. Although the FRAX model used in this study was not country specific, a recent abstract has highlighted that there is very little difference between the Singapore FRAX used as a surrogate for fracture probabilities in the Malaysian population. [27]

In addition, certain Malaysian populations such as the indigenous people of Sabah and Sarawak were not represented in this analysis, indicating the need for future studies to include centers in Borneo. Another important limitation is higher than usual proportion of patients with rheumatoid arthritis (11.7%) that could have potentially confounded clinical risks incorporated in the analysis. This was due to

the fact that one of the study sites was a rheumatology referral center and that could have potentially biased the sample recruited.

Conclusion

This study provides a guide for making decision in osteoporosis treatment with age-specific ITs based on the Malaysian population. Less than half of the study population (44.8%) required BMD for osteoporosis management when these age-specific ITs were applied. This study will help the clinicians in resource limited settings to make decisions and initiate prompt treatment where required, without the need for BMD.

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Data availability Data will be provided upon request.

Declarations

Conflicts of interest None.

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