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Original Article

# Discriminatory Accuracy of Fracture Risk Assessment Tool in Asian Populations: A Systematic Review and Meta-Analysis

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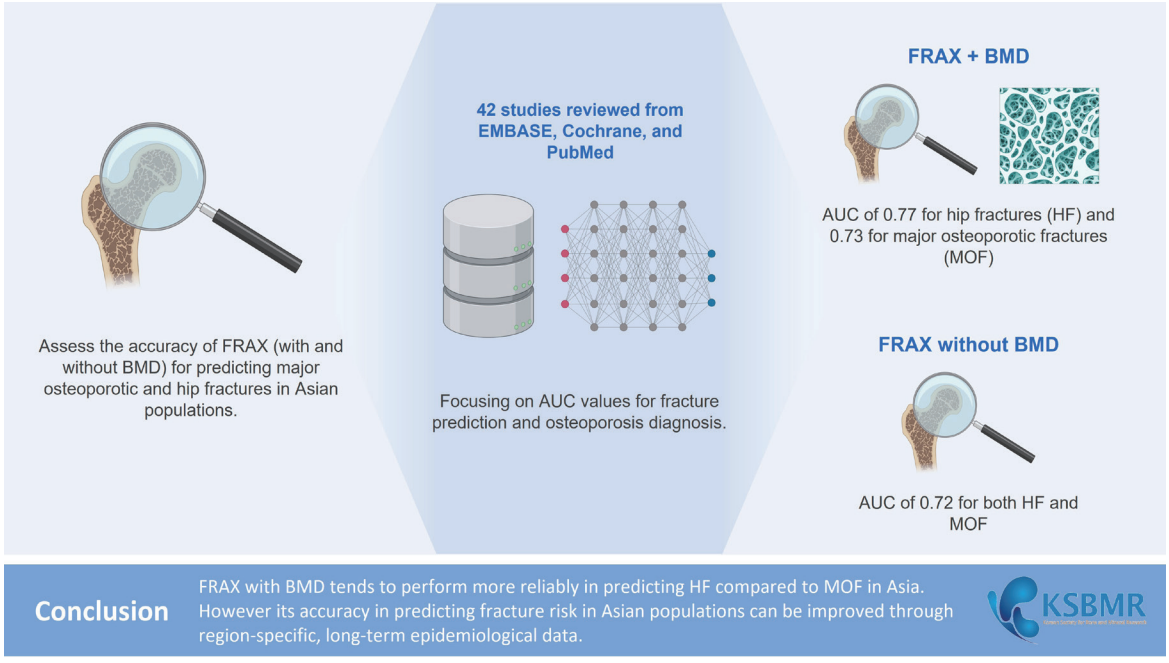
**Background:** This review explores the discriminative ability of fracture risk assessment tool (FRAX) in major osteoporotic fracture (MOF) and hip fracture (HF) risk prediction and the densitometric diagnosis of osteoporosis in Asian populations. **Methods:** We systematically searched the EMBASE, Cochrane, and PubMed databases from the earliest indexing date to January 2024. Studies were included if FRAX was used to identify future osteoporotic fractures or a densitometric diagnosis of osteoporosis in an Asian population and reported the area under the curve (AUC) values. Meta-analyses were conducted after quality assessment for AUC with 95% confidence intervals across the following categories: standard FRAX without/with bone mineral density (BMD), adjusted FRAX, and BMD alone for fracture prediction, as well as standard FRAX for densitometric diagnosis of osteoporosis. **Results:** A total of 42 studies were included. The AUC values for predicting fracture risk using FRAX-MOF with BMD (0.73 [0.70–0.77]) was highest compared to FRAX-MOF without BMD (0.72 [0.66–0.77]), and adjusted FRAX-MOF (0.71 [0.65–0.77]). The AUC values for predicting fracture risk using FRAX-HF with BMD (0.77 [0.71–0.83]) was highest compared to FRAX-HF without BMD (0.72 [0.65–0.80]), and adjusted FRAX-HF (0.75 [0.63–0.86]). The AUC values for BMD alone (0.68 [0.62–0.73]) was lowest for fracture prediction. The AUC values for identifying a densitometric diagnosis of osteoporosis was 0.77 [0.70–0.84] and 0.76 [0.67-0.86] using FRAX-MOF and FRAX-HF, respectively. **Conclusions:** FRAX with BMD tends to perform more reliably in predicting HF compared to MOF in Asia. However, its accuracy in predicting fracture risk in Asian populations can be improved through region-specific, long-term epidemiological data.

**Key Words:** Fractures, bone · Osteoporosis · Risk assessment · Meta-analysis as topic · Systematic reviews as topic

## INTRODUCTION

Osteoporosis is a silent chronic disease that is manifested by low bone mass and reduced structural integrity at the microarchitectural level, resulting in increased bone fragility and fracture risk with age.[1] By 2050, more than 50% of hip fractures (HFs) are expected to occur in Asia.[2] HFs are associated with high costs and

**Graphical Abstract**




mortality.[3,4] In Asia alone, the number of HFs is estimated to rise from 1.12 million to 2.56 million between 2018 and 2050, leading to an increase in the annual direct medical cost of treating HFs from USD 9.5 billion to USD 15 billion.[2] These fractures have a combined lifetime risk in terms of needing clinical attention equivalent to that of cardiovascular disease.[5] Osteoporotic fractures result in pain and disability, causing individuals to often lose their capacity for leading active, productive, and independent lives.[6] However, there remains an insufficient emphasis on managing the burden of osteoporotic fractures in Asia, leading to underdiagnosis and consequently undertreatment of this disease in the region.[6]

The main goal in managing osteoporosis is to prevent fractures, which necessitates identifying individuals at elevated risk. Bone mineral density (BMD) obtained from dual energy X-ray absorptiometry (DXA) imaging is the current gold standard for doing so. However, BMD alone has been deemed to lack sensitivity in terms of predicting future fractures.[7] Furthermore, DXA imaging is not widely accessible in many Asian countries.[6] This is especially critical in countries like China, India, Indonesia, Pakistan, Sri Lanka, Thailand, and Vietnam, where majority of the population live in rural areas.[6] This has led to increased interest in the use of the fracture risk assessment tool (FRAX), developed by the University of Sheffield, and launched in 2008. FRAX can estimate the 10-year fracture probability of a major osteoporotic fracture (MOF) and HF (https://frax.shef.ac.uk/FRAX/) based on clinical risk factors, with or without BMD. The clinical risk factors include age, gender, weight, height, fracture history, parent fracture history, smoking status, glucocorticoid intake, rheumatoid arthritis, secondary osteoporosis, alcohol intake, and BMD.[8] Some systematic reviews have evaluated the discriminatory ability of FRAX in predicting osteoporotic fractures and found that it performed moderately well in predicting the 10-year probability of MOF and HF with or without BMD.[9-11] Several studies have also demonstrated that FRAX, without BMD, performs comparably to BMD in identifying a densitometric diagnosis osteoporosis, making FRAX a convenient tool for identifying poor bone health in Asian populations, especially where access to medical imaging may be limited.[12-16]

While FRAX enables country-specific calculations of fracture probability, the development of FRAX was unfortunately primarily dependent on data from Caucasian populations.[9-11,17] There is a need to understand the performance of FRAX within Asian populations specifically since

it is burdened with a rapidly increasing rate of osteoporotic fractures. Therefore, the aim of this systematic review and meta-analysis was to determine if FRAX has discriminative power to identify individuals at risk of fractures in Asia and to evaluate the limitations of FRAX with respect to Asia specifically. A secondary aim was to explore the discriminative power of FRAX to identify a densitometric diagnosis of osteoporosis in Asian populations.

## METHODS

### 1. Search strategy

Electronic databases EMBASE, Cochrane, and PubMed were searched systematically from the earliest indexing date to January 21, 2024. '*FRAX*,' '*fracture risk assessment tool*,' and '*fracture*' constituted the search terms and were formatted for different electronic databases. The full search term strategy can be found in Supplementary Appendix 1. We followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines for the review.[18] Rayyan (http://rayyan.qcri.org),[19] a free online application, was used to resolve duplicates and apply study eligibility criteria.

### 2. Study selection criteria

The following inclusion criteria was applied to all studies: (1) the study used FRAX to identify a densitometric diagnosis of osteoporosis or future osteoporotic fractures; (2) the study population was from Asia; (3) the study was in English and on human subjects; (4) the study was a journal article; and (5) reported area under the curve (AUC) values. Studies were excluded if found to be irrelevant during full-text review, or the studies were identified as statements, conference papers, case reports, or reviews. Authors DJ and ADP carried out independent screening of the entire collection based on the study selection criteria. The screening was two phased, where articles were first identified based on titles and abstracts and the second phase of screening involved selection based on full-text review. Additionally, manual search through references in the included studies was carried out for identifying studies not captured by the search strategy. Disagreements between the two reviewers were resolved by discussion.

### 3. Data extraction

The following data was extracted from the studies selected after full-text review by DJ and ADP independently: Country, study design, follow-up period in years if reported, sample size at baseline, subject demographics in terms of mean age, percentage of women, type of fracture recorded, fracture ascertainment method, BMD measurement site, and performance measures reported (AUC, sensitivity, specificity, and any other outcomes). The primary outcome considered in this review was the AUC from receiver operating characteristic curve. A formula (Eq. 1) was used to approximate the 95% confidence interval (CI) values for the studies that did not explicitly report it.[20]

$$\mathrm{CI} = \mathrm{AUC} \pm se * z_{\mathrm{crit}} \quad \textbf{-Eq. 1}$$

where, $z_{crit}$ = two-tailed critical value of the standard normal distribution

$$\text{standard error}, se = \sqrt{\frac{q_0+(n_1-1)q_1+(n_2-1)q_2}{n_1 n_2}} \quad \textbf{-Eq. 2}$$

where $n_1$ = Number of cases, $n_2$ = number of non-cases; q0, q1, q3 = Eq. 3a–3c

$$q_0 = AUC(1-AUC) \textbf{ -Eq. 3a}; \; q_1 = \frac{AUC}{2-AUC} - AUC^2 \textbf{ -Eq. 3b}; \; q_2 = \frac{2AUC^2}{1+AUC} - AUC^2 \textbf{ -Eq. 3c}$$

### 4. Quality assessment

The quality assessment was independently carried out by authors DJ and ADP using the quality assessment of diagnostic accuracy studies 2 (QUADAS-2) checklist.[21] The checklist was updated to carry out a quality assessment within the purview of this review (Supplementary Table 1). Disagreements were resolved by discussion. A potential selection bias was considered if fracture ascertainment was not verified and if more than 10% of eligible study participants were excluded from the analysis.

### 5. Statistical analysis

The included studies either evaluated the discriminatory power of FRAX in terms of predicting osteoporotic fractures or presence of osteoporosis. MOFs were defined as hip, vertebral, wrist, and humerus fractures. We analysed subgroups of the included studies that reported AUC estimates based on standard FRAX probabilities with and without BMD, adjusted FRAX probabilities, and BMD alone, in the prediction of either osteoporotic fractures or a densitometric diagnosis of osteoporosis. Subgroup analyses were performed separately for FRAX-MOF and FRAX-HF,



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except for the prediction using BMD alone due to the limited number of studies reporting AUC values. Adjusted FRAX refers to the modification of the standard FRAX by one or more clinical risk factors (i.e., increased age, reduced BMD, T-Score measured at different sites, falls, trabecular bone score [TBS], and sarcopenia). Separate meta-analyses were conducted on studies to evaluate the potential impact of class imbalance, as AUC values can be affected by unequal distribution between fracture and non-fracture cases.[22] We assumed that there was a class imbalance when less than 10% of the sample population experienced fractures. These studies reported AUC estimates for standard FRAX with and without BMD. A three-level random effects model was employed using the *metafor* package in the R programming environment (version 3.4.5; The R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org/) [23] to account for multiple AUC values presented by most of the studies. This model was utilized to address the interdependence between reported values. Forest plots were used to compare AUC estimate values along with their corresponding 95% CIs. Heterogeneity was evaluated using the Q-test and the multi-level $I^2$ statistic, allowing separate estimation of 'within-study' ($I^2_{Level\ 2}$) and 'between-studies' ($I^2_{Level\ 3}$) variance.[24] As individual effect sizes within a cluster or a study, are derived from the same sample, their sampling errors are presumed to be correlated.[25] To accommodate this within-study dependence, cluster-robust variance estimation was implemented by assuming a correlation factor of $\rho=0.60$. Statistical significance was defined as a *P*-value less than 0.05.

## RESULTS

### 1. Study selection

The initial search strategy yielded 10,622 articles. After removing duplicates (N=2,894) and screening titles and abstracts, 53 articles were considered for full-text reading (Fig. 1). This led to further exclusion of fourteen articles. Reasons for exclusion were irrelevance for the purpose of the review (N=8), or articles found to be conference abstracts (N=6). Three additional articles were included after the manual search through references of studies that passed the inclusion criteria. In total, 42 articles were included in this review.

### 2. Study characteristics

The summary of study characteristics is provided in Table 1 for the use of FRAX for predicting osteoporotic fractures

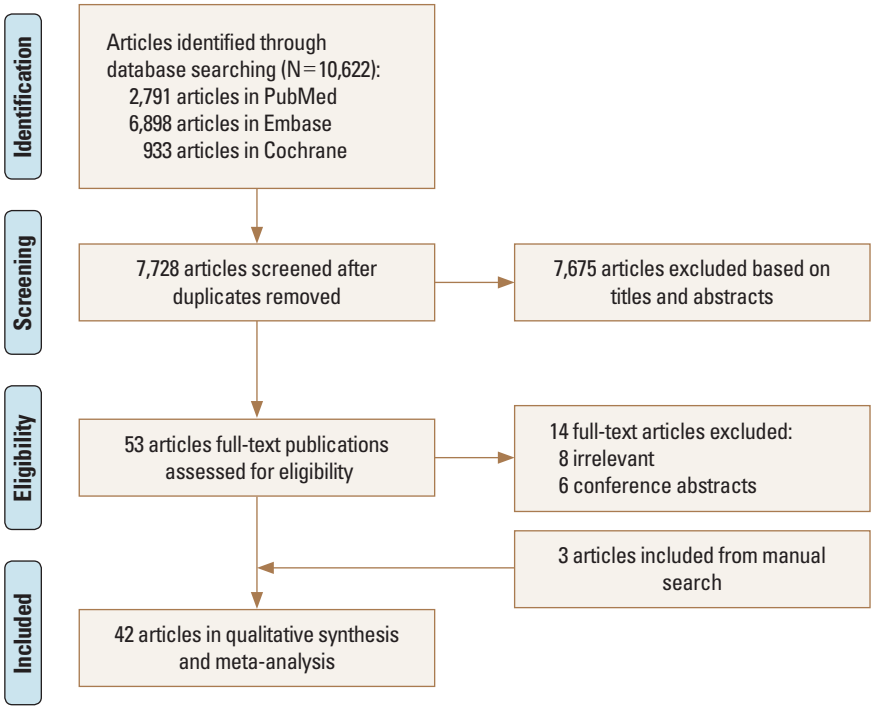


**Fig. 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines-based review process flow chart.

**Table 1.** Summary of main characteristics of studies that used FRAX to identify subjects with osteoporotic fractures (N=32)

| References | Population | FRAX country | Study design | Follow-up (yr) | Sample characteristics | Region of interest | Sample size (females) | Mean age (yr) | Reported outcomes |
|---|---|---|---|---|---|---|---|---|---|
| Amininezhad et al. (2015) [63] | Iran | Jordan, USA, Lebanon | R (CC) | 0 | Patients aged over 50 years who were referred to the BMD centre. Case: MOF/HF; Control: no fracture. | Femoral neck | 233 (159); Cases: 74 (48); Controls: 159 (111) | Cases: 70±10 (female), 70±12 (male); Controls: 66±8 (female), 66±9 (male) | Standard FRAX |
| An et al. (2021) [26][a] | China | China | CS | 0 | Han Chinese men aged ≥50 years, who lived locally ≥20 years, and willing to participate in this study and signed the informed consent. | Femoral neck, total hip, lumbar spine | 846 (0) | | Standard FRAX, BMD |
| Bansal et al. (2018) [54] | India | India | R (CC) | 0 | Patients admitted to the orthopaedic ward. Case: fragility fracture; Control: no fracture. | No BMD | 500 (345); Case: 62 (40); Control: 438 (305) | 63.1; Case: 68.5±10.5; Control: 62.3±10.1 | Standard FRAX |
| Chang et al. (2016) [27][a] | China | China | R (CC) | 0 | Haemodialysis patients aged ≥18 years, had at least one BMD measurement by onsite DXA, and had maintenance dialysis for over 4 months. Case: OVCF; Control: no fracture. | Femoral neck, total hip, lumbar spine | 136 (56); Case: 16 (6); Control: 120 (50) | 59 (47–66.8); Case: 69 (60.8–75.8); Control: 57 (44.3–64.0) | Standard FRAX, BMD |
| Chanplakorn et al. (2021) [60][a] | Thailand | Thailand | R (CC) | 0 | Women aged ≥50 years, and who underwent DXA and VF assessment for osteoporosis screening. Case: osteoporotic compression VF; Control: no fracture. | No BMD | 617 (617); Case: 179 (179); Control: 438 (438) | 68.5±8.6; Case: 72.3±7.98; Control: 66.9±8.32 | Standard FRAX, BMD |
| Chen et al. (2016) [38] | Taiwan | Taiwan | P | 1 | Persons aged ≥60 years who had a registered household in Tanzi district and were able to ambulate independently. | Total hip | 553 (367) | 67.4±6.4 | Standard FRAX |
| Cheung et al. (2012) [7] | Hong Kong | Hong Kong | P | 4.5 | Community-dwelling ambulatory Southern Chinese postmenopausal women aged ≥40 years recruited during health fairs and road shows on osteoporosis. | Femoral neck, total hip, lumbar spine | 2,266 (2,226) | 62.1±8.5 | Standard FRAX |
| Chuan et al. (2023) [28] | China | China | P | 5 (median) | Patients aged ≥50 years with T2DM. | Femoral neck | 1,855 (844) | 64 (median) | Standard FRAX, adjusted FRAX with RA, with age increase, and with T-score reduction |
| Guo et al. (2022) [29][a] | China | China | R (CC) | 0 | Han Chinese postmenopausal women, residing in Beijing ≥20 years. Case: painful new osteoporotic VF who underwent percutaneous vertebroplasty; Control: community-enrolled females. | Femoral neck, total hip, lumbar spine | Case: 644 (644); Control: 2,230 (2,230) | Case: 72.8±8.5; Control: 61.1±8.6 | Standard FRAX, BMD |
| Huang et al. (2021) [30][a] | China | China | R (CC) | 0 | Ambulatory women ≥60 years who could walk independently and of Chinese descent with all four grandparents being ethnic Chinese. Case: asymptomatic VF; Control: no fracture. | Femoral neck, total hip, lumbar spine | Case: 102 (102); Control: 73 (73) | Case: 69.7±5.1; Control: 66.7±5.0 | Standard FRAX, BMD |
| Iki et al. (2015) [46] | Japan | Japan | P | 4.5 (median) | Community-dwelling men ≥65 years, living at home, ability to walk without assistance, and to provide self-reported information and written informed consent. | Femoral neck | 1,805 (0) | 73±5.1 | Standard FRAX, adjusted FRAX with TBS |
| Ji et al. (2022) [31] | China | China | P | Internal: 4.1±2.2; External: 5.4±1.9 | Primary breast cancer diagnosed by pathological examination. | No BMD | 599 (599) | | Standard FRAX |
| Kim et al. (2016) [50][a] | Korea | Korea | R | 0 | Female RA patients aged ≥50 years who visited a university hospital for periodic examinations. | Total hip, lumbar spine | 100 (100) | 61.2±8.2 | Standard FRAX, BMD |
| Kong et al. (2020) [51] | Korea | Korea | P | 7.5 | Korean men and women aged 40–69 years, who had lived in the survey area for at least 6 months before enrolment. | Femoral neck, total hip, lumbar spine | 2,227 (1,257) | 61.2±8.7 | Standard FRAX, adjusted FRAX with TBS |

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**Table 1.** Continued

| References | Population | FRAX country | Study design | Follow-up (yr) | Sample characteristics | Region of interest | Sample size (females) | Mean age (yr) | Reported outcomes |
|---|---|---|---|---|---|---|---|---|---|
| Kong et al. (2022) [32] | China | China | R | 10 (median) | Patients with T2DM who were hospitalized. | Femoral neck | 1,730 (588) | 55.1±11.9 | Standard FRAX, adjusted FRAX with TBS |
| Lam et al. (2020) [43] | Hong Kong | Hong Kong | P | Derivation cohorts: 8.9 (median); Validation cohorts: 2.6 (median) | Community-dwelling Southern Chinese men and women of Han descent aged ≥80 years recruited from public road shows and health fairs. | Femoral neck | Derivation cohort: 251 (153); Validation cohort: 599 (517) | Derivation cohort: 83±3.1; Validation cohort: 84.9±3.6 | Standard FRAX |
| Lee et al. (2015) [52] | Korea | Korea | CS (CC) | 0 | Patients aged ≥60 years who were admitted to hospital for treatment of degenerative spine disease or osteoporotic VF. Case: osteoporotic VF; Control: non-osteoporotic VF. | Femoral neck, lumbar spine | 110 (70); Case: 58 (42); Control: 52 (28) | 75.6±6.65; Case: 74±6.7; Control: 76±6.4 | Standard FRAX, adjusted FRAX with different T-score site |
| Lee et al. (2023) [53][a] | Korea | Korea | CS | 0 | Patients with systemic sclerosis, RA and postmenopausal women. Case: systemic sclerosis; Control: RA and postmenopausal women | Femoral neck, total hip, lumbar spine | 165 (152); Systemic sclerosis: 69 (62); RA: 58 (52); Postmenopausal women: 38 (38) | Systemic sclerosis: 61.1±7.7; RA: 63.2±8.7; Postmenopausal women: 59.8±8.2 | Standard FRAX, BMD, adjusted FRAX with TBS |
| Lekamwasam (2010) [14] | Sri Lanka | USA, Japan, China | R | 0 | Postmenopausal women older than 65 years and women younger than 65 years with additional risk factors for osteoporosis. | Femoral neck | 481 (481) | 57.9±8.5 | Standard FRAX |
| Lekamwasam et al. (2020) [62] | Sri Lanka | Sri Lanka | R | 0 | Postmenopausal women between 40–84 years, who underwent DXA for the evaluation of fracture risk in our tertiary care referral centre. | Femoral neck, total hip, lumbar spine | 481 (481) | 63.1±10.4 | Standard FRAX, adjusted FRAX with TBS |
| Lin et al. (2016) [33][a] | China | China | CS (CC) | 0 | Han Chinese men ≥50 years, residing in Beijing ≥20 years, willing to participate and read informed consent form. Case: painful VF within past 6 months; Control: no specific osteoporosis-associated symptoms. | Femoral neck, total hip, lumbar spine | 496 (0) | | Standard FRAX, BMD |
| Liu et al. (2022) [39] | Taiwan | Taiwan | | 6.8 (1.1) | Subjects aged ≥40 years, with complete data of clinical risk factors and probability estimates and had medical coverage from the National Health Insurance Research Database. | Femoral neck, total hip, lumbar spine | 1,975 (1043) | 64.42±12.08 | Standard FRAX |
| Rajan et al. (2020) [55] | India | India | CS | 0 | Postmenopausal women ≥60 years, ambulating independently. | Femoral neck, lumbar spine | 301 (301); Case: 88 (88); Control: 213 (213) | 65.6±5.1; Case: 64.4±4.1; Control: 68.4±5.6 | Standard FRAX, adjusted FRAX with TBS |
| Sheng et al. (2024) [42] | Taiwan | Taiwan | P | 11 | Asymptomatic health examinees aged ≥55 years, who underwent senior citizens' health examinations and in general good health. | No BMD | 708 (348) | 74.9±6.4 | Standard FRAX |
| Sribenjalak et al. (2022) [61] | Thailand | Thailand | CS | 0 | Postmenopausal Thai women aged 40–90 years, who had their BMD measured for osteoporosis. | Femoral neck, lumbar spine | 2,872 (2,872) | No HF: 76 (68–82); With HF: 63 (56–71) | Standard FRAX |
| Su et al. (2017) [44] | Hong Kong | Hong Kong | P | Male: 9.9±2.8; Female: 8.8±1.5 | Community-dwelling men and women aged ≥65 years, able to walk without assistance. | Femoral neck, total hip, lumbar spine | 3,873 (1,950) | Male: 72.29±4.87; Female: 72.52±5.26 | Standard FRAX, adjusted FRAX with TBS |
| Su et al. (2018) [45] | Hong Kong | Hong Kong | P | Male: 9.9±2.8; Female: 8.8±1.5 | Community-dwelling men and women aged ≥65 years, able to walk without assistance. | Femoral neck, total hip, lumbar spine | 4,000 (2,000) | 0 fall: 72.3±5 (male), 72.6±5.3 (female); 1 fall: 72.8±5.3 (male), 72.3±5.2 (female); ≥2 falls: 73.6±5.0 (male), 73.4±5.9 (female) | Standard FRAX, adjusted FRAX with previous fall |
| Tamaki et al. (2011) [47][a] | Japan | Japan | P | 10 | Women (15–79 years) were randomly selected from 5-year age groups using resident registrations in seven municipalities throughout Japan. | Femoral neck | 815 (815) | 56.7±9.6 | Standard FRAX, BMD |

(*Continued to the next page*)

**Table 1.** Continued

| References | Population | FRAX country | Study design | Follow-up (yr) | Sample characteristics | Region of interest | Sample size (females) | Mean age (yr) | Reported outcomes |
|---|---|---|---|---|---|---|---|---|---|
| Tamaki et al. (2019) [48] | Japan | Japan | P | 10 | Women aged ≥40 years, taking no medications, were randomly selected from 5-year age groups using resident registrations in seven municipalities. | Femoral neck, lumbar spine | 1,541 (1,541) | 58.1 ± 10.6 | Standard FRAX, adjusted FRAX with TBS |
| Yang et al. (2023) [40] | Taiwan | Taiwan | CS | 0 | Residents of long-term care institutions. | No BMD | 444 (126) | 82.2 ± 9.2 | Standard FRAX |
| Yu et al. (2014) [34] | China | China | P | 10.2 | Community-dwelling Chinese aged ≥65 years, able to walk independently and give informed consent. | Femoral neck | 4,000 (2,000) | 72.5 ± 5.2 | Standard FRAX, adjusted FRAX with sarcopenia |
| Yu et al. (2022) [41] | Taiwan | Taiwan | R | 3 | Patients with RA between 40–90 years, who had visited the rheumatology clinic, fulfilled the classification criteria of RA, completed BMD and >3 years follow-up. | Femoral neck, total hip, lumbar spine | 493 (421) | 59.3 ± 8.7 | Standard FRAX |

[a]Study reported bone mineral density (BMD) based area under the curve for osteoporotic fracture prediction (N=9).
FRAX, fracture risk assessment tool; R, retrospective; CC, case-control; CS, cross-sectional; P, prospective; MOF, major osteoporotic fracture; HF, hip fracture; DXA, dual energy X-ray absorptiometry; OVCF, osteoporotic vertebral compression fracture; VF, vertebral fracture; T2DM, type 2 diabetes mellitus; RA, rheumatoid arthritis; TBS, trabecular bone score.

(N=32), and Table 2 for a densitometric diagnosis of osteoporosis (N=11). Studies were from the following eleven countries: China,[12,26-37] Taiwan,[38-42] Hong Kong,[7, 43-45] Japan,[46-49] Korea,[50-53] India,[54-56] Singapore,[57-59] Thailand,[60,61] Sri Lanka,[14,62] Iran,[63] and Palestine.[64] Studies that adjusted FRAX did so with increased age,[28] reduced BMD [28], T-score measured at different sites,[52] falls,[45] TBS,[32,44,46,48,51,55,62] and sarcopenia.[34] Nine studies reported discriminative ability of BMD alone for fracture prediction, in addition to FRAX outcomes.[26,27,29,30,33,47,50,53,60] There were seven cross-sectional studies for the prediction of osteoporotic fractures based on prevalent fracture history,[26,33,40,52, 53,55,61] and five cross-sectional studies for the prediction of osteoporosis.[12,36,37,59,64] Out of 16 prospective studies that used FRAX to predict fractures, the follow-up period ranged from 2.6 to 11 years.[7,28,31,32,34,38,39,41-48,51] Some studies focused on specific populations at risk of developing secondary osteoporosis, such as patients with differentiated thyroid carcinoma after postoperative thyroid-stimulating hormone suppression therapy,[35] breast cancer,[31] diabetes,[28,32] systemic sclerosis,[53] and rheumatoid arthritis.[41,53]

## 3. Assessment of methodological quality

Evaluation of study quality is presented in Supplementary Tables and Figures. Out of the 43 studies reviewed, 9 were assessed to have a low risk of bias for participant selection, 4 for index test, 38 for reference standard, and 34 for flow and timing (Supplementary Table 2). Additionally, 37 studies for participant selection and 41 studies each for index test and reference standard were assessed to have minimal concerns regarding applicability. Twenty-two studies did not report whether patient enrolment was randomized (Supplementary Fig. 1). Out of the studies analyzed, 12 used a case-control design, indicating a higher risk of bias. Most (36 studies) did not specify if investigators were blinded to fracture status. Fractures were confirmed using established protocols in 38 studies. Out of the studies, 23 had fewer than 100 events of interest, and only 16 had sample sizes exceeding 1,000. Risk factors were primarily collected through clinical interviews (31 studies), with 4 relying on self-reports and 8 not clearly stating the information source for clinical risk factors.



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**Table 2.** Summary of main characteristics of studies that used FRAX to identify a densitometric diagnosis of osteoporosis (N=11)

| References | Population | FRAX country | Study design | Follow-up (yr) | Sample characteristics | Region of interest | Sample size (females) | Mean age (yr) | Reported outcomes |
|---|---|---|---|---|---|---|---|---|---|
| Ang et al. (2022) [57] | Singapore | Singapore | R | 0 | Postmenopausal Singaporean women aged 46–79 years referred for BMD measurement at KK Women's and Children's Hospital (never been treated for osteoporosis). | Femoral neck, lumbar spine | 188 (188) | 57.3±5.9 | Standard FRAX |
| Chandran et al. (2020) [58] | Singapore | Singapore | R | 0 | Postmenopausal community-dwelling Singaporean women aged ≥50 years, who had a DXA scan done. | Total hip, lumbar spine | 1,056 (1,056) | 59.6±7.5 | Standard FRAX |
| Cherian et al. (2018) [56] | India | India | R | 0 | Ambulatory rural postmenopausal women aged ≥50 years recruited from the Vellore district of southern India. | Femoral neck | 2,108 (2,108) | 60.9±7.6 | Standard FRAX |
| Fan et al. (2020) [12] | China | China | CS | 0 | Community-dwelling Han Beijing postmenopausal women aged ≥45 years with the ability to read and provide informed consent. | No BMD | 2,055 (2,055) | 62.1±9.1 | Standard FRAX |
| Fujimaki et al. (2022) [49] | Japan | Japan | R | 0 | Patients aged ≥40 years at their first and repeat visits, regardless of their complaints, as part of the strengthening of osteoporosis care. | Femoral neck, total hip, lumbar spine | 614 (452) | 77±9 | Standard FRAX |
| Jia et al. (2023) [35] | China | China | R (CC) | 0 | Patients with differentiated thyroid carcinoma after postoperative TSH suppression therapy for at least 6 months and unable to carry out normal activities and adhere to follow-up. Case: TSH suppression; Control: no TSH suppression with gender- and age- matched. | Total hip | 94 (58); Case: 64 (40); Control: 30 (18) | Case: 48.9±11.6; Control: 46.1±14.2 | Standard FRAX |
| Kharroubi et al. (2017) [64] | Palestine | USA | CS (CC) | 0 | Postmenopausal Palestinian women aged ≥45 years recruited from various clinics and community centres. Case: osteoporosis; Control: no osteoporosis. | Femoral neck, total hip, lumbar spine | 287 (287); Case: 83 (83); Control: 204 (204) | | Standard FRAX |
| Lekamwasam (2010) [14][a] | Sri Lanka | USA, Japan, China | R | 0 | Postmenopausal women older than 65 years and women younger than 65 years with additional risk factors for osteoporosis. | Femoral neck | 481 (481) | 57.9±8.5 | Standard FRAX |
| Liu et al. (2021) [36] | China | China | CS | 0 | Postmenopausal Chinese women aged ≥50 years randomly enrolled from community medical centres. | Femoral neck, total hip, lumbar spine | 264 (264) | | Standard FRAX |
| Logan et al. (2017) [59] | Singapore | Singapore | CS | 0 | Women aged 45–69 years attending gynaecology clinics, willing to follow study procedures and provide blood samples, with the ability to read and sign informed consent. | Lumbar spine | 512 (512) | 57±6.3 | Standard FRAX, FRAX plus |
| Zhang et al. (2018) [37] | China | China | CS | 0 | Community-dwelling elderly Han Chinese men ≥50 years, residing in Beijing ≥20 years, able to participate and read informed consent form. | Femoral neck, total hip, lumbar spine | 1,349 (0) | 65.2±8.68 | Standard FRAX |

[a]Study is repeated in Table 1.

FRAX, fracture risk assessment tool; R, retrospective; CS, cross-sectional; CC, case-control; BMD, bone mineral density; DXA, dual energy X-ray absorptiometry; TSH, thyroid-stimulating hormone.

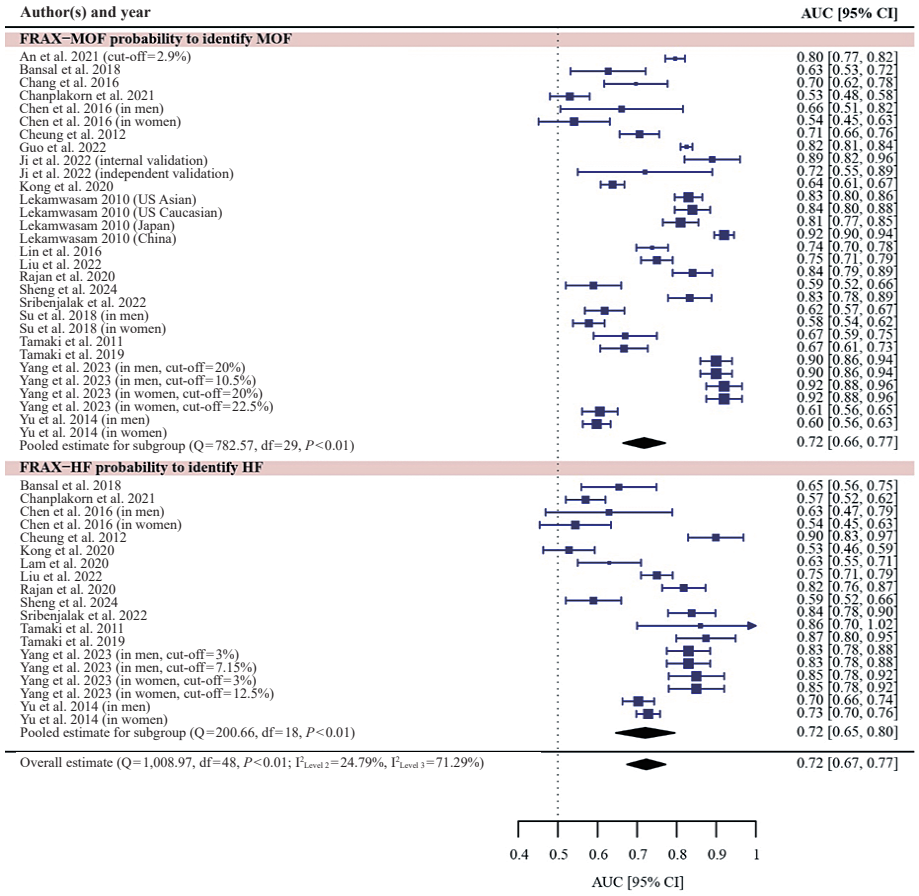


**Fig. 2.** Forest plot for the area under the curve (AUC) and 95% confidence intervals (CIs) of standard fracture risk assessment tool (FRAX) without bone mineral density in discriminating subjects with and without hip or major osteoporotic fractures. MOF, major osteoporotic fracture; HF, hip fracture.

## 4. Meta-analysis

Twenty studies reported 49 AUC values for predicting osteoporotic fractures using standard FRAX without BMD (Fig. 2). The overall pooled AUC of FRAX for the prediction of any osteoporotic fracture was 0.72 (95% CI, 0.67–0.77; Q=1,008.97; df=48; $P<0.01$), with $I^2_{Level\ 2}=24.79\%$ and $I^2_{Level\ 3}=71.29$. Subgroup analysis for the prediction using FRAX-MOF without BMD revealed an AUC of 0.72 (95% CI, 0.66–0.77; Q=782.57; df=29; $P<0.01$) and was similar to the prediction using FRAX-HF with an AUC of 0.72 (95% CI, 0.65–0.80; Q=200.66; df=18; $P<0.01$). In the additional meta-analyses conducted only for studies, where more than 10% of the sample population experienced fractures, the exclusion resulted in a lower overall pooled AUC of 0.70 (95% CI, 0.64–0.77; Q=838.24; df=30; $P<0.01$) using FRAX without BMD (Supplementary Fig. 2), compared to an AUC of 0.72 without the exclusion (Fig. 2).

Twenty-two studies reported 62 AUC values for predicting osteoporotic fractures using standard FRAX with BMD (Fig. 3). The overall pooled AUC of FRAX for the prediction of any osteoporotic fracture was 0.74 (95% CI, 0.71–0.77; Q=615.67; df=61; $P<0.01$), with variances of $I^2_{Level\ 2}=35.57\%$ and $I^2_{Level\ 3}=53.95\%$. Subgroup analysis for the prediction using FRAX-MOF with BMD revealed an AUC of 0.73 (95% CI, 0.70–0.77; Q=334.03; df=40; $P<0.01$) and an AUC of 0.77 (95% CI, 0.71–0.83; Q=150.51; df=20; $P<0.01$) for the prediction using FRAX-HF. Considering only the studies that had more than 10% of fracture events, the exclusion resulted in a lower AUC of 0.73 (95% CI, 0.68–0.77; Q=388.29; df=43; $P<0.01$) using FRAX with BMD (Supplementary Fig. 3), compared to an AUC of 0.74 without the exclusion (Fig. 3).

Twelve studies reported 36 AUC values for predicting osteoporotic fractures using adjusted FRAX (Fig. 4) with or without BMD. The overall pooled AUC of FRAX for the prediction of any osteoporotic fracture was 0.71 (95% CI, 0.66–



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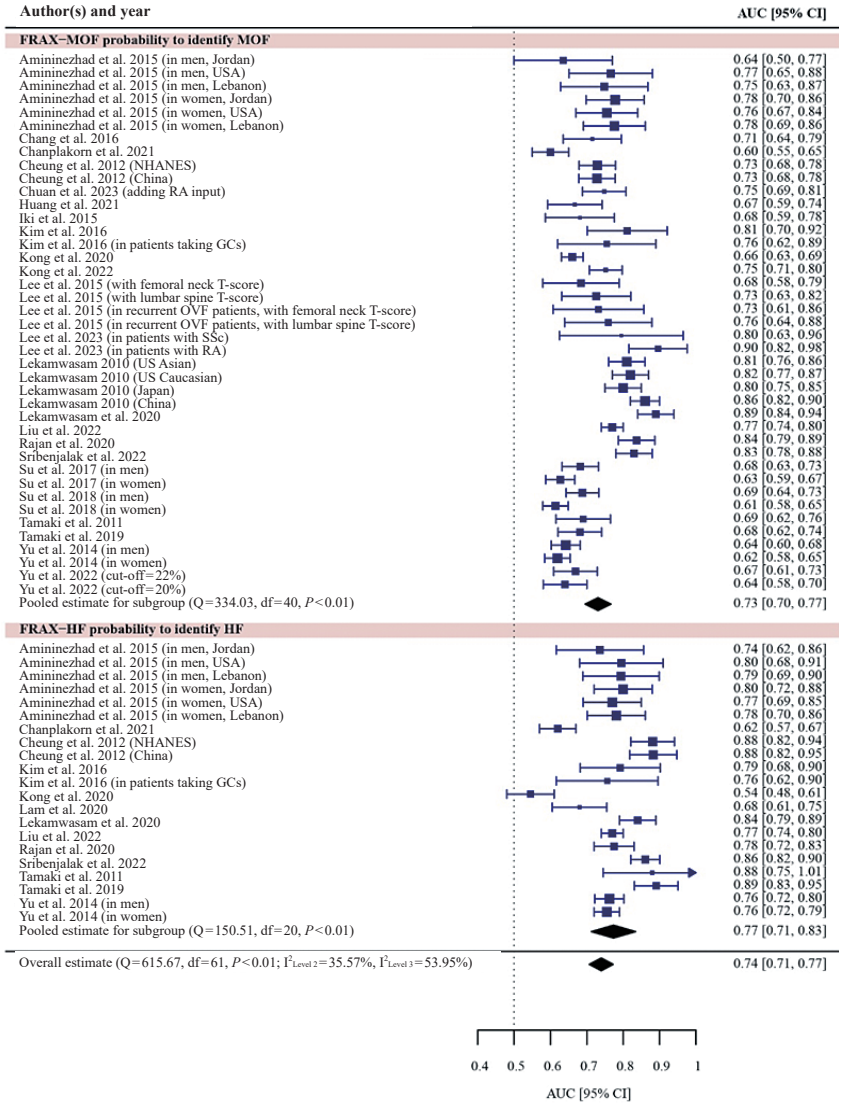


**Fig. 3.** Forest plot for the area under the curve (AUC) and 95% confidence intervals (CIs) of standard fracture risk assessment tool (FRAX) without bone mineral density in discriminating subjects with and without hip or major osteoporotic fractures. MOF, major osteoporotic fracture; NHANES, national health and nutrition examination survey; RA, rheumatoid arthritis; GCs, glucocorticoids; OVF, osteoporotic vertebral fracture; SSc, systemic sclerosis; HF, hip fracture.

0.76; Q=547.69; df=35; $P<0.01$), with an $I^2_{Level\ 2}$ of 43.97% and $I^2_{Level\ 3}$ of 49.55%. Subgroup analysis for the prediction using adjusted FRAX-MOF and FRAX-HF revealed an AUC of 0.71 (95% CI, 0.65–0.77; Q=244.34; df=25; $P<0.01$) and an AUC of 0.75 (95% CI, 0.63–0.86; Q=56.32; df=9; $P<0.01$) respectively.

Nine studies reported 24 AUC values for predicting osteoporotic fractures using BMD (Fig. 5). The overall pooled AUC of BMD for the prediction of osteoporotic fractures was 0.68 (95% CI, 0.62–0.73; Q=298.95; df=23; $P<0.01$), with variances of $I^2_{Level\ 2}$=25.76% and $I^2_{Level\ 3}$=69.05%.

Eleven studies reported 52 AUC values for identifying a densitometric diagnosis of osteoporosis using standard FRAX (Fig. 6). The overall pooled AUC using FRAX for the densitometric diagnosis of osteoporosis was 0.78 (95% CI, 0.71–0.85; Q=2,217.58; df=50; $P<0.01$), with $I^2_{Level\ 2}$=21.84% and $I^2_{Level\ 3}$=75.89%. Subgroup analysis for the prediction using FRAX-MOF revealed an AUC of 0.77 (95% CI, 0.70–0.84; Q=1,068.96; df=31; $P<0.01$) and an AUC of 0.76 (95% CI, 0.67–0.86; Q=1,127.19; df=18; $P<0.01$) using FRAX-HF. The AUC values obtained from each meta-analysis are shown in the forest plots (Fig. 2-6, Supplementary Fig. 2, 3)

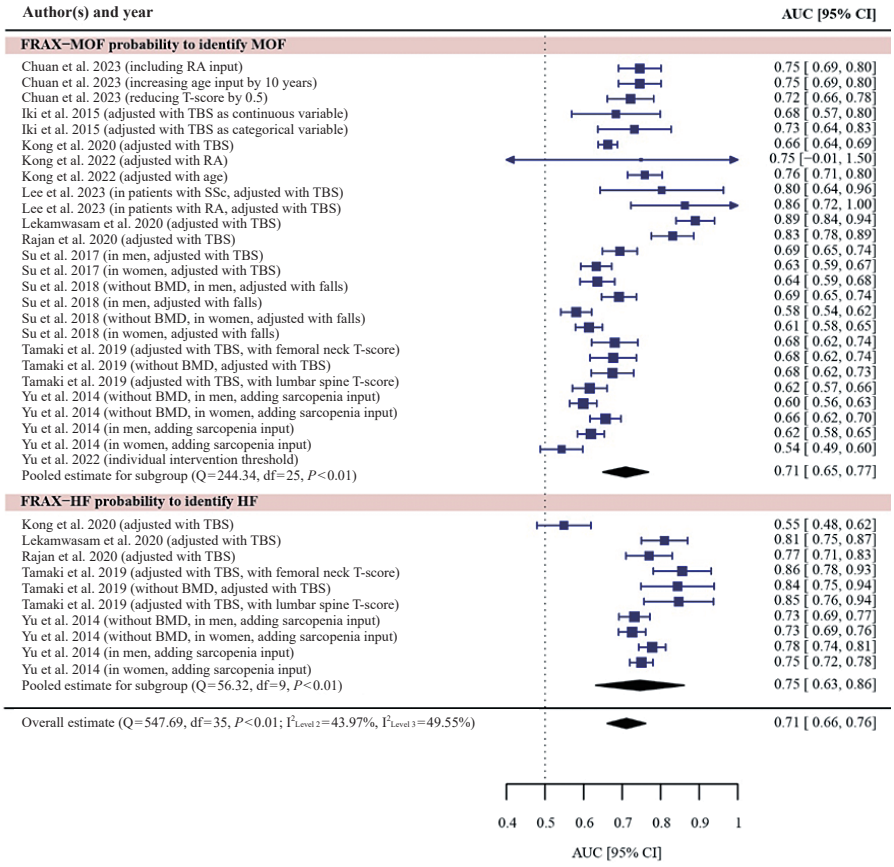


**Fig. 4.** Forest plot for the area under the curve (AUC) and 95% confidence intervals (CIs) of adjusted fracture risk assessment tool (FRAX) in discriminating subjects with and without hip or major osteoporotic fractures. MOF, major osteoporotic fracture; RA, rheumatoid arthritis; TBS, trabecular bone score; SSc, systemic sclerosis; BMD, bone mineral density; HF, hip fracture.

and were also tabulated according to the predictive outcomes and tools used (Table 3).

## DISCUSSION

In this review, our primary objective was to assess the discriminatory power of FRAX in terms of predicting future fractures in Asian populations. The findings from our systematic review and meta-analysis suggest that FRAX may not perform as well in Asian populations, as it has been observed to do in meta-analyses conducted in Caucasian populations.[9,10] A systematic review encompassing 47 Caucasian and 6 Asian populations found that the discriminative ability of FRAX-MOF without BMD was 0.77 (95% CI, 0.73–0.80) and with BMD was 0.78 (95% CI, 0.75–0.81).[9] FRAX-HF, on the other hand, had an AUC of 0.75 (95% CI, 0.72–0.79) without BMD and 0.79 (95% CI, 0.77–0.81) with BMD.[9] These findings suggest that the AUC values were comparatively lower for both FRAX-MOF (AUC of 0.72 without BMD and 0.73 with BMD) and FRAX-HF (AUC of 0.72 without BMD and 0.77 with BMD) in Asian populations. The scarcity of FRAX calibration data for Asian populations highlights potential limitations in its predictive ability across diverse Asian ethnic groups.[65]

The reduction in discriminative power was more pronounced when only considering studies with over 10% of fracture cases in their sample populations. While there was no change in AUC for FRAX-MOF with BMD, subgroup analysis showed a 1-point decrease in AUC for FRAX-MOF without BMD. Additionally, the AUC for FRAX-HF showed a 4-point decrease without BMD and a 2-point decrease with BMD. Highly imbalanced data, like the occurrences of fracture events, represents a true clinical challenge. Several studies included in our review reported fracture events below 10% among their study populations.[7,28,31,32,38,39,44-48,51,54,61] Therefore, this demonstrates the necessity


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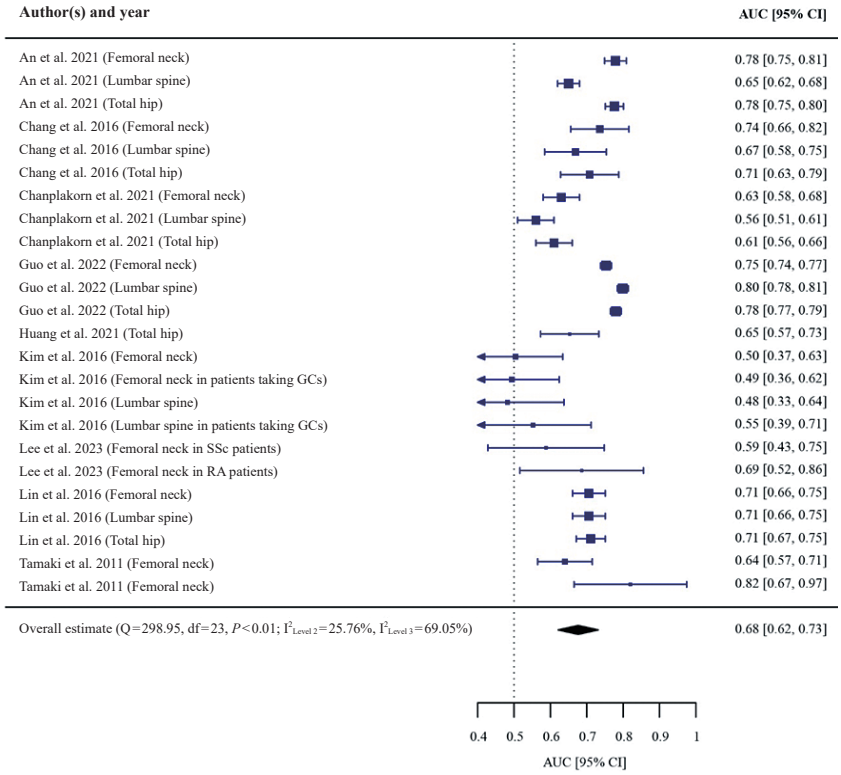


**Fig. 5.** Forest plot for the area under the curve (AUC) and 95% confidence intervals (CIs) of bone mineral density alone in discriminating subjects with and without fractures. GCs, glucocorticoids; SSc, systemic sclerosis; RA, rheumatoid arthritis.

for cautious interpretation of findings from such studies when establishing the reliability of FRAX in predicting fracture risk.

This review also found that FRAX demonstrated superior discriminatory performance compared to BMD alone in identifying individuals at risk of fractures. In fact, our review suggests that it may exhibit stronger, albeit moderate, predictive capabilities for identifying a densitometric diagnosis of osteoporosis in Asian populations. This could be attributed to the limitations of BMD as a two-dimensional measure of bone health,[66] whereas FRAX incorporates clinical risk factors that provide a more comprehensive assessment. Caution should be exercised when using FRAX to identify a densitometric diagnosis of osteoporosis, as it was originally developed for assessing fracture probability. Nonetheless, FRAX may be useful in guiding treatment decisions in resource-constrained settings with limited availability of DXA machines, particularly in some Asian countries, offering a practical alternative for identifying high-risk individuals.[14,56]

Our review indicates that FRAX with BMD tends to perform more reliably in predicting HF (AUC=0.77) compared to MOF (AUC=0.73). FRAX without BMD had the same AUC of 0.72 for both HF and MOF with a wider 95% CI for FRAX-HF indicating greater uncertainty of FRAX in predicting HFs in the absence of BMD. It is worth noting that in FRAX calculations where BMD is integrated, the femoral neck is typically utilized as the measurement site. Lumbar spine BMD could offer a modest improvement in predicting vertebral and potentially also MOF, though more research is needed to confirm these findings.[67]

FRAX was initially validated using 11 Caucasian and 1 Japanese cohort studies, with participants aged between 50 and 65 years.[17] This demographic skew might contribute to the underestimation of fracture risk in individuals above 65 years of age. For instance, a study conducted in Hong Kong revealed that FRAX failed to predict fracture risk accurately in the oldest age group (>80 years).[43] The National Health and Nutrition Examination Survey (NHANES) proposes fixed intervention cut-offs of 20% for MOF and 3% for HFs prediction. However, studies indicate that FRAX might underestimate fracture risk in certain Asian sub-

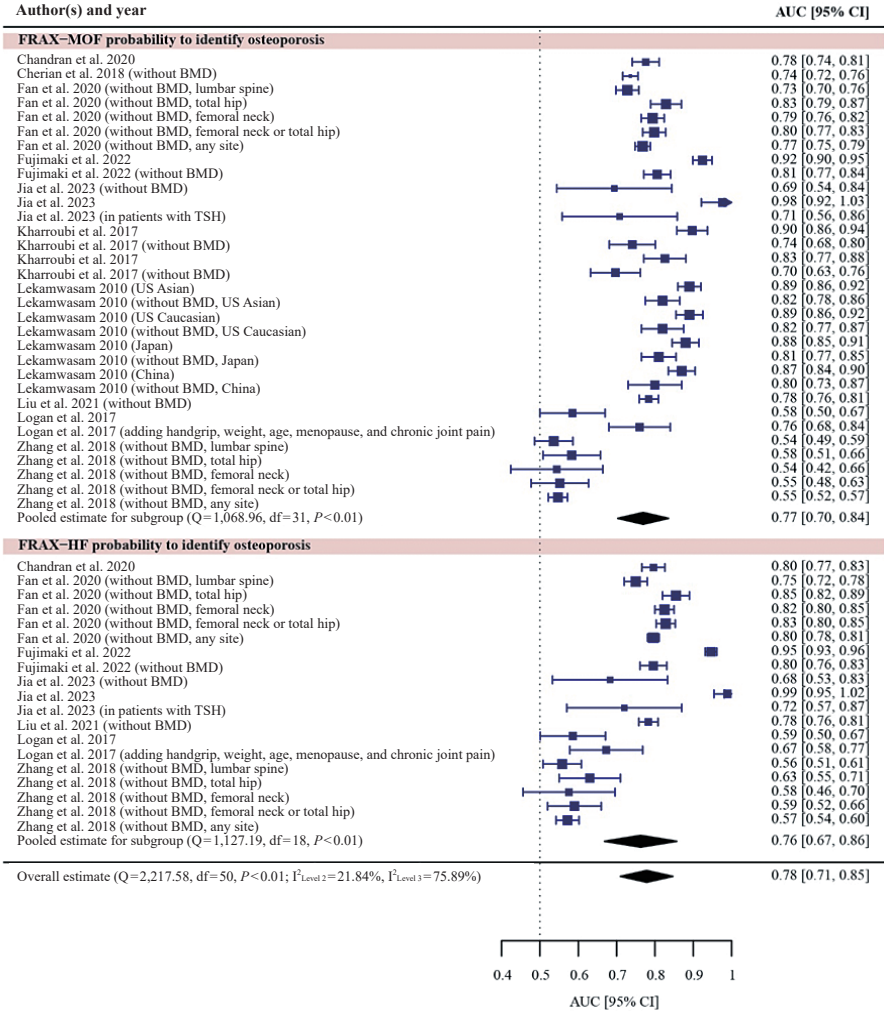


**Fig. 6.** Forest plot for the area under the curve (AUC) and 95% confidence intervals (CIs) of adjusted fracture risk assessment tool (FRAX) in discriminating subjects with and without hip or major osteoporotic fractures. MOF, major osteoporotic fracture; BMD, bone mineral density; HF, hip fracture; TSH, thyroid-stimulating hormone.

groups due to the utilization of a single cut-off point. This approach could classify almost all individuals above 70 years as high risk solely based on age, which is a significant risk factor.[54] To establish appropriate and accurate cut-offs, various factors such as the cost of DXA, consultation fees, medication costs, and cost-effectiveness need careful consideration.[58] While the majority of studies used the fixed intervention cut-offs proposed by NHANES,[7,14,28,31,32,34,38,40,41,43,46-48,50-52,57,63] some studies have evaluated the cut-offs based on the Youden's Index and used these optimal cut-offs to determine the accuracy of FRAX.[12,26,27,29,30,33,35-37,39-42,44,45,49,54-56,58-62,64] Table 4 provides the recommended FRAX cut-off values for various countries to assess fracture risk. Studies reviewed for Japan and Korea utilized NHANES cut-offs for predicting fracture risk. In China, the recommended FRAX-MOF cut-off values ranged between 2.9% and 3.6%, with one study suggesting a cut-off of 9.25%.[30] This high cut-off of 9.25% could have resulted from the high risk of bias in patient selection and unclear applicability of the FRAX.[30] In India, the recommended cut-offs ranged between 9% and 10.5% for FRAX-MOF and between 2.5% and 3.5% for FRAX-HF.[54,55] There was only one study from Sri Lanka that recommended a cut-off of 9% for FRAX-MOF and 2.7% for FRAX-HF.[62] In Thailand, the recommended cut-offs for FRAX-MOF ranged from 8.9% to 10%, while for FRAX-HF they ranged from 3% to 4.9%.[60,61] In Hong Kong, two studies recommended a cut-off for FRAX-MOF


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**Table 3.** Subgroup area under the curve estimates (95% confidence interval) for FRAX-MOF, FRAX-HF, and overall area under the curve estimates (95% confidence interval) for all fractures obtained from meta-analysis

| Prediction type | Prediction tool | FRAX-MOF | FRAX-HF | All fractures |
|---|---|---|---|---|
| Fracture prediction | Standard FRAX without BMD | 0.72 (0.66–0.77) | 0.72 (0.65–0.80) | 0.72 (0.67–0.77) |
| | Standard FRAX (≥10% cases in study population) without BMD | 0.71 (0.63–0.78) | 0.68 (0.57–0.78) | 0.70 (0.64–0.77) |
| | Standard FRAX with BMD | 0.73 (0.70–0.77) | 0.77 (0.71–0.83) | 0.74 (0.71–0.77) |
| | Standard FRAX (≥10% cases in study population) with BMD | 0.73 (0.67–0.78) | 0.75 (0.69–0.81) | 0.73 (0.68–0.77) |
| | Adjusted FRAX | 0.71 (0.65–0.77) | 0.75 (0.63–0.86) | 0.71 (0.66–0.76) |
| | BMD alone | - | - | 0.68 (0.62–0.73) |
| Osteoporosis | Standard FRAX | 0.77 (0.70–0.84) | 0.76 (0.67–0.86) | 0.78 (0.71–0.85) |

FRAX, fracture risk assessment tool; MOF, major osteoporotic fracture; HF, hip fracture; BMD, bone mineral density.

**Table 4.** Country-specific recommended FRAX cut-offs for identifying individuals at high fracture risk by the included studies

| References | Country | Follow-up time (yr) | FRAX-MOF without BMD (%) | FRAX-MOF with BMD (%) | FRAX-HF without BMD (%) | FRAX-HF with BMD (%) |
|---|---|---|---|---|---|---|
| An et al. (2021) [26] | China | 0 | 2.9 | - | - | - |
| Chang et al. (2016) [27] | China | 0 | 2.8 | 3.3 | - | - |
| Guo et al. (2022) [29] | China | 0 | 3.6 | - | - | - |
| Huang et al. (2021) [30] | China | 0 | - | 9.25 | - | - |
| Lin et al. (2016) [33] | China | 0 | 2.9 | - | - | - |
| Bansal et al. (2018) [54] | India | 0 | 10.5 | - | 3.5 | - |
| Rajan et al. (2020) [55] | India | 0 | 9 | - | 2.5 | - |
| Lekamwasam et al. (2020) [62] | Sri Lanka | 0 | - | 9 | - | 2.7 |
| Liu et al. (2022) [39] | Taiwan | 6.8 | - | 9.5 | - | 4 |
| Sheng et al. (2024) [42] | Taiwan | 11 | 16 | - | 3.14 | - |
| Yang et al. (2023) [40] | Taiwan | 0 | Male: 10.5; Female: 22.5 | | Male: 7.15; Female: 12.5 | |
| Yu et al. (2022) [41] | Taiwan | 0 | - | 22 | - | - |
| Chanplakorn et al. (2021) [60] | Thailand | 0 | - | 10 | - | 3 |
| Sribenjalak et al. (2022) [61] | Thailand | 0 | 9.8 | 8.9 | 4.9 | 4 |
| Su et al. (2017) [44], Su et al. (2018) [45] | Hong Kong | Male: 9.94; Female: 8.82 | - | Male: 12.5; Female: 15 | - | - |

FRAX, fracture risk assessment tool; MOF, major osteoporotic fractures; HF, hip fractures; BMD, bone mineral density.

of 12.5% for men and 15% for women.[44,45] The recommended cut-offs from Taiwan had the widest variability and ranged between 9.5% and 22.5% for FRAX-MOF and between 3.14% and 12.5% for FRAX-HF,[39-42] which could be attributed to the difference in follow-up times and sample population characteristics. Additionally, two studies from Taiwan compared the AUC for FRAX-MOF using NHANES cut-offs and recommended cut-offs.[40,41] The first study showed an increase in AUC with the recommended cut-off compared to the NHANES cut-off,[41] while the second study reported improved sensitivity and specificity for FRAX-MOF at the recommended cut-off, whilst maintaining the same AUC as the NHANES cut-off. [40] This variability in recommended cut-offs demonstrates the need for more standardized studies for better comparability. Also, the diverse recommendations across these studies emphasize the need to tailor FRAX cut-offs to the specific demographic characteristics and prevalent risk factors of each country. Interestingly, a recent study explored individual intervention thresholds (IIT) by comparing fracture risk with a comparator score derived solely from the history of osteoporotic fracture.[41] If the actual risk was higher than the comparator score, the fracture risk was deemed to be higher than or equal to the IIT score. However, the study also found that intervention thresholds determined by Youden's Index remained more accurate

than both IIT and fixed intervention thresholds suggested by NHANES.[41] Although this study focused on rheumatoid arthritis patients, it highlights the need for further investigation to establish optimal cut-offs for fracture risk assessment.

While FRAX incorporates multiple risk factors beyond BMD, such as age, gender, previous fracture history, and other clinical risk factors, these risk factors may not universally apply to all populations. Therefore, its widespread adoption could be limited, affecting its suitability for large-scale screening and community-level applications.[26] Many studies emphasize the importance of considering ethnic-specific risk factors and population characteristics when using FRAX. The effectiveness of FRAX in predicting fracture risk in Asian populations may vary due to differences in lifestyle factors, genetic predispositions, and bone structure. Firstly, alcohol use is limited in Asian countries and may be less relevant as a risk factor.[47,68] Incorporating handgrip strength, weight, age, postmenopausal status, and chronic joint pain yielded a more accurate model (AUC of 0.84) compared to the standard FRAX tool for identifying a densitometric diagnosis of osteoporosis.[59] Secondly, integrating genetic and physiological differences, such as fracture susceptibility due to varying physical activity patterns,[69,70] along with incorporating biomarkers like TBS,[71,72] using local epidemiological data for calibration, and conducting long-term cohort studies in specific ethnic groups, is crucial for refining FRAX's predictive capabilities.

Some studies have also demonstrated improved fracture prediction accuracy using machine learning approaches in combination with FRAX.[31,51] This advancement often leverages data from wearable health technologies or utilizes advanced imaging techniques and post-processing methods to refine predictions. Structural biomarkers computed from finite element models based on computed tomography (CT) imaging have been shown to be more effective at predicting osteoporotic fractures, compared to BMD.[73,74] Advances in automatic CT scan segmentation using machine learning algorithms have also made the evaluation of these structural biomarkers computationally efficient and clinically feasible.[75] A recent study on a Swedish cohort has demonstrated an improved AUC of bone strength computed from finite element modeling based on DXA images over BMD for predicting HFs.[76] Future research with larger samples could help validate the inclusion of structural biomarkers such as bone strength in the FRAX algorithm to enhance fracture prediction accuracy.

This review has certain limitations that warrant consideration. First, while we compared the AUC values of FRAX, assessing the sensitivity and specificity of FRAX would have provided valuable insights. However, reported sensitivity and specificity values were limited, making meta-analyses infeasible. Additionally, studies were either cross-sectional or longitudinal in nature. However, it is crucial to acknowledge that fracture risk estimated by FRAX can only be accurately evaluated in studies with long-term follow-up. Correlations drawn from cross-sectional studies or studies with less than 10 years of follow-up may not fully capture the predictive ability of FRAX, especially considering that FRAX is designed to estimate 10-year fracture probability. Therefore, incorporating weightage based on study design and follow-up duration could potentially provide a more accurate estimation of the predictive ability of FRAX.

In conclusion, despite its limitations, FRAX remains a valuable tool, particularly in regions where guidelines for managing osteoporotic fractures are lacking. However, given that this review shows FRAX performs less effectively in Asian populations, its use requires careful attention to ethnic-specific factors, validation studies, and potential modifications to enhance its accuracy and usefulness in clinical settings. While FRAX exhibits better discrimination ability for osteoporosis, its effectiveness in predicting osteoporotic fractures in Asia remains uncertain. Future research endeavours should prioritise refining fracture risk assessment tools to enhance prediction accuracy so that ultimately, the burden of osteoporotic fractures in Asian communities can be alleviated.

## DECLARATIONS

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## Ethics approval and consent to participate

Not applicable.

## Conflict of interest

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

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