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Review article

The diversity of Fracture Risk Assessment Tool (FRAX)-based intervention thresholds in Asia

Sarath Lekamwasam

Population Health Research Center, Department of Medicine, Faculty of Medicine, Galle, Sri Lanka

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ABSTRACT

Fracture Risk Assessment Tool (FRAX), introduced in 2008, is the most frequently used fracture risk calculator. Many Asian countries have developed own FRAX models to suit their country needs. Only a few Asian countries, however, have developed country-specific intervention thresholds to demarcate high-risk patients. A wide variation is seen in these intervention thresholds partly due to the different approaches used in developing the cutoff values. This paper discusses the diversity of the intervention thresholds in Asian countries and possible reasons. It also discusses the future directions for the countries in the Asian region.

1. Osteoporosis and fragility fracture

Osteoporosis is a major health concern particularly among elderly men and women. Osteoporosis related fractures especially those in the proximal femur and spine are associated with increased mortality, morbidity and health care cost [1–3]. Hip fracture is the most sinister clinical outcome of osteoporosis leading to high mortality and dependence during postfracture period [2,4]. The burden of osteoporosis-related fractures has been estimated in individual countries and collectively as regions. In 2010, 22 million women and 5.5 million men in the European Union were estimated to have osteoporosis. This resulted in 3.5 million fragility fractures including 620,000 hip fractures, 520,000 vertebral fractures, 560,000 forearm fractures, and 1,800,000 other fractures. In 2010, the economic burden of incident and prior fragility fracture in the European Union was 37 billion euros and this would increase by 25% in 2025 [5,6]. In addition, the burden of osteoporosis or fragility fractures has been estimated in individual countries such as Switzerland [7], Sweden [8], New Zealand [9], and Canada [10].

It has been predicted that the incidence of fragility hip fracture would increase across the world but the main increase would be seen in the Asian region [11,12]. Unlike in Western populations, the burden of fragility fracture among Asians has not been well documented. Studies estimate that out of 15 million people with osteoporosis in Japan, only 20% of them receive treatment. In 2007, 130,000 hip fractures occurred in Japan and this is 2.8-fold higher when compared with 1987 figures [13]. A survey covering Thailand (Chiang Mai), Malaysia, Singapore, and Hong Kong in 2001 reported a wide variation of hip fracture incidence in the 4 countries and predicted that fracture burden would rise further in those countries causing an enormous burden to the health care systems [14].

Despite alarming fracture predictions in the Asian region, the preparedness of these countries to face the challenge of high fracture burden is not clearly evident. There is scarcity of epidemiological data and studies related to disease burden in this region [15]. Further, osteoporosis or related fractures are not health priorities in most of these countries. Mithal and Kaur [16] in 2012 have highlighted the major deficiencies in the Asian region such as lack of epidemiological data, high prevalence of vitamin D deficiency, low calcium intake, and restricted access to diagnostic and therapeutic facilities.

2. Fracture risk assessment tool in Asian countries

The primary aim of osteoporosis is prevention of fragility fractures and this requires identification of those with high fracture risk. It is generally agreed that those who have already sustained a fragility fracture carry a high risk of subsequent fracture, hence are considered for specific therapy regardless of baseline bone mineral density (BMD) and other clinical risk factors [17,18]. Risk

E-mail address: slekamwasam@gmail.com.
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assessment tools have been devised to determine the fracture risk of those suspected to have high fracture risk or with low BMD. Of these, Fracture Risk Assessment Tool (FRAX) is the most validated and widely used. Currently FRAX is available in 65 countries including 10 Asian, 35 European, 9 Middle East & Africa, 2 North America, 7 Latin America, and 2 Oceania. Of Asian countries, country-specific FRAX is available for China, India, Indonesia, Japan, Philippines, Singapore, South Korea, Sri Lanka, Taiwan, and Thailand. Countries such as Pakistan, Nepal, and Bangladesh, however, still have no own FRAX calculators (https://www.sheffield.ac.uk/FRAX/). The lack of country-specific risk estimators is a drawback in patient evaluation and rational prescribing. The major reason for the lack of country-specific FRAX is the scarcity of local data. FRAX is built on age-specific fragility fracture data and age-specific mortality data of the particular population. When fracture data are not readily available, data of surrogate populations are used and countries which have no robust fracture data could follow this pathway [19]. In a survey done in 2012 among health care professional, although 76% were aware of FRAX, only 62% used it in clinical decision making. In this survey, lack of a country-specific FRAX model was the main reason for not using FRAX in patient evaluation [20].

3. FRAX-based intervention thresholds

While it is important to have a reliable screening tool to identify high-risk patients for interventions, it is equally or more important to have intervention thresholds (ITs) appropriate for the country or populations. Although FRAX is available in 10 different Asian countries, only a few have developed own ITs. This is not unique to Asian region and has been highlighted in the systematic review of ITs prepared for the National Osteoporosis Guideline Group (NOGG) and the International Osteoporosis Foundation in 2016 [21]. The report indicates that although 120 guidelines or academic papers incorporated FRAX as the screening tool to identify high-risk individuals, 38 provided no clear guidance on ITs [21].

Although defining a cut point to implement interventions is not logical as the risk of fracture is continuum, clinicians expect this information in risk categorization of their patients. Although sounds unscientific, cutoff values have been defined for other diseases such as blood pressure, lipids and blood glucose. ITs in osteoporosis are mainly of 2 types; fixed and age-dependent, and countries have adopted either or both methods. Fixed ITs popularized by the National Osteoporosis Foundation (NOF) in the United States (US) recommends one fixed cut point for a particular type of fracture; 20% for the major osteoporotic fracture and 3% for hip fracture [18]. In contrast, the NOGG in the United Kingdom has adopted age-dependent ITs where ITs change with the age of the individual [17,22]. Many countries have followed these methods, with and without necessary changes to suit the particular country.

Age-dependent ITs have been developed based on the assumption that if a woman with fragility fracture qualifies for treatment regardless of baseline BMD and other clinical risk factors, a same-aged woman who has not developed a fracture but has same fracture risk, also qualifies for treatment [22]. Although the principle used in generating age-dependent ITs appears clinically sound, there are inherited weaknesses of this approach. Fracture probabilities of an old patient with clinical risk factors may fall below those of a same-aged patient with a fracture and in contrast fracture probabilities of a young patient with a few clinical risk factors may exceed those of a same-aged patient with a fracture. For instance, based on Sri Lankan FRAX model, a woman of 50 years (body mass index [BMI], 25 kg/m^2) with parental history of hip fracture and femoral neck T score of −1.5 has major osteoporotic fracture risk of 3% and this exceeds the IT (2.6%) given for that age. Further, she will reach 2.6% IT even if her femoral neck BMD is in the normal range in the femoral neck. In contrast, major osteoporotic fracture risk of a 70-year-old woman (BMI, 25 kg/m^2) with parental history of hip fracture and T score of −1.5 (13%) is below the IT of 15% given for that age. Further, a woman of 70 years with rheumatoid arthritis and T score of −1.5 is also unable to reach the IT set for that age. This illustrates that age-dependent ITs leads to undertreatment in old patients and overtreatment in young patients.

Fixed ITs, originally introduced by the NOF, are used in many countries with and without local adaptations. The NOF ITs of 20% for major fracture and 3% for hip fracture are only applicable for those with BMD in the osteopenic range [18]. They have been developed based on an economic evaluation considering alendronate as the main therapeutic option. Many newer treatment options have been introduced and the cost of drugs also has changed. While the validity of these ITs in the US population, after 10 years of introduction is questionable, their applicability outside the US is not appropriate [21]. Many countries such as Austria, Hungary, Sweden, and Thailand, however, have adopted NOF ITs without adequate explanations [21].

While age-dependent ITs lead to overtreatment of young and undertreatment of old, fixed ITs reverse this phenomenon. Of these, overtreatment of young and undertreatment of old are major concerns. Young patients are less likely to fracture and would need prolonged period of treatment due to the longer lifespan, exposing them to serious adverse effects. Hence, attempts should be made to avoid over treating them. In contrast, older person may require intervention despite low FRAX score due to the presence of other risk factors of fractures such as recurrent falls and frailty which are not captured by FRAX.

Attempts have been made recently to introduce different types of ITs. Hybrid ITs which is a combination of fixed (for patients younger than 70 years) and age-dependent ITs (for those aged 70 and above) have been introduced to avoid overtreatment of young patients. This, however, would not overcome the undertreatment of older patients. Hybrid ITs have been advocated in Lebanon [23] and Sri Lanka [24]. Two-tier ITs where 2 sets of fixed ITs, one for those younger than 70 years and another for those 70 and above have been introduced recently in order to overcome both overtreatment of young and undertreatment of older patients [24].

4. Interpretation of ITs

The common misconception in the interpretation of ITs is that those above the ITs should be treated pharmacologically (treatment thresholds). Although this is true (ITs equal to treatment thresholds) for most of the guidelines some ITs, however, are used to select patients for further evaluation. The NOGG age-dependent ITs given for FRAX estimated using clinical risk factors alone (without BMD input) are used to select patients for treatment as well as for further evaluation with dual-energy X-ray absorptiometry (DXA) [17,22]. Similar recommendations have been made by the US Preventive Services Task Force which recommends BMD testing for all women above 65 and those younger than 65 with major fracture probability of >9.5% [25]. A study in 2015 reported that compared to the NOF guidelines which required BMD testing in all subjects, only 32.3% subjects required BMD testing when the NOGG guidelines were applied [26].

5. Methods of developing ITs

Different methods have been used to develop ITs. Age-dependent ITs have been developed based on the rationale that if a woman with a prior fragility fracture is eligible for treatment, a

same-aged woman with the same fracture probability but not had a fracture should also be eligible for treatment [22]. Many Asian countries such as Sri Lanka [24], Singapore [27], and India [28] have adopted this method in developing age-dependent ITs. In 2009, the US used an economic model taking alendronate as the main therapy in osteoporosis. In the Asian region, ITs based on economic evaluations have been made in Taiwan [29]. Australia [30], and Japan [31] have determined thresholds in such a way that demarcate the correct proportion of women with fracture risk in the population. In summary, there is no uniform method to develop ITs and a country should decide on the best method that suit the country's economy, capacity of the health care system, screening facilities and insurance reimbursement policies [21].

6. ITs in Asian countries

6.1. China

A study in China in 2014 found 10y hip fracture probability of a woman with a prior hip fracture estimated using Chinese FRAX to be substantially lower when compared with Hong Kong and England FRAX models. In the same study, the 62.5th percentiles of major osteoporotic fracture and hip fracture probability calculated with BMD were 4.0% and 1.3%, respectively and this corresponded to 37.5% subjects having osteoporosis and high fracture risk. This solitary study involving central Southern Chinese postmenopausal women may have restricted external validity in heterogeneous Chinese population and authors advocate caution when applying these ITs [32].

6.2. Hong Kong

In Hong Kong a group of treatment-naïve postmenopausal women has been followed up for mean of 4.5 years to record incident fractures. Authors found major fracture cut point of 9.95% (BMD included) to be the most appropriate value to trigger interventions in this group of women [33].

6.3. India

Age-dependent ITs have been developed in India in 2013 adopting the NOGG approach. In this assessment ITs of major osteoporosis fracture ranged from 2.8% at the age of 50 years to 17% at the age of 75 years or more [28].

6.4. Japan

Fujiwara et al. [34], in 2018 estimated ITs by determining the FRAX output cut point that corresponded to the ITs in practice then. In this analysis major osteoporosis ITs ranged from approximately 5% at the age of 50 years to more than 20% at the age of 80 years. Orimo et al. [35] in 2011 updating the previous guidelines (1998) on the management of osteoporosis, however, recommended major osteoporosis fracture IT of 15%. In 2013, Nakatoh and Takemaru [36] found major osteoporosis fracture ITs of 8% for men and 10.5% for women were more suitable to narrow down subjects for specific health check-ups and to motivate them to seek follow-up.

6.5. Malaysia

The Malaysian Clinical Guidance on the management of postmenopausal osteoporosis published in 2012 recommends using the NOF guidelines in making treatment decisions. This recommendation has not been supported by local data or an adequate explanation [37].

6.6. Philippines

A consensus statement on the management of osteoporosis in Philippines recommends adopting the NOF guidelines in the evaluation of patients [38].

6.7. Singapore

Singapore developed ethnic-specific ITs as well as common ITs for Singaporean women aged 50–90 years. In this analysis, fixed ITs and age-dependent ITs showed a wide ethnic variation. Age-dependent major fracture ITs of Chinese women varied from 3.1% to 33% while they varied from 2.5% to 17%, and 2.5%–16% in Indian and Malay, respectively. Similar difference was seen in hip fracture ITs which varied from 0.7% to 17% in Chinese, 0.4%–6% in Indian and 0.4%–6.3% in Malay. Fixed major fracture ITs of Chinese, Indian, and Malay women aged 50–90 years were 5.5%, 2.5%, and 2.5%, respectively. The corresponding values of hip fracture ITs were 1%, 0.25%, and 1% [27].

Since the application of ethnic-specific ITs could potentially lead

Table 1
FRAX-based intervention thresholds recommended/used in Asia.

Country/region	Age-dependent ITs	Major osteoporotic fracture IT (fixed)	Hip fracture IT (fixed)	References
China	–	4.0%	1.3%	32
Hong Kong	–	9.95%	–	33
India	2.8%–17% (major fracture)	–		28
Japan	5%–20% (major fracture)	15%, 10.5%	–	34–36
Malaysia	–	NOF cutoff values	NOF cutoff values	37
Philippines	–	NOF cutoff values	NOF cutoff values	38
Singapore[a]	2.9%–28% (major) 0.6%–1.4% (hip)	4%	1%	27
Sri Lanka	2.7%–18.6% (major) 0.4%–7.1% (hip)	9%	3%	24
	[b]15%–18.6% for major and 4.7%–7.1% for hip fracture for 70 and above)	6% (below 70 yr)	2% (below 70 yr)	
	–	[c]6% (below 70 yr)	2% (below 70 yr)	
	–	12% (70 and above)	5% (70 and above)	
Taiwan		15%	7%	29
Thailand		–	3%	40

FRAX, fracture risk assessment tool; IT, intervention threshold; NOF, National Osteoporosis Foundation.
[a] Mean weighted values adjusted for population composition.
[b] Hybrid intervention thresholds.
[c] Two-tier intervention thresholds.

to problems, authors have developed mean weighted ITs taking the population composition of the country into account. In this analysis, age-dependent ITs varied from 2.9% to 28% for major fracture and 0.6%–14% for hip fracture. The fixed ITs for major and hip fracture were 4% and 1%, respectively [27].

6.8. Sri Lanka

In Sri Lanka, ITs were first published in 2013 [39] and they were revised in 2019 [24]. Both studies followed the same approach while and sample sizes and statistical methods were different. In the revised version, age-dependent ITs of women aged 50–80 years varied from 2.7% to 18.6% for major osteoporotic fracture and 0.4%–7.1% for hip fracture. The fixed IT of major fracture was 9% while hip fracture IT was 3%.

In the hybrid method, 6% and 2% major fracture and hip fracture ITs of women below 70 years were combined with age-dependent ITs of those aged 70 or more. In the 2-tier system, 2 sets of ITs were recommended for those below 70 (major fracture and hip fracture: 6% and 2%) and those of 70 or more (major fracture and hip fracture: 12% and 5%). Compared to age-dependent ITs, sensitivities of the fixed, hybrid, and 2-tier ITs were found to be 0.63, 0.73, and 0.74, respectively. The specificities were 0.76, 0.86, and 0.80 in the same order. When a group of women with recent fracture was included in the analysis, sensitivities of the age-dependent, fixed, hybrid, and 2-tier ITs in identifying a woman with an incident fracture were 26%, 48%, 61%, and 61%, respectively [24].

6.9. Taiwan

Taiwan developed ITs based on an economic evaluation (Markov model) using branded alendronate as the first choice of treatment. According to the cost-effectiveness analysis, major fracture probability of 15% and hip fracture probability of 7% have been recommended as suitable ITs for Taiwanese postmenopausal women [29].

6.10. Thailand

Thailand developed ITs in 2012 based on consensus among experts in the field. In this treatment has been recommended for postmenopausal women with hip fracture probability>3% [40]. ITs in Asian countries are summarized in Table 1.

7. Future directions

Asia as a region needs to make major advances in the research related to osteoporosis and fragility fracture. Many have questioned the relevance and validity of risk assessment tools such as FRAX in Asian countries. In Chinese women, ethnic-specific clinical risk factors together with T score performed better than FRAX with T score in predicting fragility fracture. In this analysis, clinical risk factor model had 10% higher sensitivity than FRAX at 80% specificity [41]. Similarly, a 5-factor clinical risk score showed better discriminatory power than FRAX among oldest-old in Hong Kong [42].

The limitations seen in the current FRAX specially when applied to Asian population could be due to many reasons. The lack of reliable epidemiological information related to gender and age-specific fragility fracture incidence and association between risk factors and fractures in Asian countries have hindered development of risk assessment tools that suit the region better. Apart from mortality and fracture occurrence, the risk factors of fragility fracture may have geographical variations and these factors should be taken to consideration when developing a reliable risk assessment tool for Asian countries. This may include either revising current Asian FRAX models or developing a separate risk assessment tool for Asian countries using regional data.

It is equally important for the Asian countries without country-specific FRAX to make an attempt to develop own FRAX calculators. The option of surrogate FRAX is available for those with limited fracture data [19]. Having an own FRAX enhances osteoporosis patient care since clinicians without access to DXA can still estimate fracture risk based on clinical risk factors sans BMD input.

Country-specific ITs for FRAX-based fracture probabilities should be estimated based on local data. This will allow rational utilization of FRAX output in patient management. Although some methods of estimating ITs are complex and require lot of information, some simple methods can be adopted in any country.

8. Conclusions

A wide variation in FRAX-based ITs is seen across Asian countries and this may be due to a multitude of reasons. Although the differences in the principles of developing ITs appear to be the main reason of this variation, a real geographic variation in fragility fracture occurrence in the Asian region cannot be ruled out. While some Asian countries still have no own FRAX algorithms, many countries have no country-specific ITs. More studies examining the risk factors and incidence of fragility fracture in the region are required to develop a FRAX dedicated to the region.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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ORCID. Sarath Lekamwasam: 0000-0002-3541-9982.

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