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Diagnostic accuracy of FRAX in predicting the 10-year risk of osteoporotic fractures using the USA treatment thresholds: A systematic review and meta-analysis☆

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ABSTRACT

Objectives: The aim of this study was to conduct a systematic review and meta-analysis on the performance of the WHO's Fracture Risk Assessment (FRAX) instrument in predicting 10-year risk of Major Osteoporotic Fractures (MOF) and Hip Fractures (HF), using the USA treatment thresholds, in populations other than their derivation cohorts.

Design: EMBASE and MEDLINE database were searched with search engine PubMed and OVID as well as Google Scholar for the English-language literature from July 2008 to July 2016. Limiting our search to articles that analyzed only MOF and/or HF as an outcome, 7 longitudinal cohorts from 5 countries (USA, Poland, France, Canada, New Zealand) were identified and included in the meta-analysis. SAS NLMIXED procedure (SAS v 9.3) was applied to fit the Hierarchical Summary Receiver Operating Characteristics (HSROC) model for meta-analysis. Forest plot and HSROC plot was generated by Review Manager (RevMan v 5.3).

Results: Seven studies (n = 57,027) were analyzed to assess diagnostic accuracy of FRAX in predicting MOF, using 20% as the 10-year fracture risk threshold for intervention, the mean sensitivity, specificity, and diagnostic odds ratio (DOR) along with their 95% confidence intervals (CI) were 10.25% (3.76%–25.06%), 97.02% (91.17%–99.03%) and 3.71 (2.73–5.05), respectively. For HF prediction, using 3% as the 10-year fracture risk threshold, six studies (n = 50,944) were analyzed. The mean sensitivity, specificity, and DOR along with their 95% confidence intervals (CI) were 45.70% (24.88%–68.13%), 84.70% (76.41%–90.44%) and 4.66 (2.39–9.08), respectively.

Conclusions: Overall, using the 10 year intervention thresholds of 20% for MOF and 3% for HF, FRAX performed better in identifying patients who will not have a MOF or HF within 10 years, than those who will. A substantial number of patients who developed fractures, especially MOF within 10 years of follow up, were missed by the baseline FRAX assessment.

1. Introduction

As one of major public health threats, osteoporotic fracture contributes significantly to nursing home, and extended care facility admissions [1]. The lifetime risk for a distal forearm, hip, or vertebral fracture is 40% for white women aged 50 years and older and 13% for white men [2]. Due to the increase in the life expectancy of the world population, the number of individuals living with osteoporosis, the

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prevalence of osteoporotic fractures, and subsequent costs will continue to rise [3–6]. Due to the morbid consequences of osteoporotic fracture, a valid fracture risk prediction instrument is critical for early intervention and prevention of this disease.

In 2008, The World Health Organization (WHO) task force developed the Fracture Risk Assessment Tool (FRAX) to identify individuals without osteoporosis who are at risk of suffering a Major Osteoporotic Fracture (MOF) and/or Hip Fractures (HF) in the next 10 years [7]. The developers of FRAX limited the number and complexity of risk factors and selected only well-recognized independent contributors identified from studying population-based cohorts from Europe, North America, Asia and Australia [8]. The USA treatment guidelines were revised and updated by the National Osteoporosis Foundation (NOF) based on a cost-effectiveness analysis by Tosteson et al. in 2008, in order to minimize the probability of overtreatment caused by the previous NOF treatment guideline [9]. Pharmacological intervention should be considered if a FRAX calculated 10-year probability of a hip fracture ≥3% or a 10-year probability of a major osteoporosis-related fracture (clinical spine, forearm, hip or shoulder fracture) ≥20%. In other countries, FRAX does not tell clinicians who to treat, instead, it remains a matter of clinical judgement that are based on expert opinion and/or on health economic grounds [7]. Thus far, several large population-based cohort studies have been conducted to assess the validity of aforementioned USA treatment threshold in predicting 10 year HF or MOF risk. We aim to conduct a meta-analysis on the performance of the FRAX instrument using USA treatment threshold for predicting 10-year risk of MOF and HF in populations other than FRAX derivation cohorts.

2. Methods

2.1. Sources

EMBASE and MEDLINE database were searched with search engine PubMed and OVID as well as Google Scholar for the English language literature from July 2008 to July 2016 using the following search terms: FRAX, FRAX accuracy, Fracture prediction, Osteoporotic fracture. In addition, we manually searched the reference lists of relevant review articles but did not identify additional articles.

2.2. Study selection

The literature search was conducted independently by two authors (XJ and MG) to identify the studies that met the following inclusion criteria: (1) written in English; (2) quantitative assessment conducted for the proper identification of individuals at risk for osteoporotic fractures (MOF or HF) using FRAX-USA treatment threshold, with true positive and true negative values reported. If only AUC was reported in article, the attempt was made to contact authors to retrieve the true positive and true negative values, otherwise, the studies were excluded.

2.3. Analysis

The quality of included studies was assessed with the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) tool (Table 1) [10]. The primary outcomes assessed were MOF or HF. Heterogeneity of estimated effects across studies was assessed by Cochran's Q test and I^2 statistics to determine the suitability of the studies to be pooled for the meta-analysis. Between-study heterogeneity was considered significant for $P < 0.10$ [11].

The relatively small number of studies in this meta-analysis makes it difficult to determine publication bias by visual inspection of a funnel plot; hence, a normal quantile plot was used for the assessment of potential publication bias. Most effect size data points falling at or near a straight oblique line and within the 95% confidence bands in a normal quantile plot would suggest no evidence of severe publication bias [12]. The Hierarchical Summary Receiver Operating Characteristics (HSROC) and Forest plot were generated by Reviewer Manager (RevMan v. 5.3). HSROC was used because the studies have moderate heterogeneity. The diagnostic accuracy of FRAX was assessed using SAS NLMIXED procedure (SAS v. 9.3).

3. Results

Our literature search identified 60 articles. After abstract review, 42 were deemed not relevant to the scope of our analysis. Therefore, 18 full manuscripts were retrieved and reviewed, and 7 were included in the meta-analysis (Fig. 1). The studies chosen were 7 longitudinal cohorts from 5 countries (USA, Poland, France, Canada, and New Zealand) [13–19]. Quality characteristics of selected studies were described in Table 2.

As is shown in the normal quantile plots, Figs. 2 and 3, all effect size data points for the 7 longitudinal studies are within 95% confidence bands, therefore, no evidence of severe publication bias was detected for MOF or HF. The statistical testing for heterogeneity shows that included studies were moderately heterogeneous for both MOF ($Q = 13.4$, $P = 0.04$, $I^2 = 55\%$) and HF ($Q = 11.1$, $P = 0.05$, $I^2 = 55\%$). Therefore, random effect model was applied for effect size calculation.

For MOF prediction, seven studies ($n = 57{,}027$) were analyzed to assess the diagnostic accuracy of FRAX using 20% as the 10-year fracture risk threshold, the mean sensitivity, specificity, and diagnostic odds ratio (DOR) along with their 95% confidence intervals (CI) are 10.25% (3.76%–25.06%), 97.02% (91.17%–99.03%), and 3.71 (2.73–5.05), respectively (Fig. 4).

For HF prediction, six studies ($n = 50, 944$) were analyzed using 3% as the 10-year fracture risk threshold. The mean sensitivity, specificity, and DOR along with their 95% confidence intervals (CI) are 45.70% (24.88%–68.13%), 84.70% (76.41%–90.44%), and 4.66 (2.39–9.08), respectively (Fig. 4).

Table 1
Assessment of selected studies for risk of bias and applicability concerns.

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Bolland [13]	☺	?	☺	☺	☺	☺	☺
Leslie [14]	?	☺	☺	?	☺	☺	☺
Fraser [15]	☹	☺	☺	?	☺	☺	☺
Ensrud [16]	?	?	?	☺	☺	☺	☺
Sornay-Rendu [17]	☺	?	?	?	☺	☺	☺
Pluskiewicz [18]	?	☺	?	?	☺	☺	☺
Tremollieres [19]	☺	☺	?	☺	☺	☺	☺

☺ low risk, ☹ high risk, ? unclear risk.

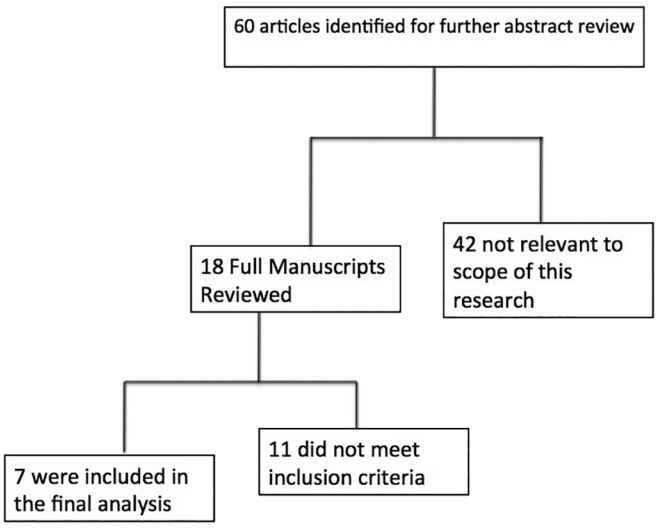


Fig. 1. Graphical outline of the selection strategy of literature review process for the meta-analysis.

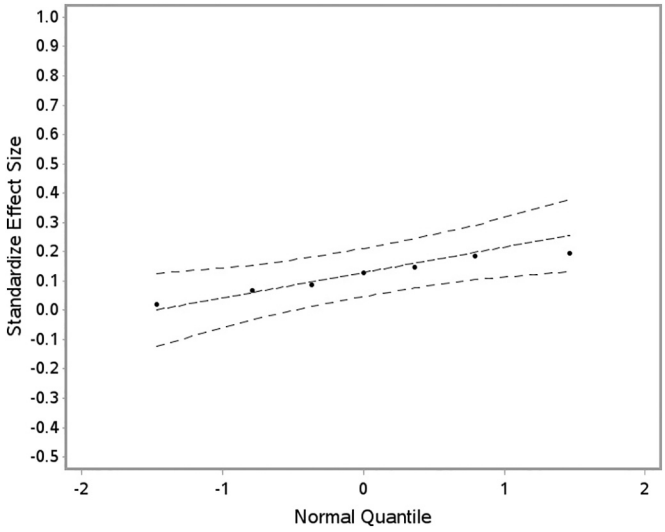


Fig. 2. Quantile plot for Major Osteoporotic Fracture (MOF) as a study outcome.

The HSROC plot of FRAX in predicting the 10-year risk of MOF using 20% as an intervention threshold portrays that the test has low sensitivity, high specificity, and a small confidence interval as can be determined using Fig. 5. The results are more precise than for HF. Compared with HF prediction, the meta-analysis shows that FRAX with NOF treatment thresholds for detecting treatment candidates seems to be more reproducible and generalizable for MOF prediction. The HSROC plot of FRAX to predict Hip Fractures within 10 years using 3% as an intervention threshold portrays that the test has moderate sensitivity, high specificity, but has a larger confidence region and is therefore less precise (Fig. 6).

4. Discussion

To our knowledge, the current study is the first systemic review and meta-analysis on the performance of the WHO's Fracture Risk Assessment (FRAX) tool for predicting 10-year risk of Major Osteoporotic

Table 2
Quality characteristics of the studies included in the meta-analysis.

Study author/year	Country	Study design	Outcome	Sample size at baseline/complete	Mean age	Observed fracture	Predicted future	Outcome determinate	Treatment at baseline (B) and follow up (FU)
Bolland [13]	New Zealand	Prospective	MOF	1471/1422	74 ± 4.2	229	69	Initial: radiograph Extension: self report	B: no FU: 20% bisphosphonates
Leslie [14]	Canada	Prospective	MOF	/39,603	W: 65.7 ± 9.8 M: 68.2 ± 10.1	2543	4219	Diagnoses, procedure codes	B: no FU: no
Fraser [15]	Canada	Prospective	MOF	/6697	W: 65.8 ± 8.8 M: 65.3 ± 9.1	635	495	Self report with confirmation	B: no FU: no
Ensrud [16]	United States	Prospective	MOF	6252/6035	71.3	1037	1368	Self report & radiograph confirmation	B: no FU: no
Sornay-Rendu [17]	France	Prospective	MOF	1039/846	Post: 62 ± 9 Pre: 47.2 ± 5	81	37	Self report with confirmation	B: 127 women HRT FU: 127 women HRT
Pluskiewicz [18]	Poland	Prospective	MOF	770/718	68.5 ± 8.8	48	3	Self report with confirmation	B: anti-resorptive therapy FU: some on anti-resorptive therapy
Trémollieres [19]	France	Prospective	MOF	4024/1706	54 ± 4	129	6	Self report with confirmation	B: PHT, calcium, vit. D FU: no
Bolland [13]	New Zealand	Prospective	Hip	1471/1422	74 ± 4.2	57	439	Initial: radiograph Extension: self report	B: no FU: 20% bisphosphonates
Leslie [14]	Canada	Prospective	Hip	/39603	W: 65.7 ± 9.8 M: 68.2 ± 10.1	549	11,243	Diagnoses, procedure codes	B: no FU: no
Fraser [15]	Canada	Prospective	Hip	/6697	W: 65.8 ± 8.8 M: 65.3 ± 9.1	157	1415	Self report with confirmation	B: no FU: no
Sornay-Rendu [17]	France	Prospective	Hip	/798	Post: 62.0 ± 9 Pre: 47.2 ± 5	17	101	Self report with confirmation	B: 127 women HRT FU: 127 women HRT
Pluskiewicz [18]	Poland	Prospective	Hip	770/718	68.5 ± 7.9	3	74	Self report with confirmation	B: anti-resorptive therapy FU: some on anti-resorptive therapy
Trémollieres [19]	France	Prospective	Hip	4024/1706	54 ± 4	11	107	Self report with confirmation	B: PHT, calcium, vit D. FU: no

All studies use the standard NOF treatment thresholds of >20% and 3% for 10 year risk of MOF and HF, respectively.
Post: Postmenopausal. Pre: Pre-menopausal.

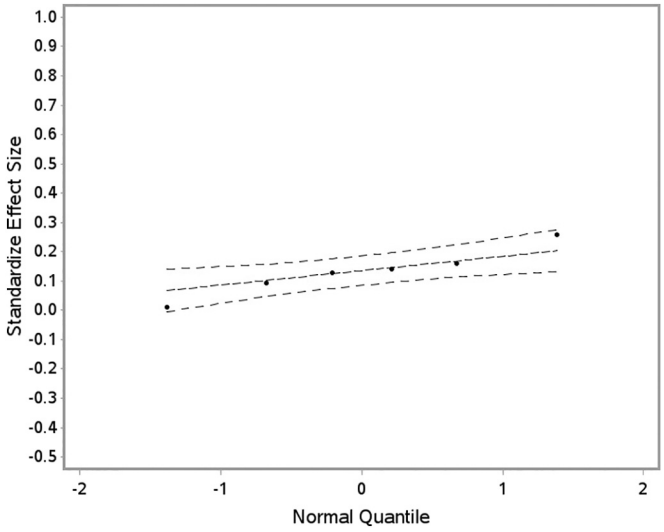


Fig. 3. Quantile plot for Hip Fracture (HF) as a study outcome.

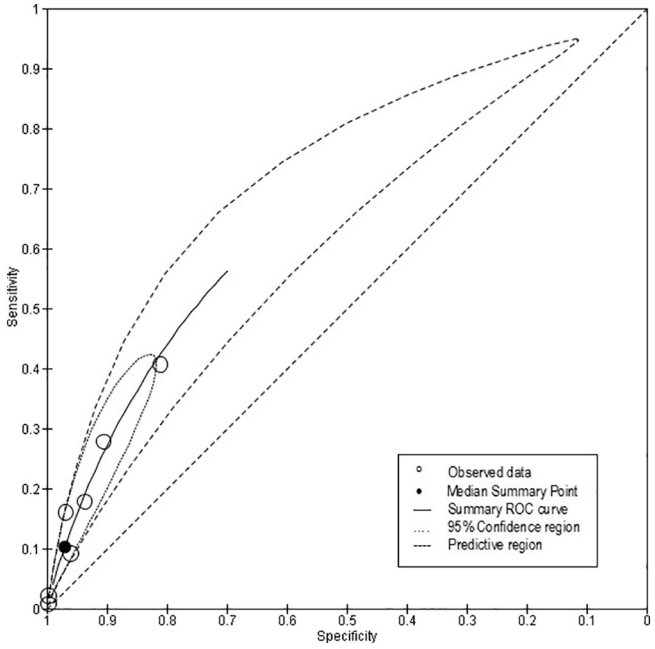


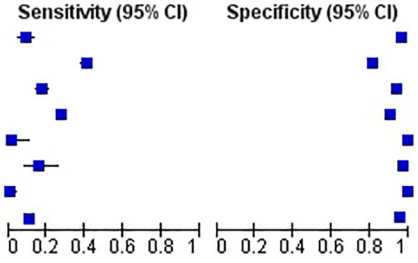
Fig. 5. HSROC plot of FRAX is the prediction of 10-year risk of MOF using 20% as an intervention threshold.

Fractures (MOF) and Hip Fractures (HF) in populations other than their derivation cohorts. Seven studies were analyzed to assess the diagnostic accuracy of FRAX with NOF guideline treatment thresholds in predicting MOF using 20% of 10-year MOF risk as a treatment threshold, whereas 6 studies were analyzed using 3% of 10-year HF risk as a treatment threshold. Our data demonstrate that FRAX with NOF treatment thresholds favors specificity over sensitivity while predicting 10-year risk for both MOF and HF. As can be seen, the summary estimate for sensitivity in predicting MOF is 10%, and for HF is 46%, however, summary estimates for specificity in predicting MOF and HF are 97% and 85%, respectively. While assessing the superiority of diagnostic test based on sensitivity and specificity, clinical implication of false positive or false negative results shall be taken into account, in other words, how to proceed with clinical management in response to positive test results should be an essential component of assessment. If a positive test result is intended to identify disease population for treatment, several questions need to be addressed while assessing the clinical validity of a test: 1. whether the treatment is invasive and/or expensive. 2. what is the risk of treatment on misdiagnosed otherwise healthy population? 3. what is the severity of clinical consequence while the test fails to detect a disease?

The NOF guideline limited the use of FRAX to patients with low bone mass for 10-year risk prediction of MOF and HF, offering both clinicians and patients information that could be considered during the treatment decision making process. The FRAX-USA defines 10-year risk of 20% for MOF and 3% for HF as a treatment threshold. Treatment strategies involves early pharmacological intervention to prevent fractures. Due to lack of more accurate fracture prediction tools, both over-treatment and under-treatment of osteoporosis for fracture prevention are compelling challenges clinicians are currently facing worldwide. While a fracture prediction tool offering both high sensitivity and high specificity does not currently exist for treatment guidance, a tool favoring high

Major Osteoporotic Fracture (20 %)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bolland 2011	21	48	208	1145	0.09 [0.06, 0.14]	0.96 [0.95, 0.97]
Ensrud 2009	422	946	615	4052	0.41 [0.38, 0.44]	0.81 [0.80, 0.82]
Fraser 2011	113	382	522	5680	0.18 [0.15, 0.21]	0.94 [0.93, 0.94]
Leslie 2010	707	3512	1836	33548	0.28 [0.26, 0.30]	0.91 [0.90, 0.91]
Pluskiewicz 2015	1	2	47	668	0.02 [0.00, 0.11]	1.00 [0.99, 1.00]
Sornay-Rendu 2010	13	24	68	741	0.16 [0.09, 0.26]	0.97 [0.95, 0.98]
Tremollieres 2010	1	5	128	1572	0.01 [0.00, 0.04]	1.00 [0.99, 1.00]
Pooled					0.10 [0.04, 0.25]	0.97 [0.91, 0.99]



Hip Fracture (3 %)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bolland 2011	26	382	31	983	0.46 [0.32, 0.59]	0.72 [0.70, 0.74]
Fraser 2011	99	1316	58	5224	0.63 [0.55, 0.71]	0.80 [0.79, 0.81]
Leslie 2010	425	10818	124	28236	0.77 [0.74, 0.81]	0.72 [0.72, 0.73]
Pluskiewicz 2015	1	73	2	642	0.33 [0.01, 0.91]	0.90 [0.87, 0.92]
Sornay-Rendu 2010	12	89	5	692	0.71 [0.44, 0.90]	0.89 [0.86, 0.91]
Tremollieres 2010	1	106	10	1589	0.09 [0.00, 0.41]	0.94 [0.92, 0.95]
Pooled					0.46 [0.25, 0.69]	0.85 [0.76, 0.90]

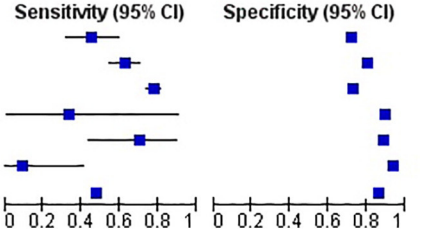


Fig. 4. Forest plots of sensitivity and specificity of FRAX in the prediction of 10-year risk of MOF and HF.

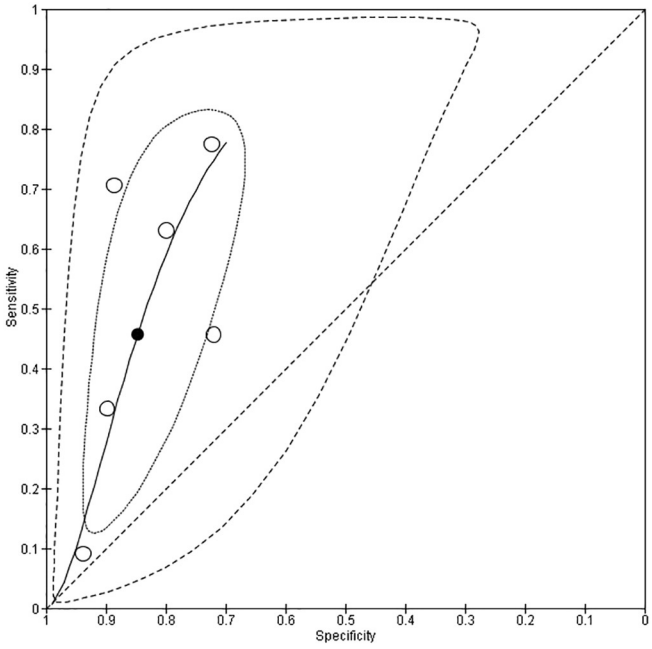


Fig. 6. HSROC plot of FRAX is prediction of 10-year risk of HF using 3% as an intervention threshold.

sensitivity (low number of false negative [FN]) is preferred. Sensitivity is calculated by dividing the number of true positive (TP) by the number of disease (TP + FN), low summary estimate for sensitivity (10%) of FRAX in predicting MOF means 90% of disease or individuals who will be suffering from a MOF within 10 years were not detected by FRAX as treatment candidates. Caution should be exercised while interpreting summary sensitivity (46%) for HF risk prediction, due to higher heterogeneity between studies that can be easily visualized in forest plot (Fig. 4) and HSROC curve (Figs. 5, 6). The underestimation of fracture risk could be clinically detrimental because preventable fracture may occur due to false reassurance of patients and physicians and no subsequent treatment recommendation. The confidence and prediction regions in the HSROC plots portray that FRAX has higher precision (not necessarily accuracy) or reliability (not necessarily validity) for prediction of MOF than HF. Therefore, summary estimates for diagnostic performance of FRAX is more generalizable in predicting MOF than HF.

The low sensitivity of FRAX may be attributed to a variety of factors. The algorithm does not take into account the dose-response relationships, and can only be used on non-treated patients with restriction to only one bone mineral density site [20]. Some of clinical risk factors in the algorithm are not significantly associated with the risk of fracture especially in younger population such as early postmenopausal women [19]. On the other hand, some important risk factors for fractures are not included in the model such as vitamin D deficiency, falls, physical activity, bone turnover markers, previous treatment for osteoporosis, medications such as antiepilepsy drugs, aromatase inhibitors, and androgen deprivation therapy [8]. Previous studies have also identified the low sensitivity of the FRAX screening tool. Lowering the intervention threshold is an option to improve the sensitivity of FRAX, and decrease the number of at risk individuals who are missed by this screening tool [21,22]. Although using the lower treatment threshold in FRAX will increase sensitivity and reduce under-treatment, it will decrease specificity and advocate overtreatment of those who will not suffer from fractures within 10 years. While a fracture prediction tool that can offer both high sensitivity and high specificity is unavailable, whether a more sensitive or a more specific algorithm is desired depends on the objective. For a screening tool, high sensitivity is favored over high specificity so that more at-risk patients can receive early treatment. Since FRAX was not designed for lifetime fracture risk assessment, the judgement of overtreatment may be only valid for certain period of time (e.g. 10 years). The risk increase with aging in addition to other clinical risk factors that may occur in a patient's later life, those who were not considered at-risk for fractures during initial FRAX assessment may become treatment candidates when they age, overtreatment of this patient population may actually be beneficial. High sensitivity of FRAX can help reduce the number of under-treatment and incidence of future fractures, thus may potentially improve public bone health and reduce the cost incurred by treating fractures and its related complications. When clinicians consider whether or how NOF treatment thresholds might be changed, it should be noted that a more specific treatment threshold was chosen by the NOF to optimize cost and clinical effectiveness.

The data obtained from the studies used in this meta-analysis originates from 5 different western countries, includes men and women, both clinical and general populations, and is fairly representative of the western population. The sensitivity of FRAX varies between the different cohorts included in this study. The study also has limitations. FRAX scores in each included study were calculated with country-specific FRAX algorism, however, the treatment thresholds tested in the study were based on USA FRAX database. It may explain the moderate heterogeneity in performance of the NOF thresholds among the 7 cohorts studied. The ethnicity of the study participants is not known in each of the studies. The study design and quality of research has met the qualification criteria for this meta-analysis but there are still limitations, like in any study, due to the fact that different researchers conducted each of the studies independently.

More studies are needed to assess the treatment threshold percentages of the FRAX, as it has been suggested by previous research that altering those percentages can increase the sensitivity [21]. It has also been suggested that the US FRAX algorithm may be extended to predict fractures at other skeletal sites, including clinically recognized vertebral fractures [23]. Future research is needed to support the use of the FRAX algorithm in relation to fractures other than Major Osteoporotic or Hip Fractures. Future research is also needed to understand why approximately two of every five women are inappropriately screened. Exploring physician education regarding screening and modifying risk-based interventions is an area of needed research [24]. Finally, there have been no studies yet to date to confirm if the use of FRAX will improve clinical outcomes [20].

5. Conclusion

Overall, using the 10 year intervention thresholds of 20% for MOF and 3% for HF, FRAX performed better in identifying patients who will not have a MOF or HF within 10 years, than those who will. However, a substantial number of patients who developed fractures, especially MOF within 10 years of follow up, were missed and left untreated at baseline by FRAX assessment.

Conflict of interest

The authors have no conflicts of interest.

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