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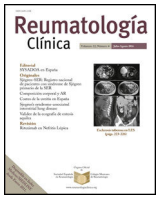

Original article

Improving fracture risk classification in Spain: A 10-year evaluation of a modified FRAX-based algorithm

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ABSTRACT

Objective: Osteoporotic fractures represent a significant clinical and public health burden. Although FRAX is widely used to estimate 10-year fracture risk, its Spanish version underestimates the probability of major osteoporotic fractures (MOF). This study assessed the performance of a modified FRAX-based algorithm, calibrated for the Spanish population, to stratify postmenopausal women into clinically meaningful risk categories.

Methods: We retrospectively followed 837 women (mean age 62 ± 9 years in 2008) referred for bone densitometry. All MOF over a 10-year period were recorded. Women were initially categorized as low risk (MOFR < 3.5%) or high risk (≥10%). Those with MOFR between 3.5% and 10% were reclassified as high risk if they had osteoporosis or if the recalculated MOFR including BMD was ≥7%.

Results: A total of 124 women experienced a MOF (66 vertebral, 39 distal forearm, 10 hip, 9 humerus). Initial risk classification identified 40% of women as low risk (fracture incidence: 9.4%, 95% CI: 6.2–12.5), 42% as intermediate (16.3%, 95% CI: 12.4–20.1), and 18% as high risk (23.5%, 95% CI: 16.7–30.3). After reclassification, 69% were considered low risk (11.0%, 95% CI: 8.4–13.5) and 31% high risk (23.2%, 95% CI: 18.1–28.3).

Conclusions: The proposed FRAX-based algorithm improves fracture risk classification in Spanish women and supports more rational use of bone densitometry and therapeutic interventions.

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Optimización de la clasificación del riesgo de fractura en España: evaluación a 10 años de un algoritmo modificado basado en FRAX

Palabras clave:
Fractura por fragilidad
Riesgo de fractura
FRAX
Algoritmo
Osteoporosis

RESUMEN

Objetivo: Las fracturas osteoporóticas representan una carga significativa tanto clínica como de salud pública. Aunque FRAX se utiliza ampliamente para estimar el riesgo de fractura a 10 años, su versión española infraestima la probabilidad de fracturas osteoporóticas mayores (FOM). Este estudio evaluó el rendimiento de un algoritmo modificado basado en FRAX, calibrado para la población española, para estratificar a las mujeres posmenopáusicas en categorías de riesgo clínicamente relevantes.

Métodos: Se siguió de forma retrospectiva a 837 mujeres (edad media: 62 ± 9 años en 2008) remitidas para densitometría ósea. Se registraron todas las FOM durante un periodo de 10 años. Inicialmente, las mujeres se clasificaron como de bajo riesgo (RFOM < 3,5%) o alto riesgo (≥ 10%). Aquellas con un RFOM entre el 3,5 y el 10% fueron reclasificadas como de alto riesgo si presentaban osteoporosis o si el RFOM recalculado incluyendo la densidad mineral ósea era ≥ 7%.

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Resultados: Un total de 124 mujeres presentaron alguna FOM (66 vertebrales, 39 de antebrazo distal, 10 de cadera y 9 de húmero). La clasificación inicial identificó al 40% de las mujeres como de bajo riesgo (incidencia de fractura: 9,4%; IC 95%: 6,2-12,5), al 42% como riesgo intermedio (16,3%; IC 95%: 12,4-20,1) y al 18% como de alto riesgo (23,5%; IC 95%: 16,7-30,3). Tras la reclasificación, el 69% se consideró de bajo riesgo (11,0%; IC 95%: 8,4-13,5) y el 31% de alto riesgo (23,2%; IC 95%: 18,1-28,3).
Conclusiones: El algoritmo propuesto, basado en FRAX y ajustado para la población española, optimiza la clasificación del riesgo de fractura en las mujeres españolas, y permite un uso más racional de la densitometría ósea y de las intervenciones terapéuticas.
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Introduction

Osteoporotic fractures are a major clinical challenge due to their substantial impact on health and quality of life.[1] They are a leading cause of pain, functional decline, and excess mortality—particularly in the case of hip and vertebral fractures. From a healthcare system perspective, their economic burden is considerable, driven by hospitalization, long-term care needs, and loss of productivity. In aging populations, the rising incidence of these fractures represents a growing strain on both clinical services and public health budgets.[2]

From the age of 50,[3] the lifetime risk of sustaining a major osteoporotic fracture (MOF)—including hip, forearm, humerus, and clinical vertebral fractures—is estimated at 46% in women and 22% in men. Accurately predicting who will sustain a fragility fracture is essential to guide preventive strategies and prioritize healthcare interventions. In this context, the development and refinement of reliable fracture risk assessment tools[4] are critical to identify high-risk individuals and ensure efficient use of diagnostic and therapeutic resources.

Bone mineral density (BMD), assessed by dual-energy X-ray absorptiometry (DXA), is the most widely used tool for estimating fracture risk, despite its limited sensitivity.[5] While BMD shows high specificity, many fragility fractures occur in individuals without densitometric osteoporosis. Incorporating clinical risk factors alongside BMD enhances predictive performance, prompting the development of integrated tools that offer a more accurate assessment of individual fracture risk.

FRAX is an algorithm available on the Internet that calculates the absolute probability of sustaining a MOF or a hip fracture (HF) over the next 10 years.[6] Developed in 2008, it combines clinical risk factors with or without BMD to estimate fracture risk. Its main advantage lies in allowing risk stratification even in the absence of BMD measurements, thereby facilitating decision-making in diverse clinical settings.

In Spain, however, its application in daily practice remains limited. While estimates for HF risk (HFR) are considered valid and clinically useful, the algorithm tends to underestimate the probability of MOF in the population.[7–9] This limitation has prompted efforts to adapt FRAX-based strategies to local epidemiology, aiming to improve their accuracy and clinical applicability.

In this context, our group previously proposed[10] a classification algorithm based on locally adapted MOFR thresholds to improve the clinical applicability of FRAX in Spain. In the present study, we aimed to assess its performance in a real-world clinical setting.

Methods

Setting and study population

This study was conducted in the Bone Densitometry Unit of the Rheumatology Department at the Bellvitge University Hospital, where approximately 8000 scans are performed annually. Patients are referred to the unit by both primary care physicians and hospital-based specialists. The term "primary care physicians" includes general practitioners as well as specialists—mainly rheumatologists, orthopedic surgeons, and gynecologists—who, while affiliated with the hospital, also provide care at primary care centers within its referral area. All scan requests are fulfilled without restriction.

Between May and October 2008, 853 women aged 40–90 years, consecutively referred from primary care, were invited to complete a questionnaire assessing the fracture risk factors included in the FRAX tool. A trained radiology technician was available to assist participants in completing the questionnaire when needed.

All participants underwent bone densitometry (BD) of the lumbar spine and proximal femur using a Hologic QDR 4500 densitometer. *T*-scores were calculated using reference databases from the NHANES III study for the femoral neck and total hip,[11] and from a Spanish population-based study for the lumbar spine.[12] Bone status was classified as normal, osteopenia, or osteoporosis according to the criteria of the International Society for Clinical Densitometry.[13]

This study was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. As this was a retrospective analysis of routine clinical practice, written informed consent was not required. All patient data were anonymized, and confidentiality was ensured in accordance with Spanish data protection regulations. The study protocol was reviewed and approved for publication by the Research Ethics Committee of Bellvitge University Hospital.

Fracture risk calculation

MOFR and HFR were calculated using the Spanish version of FRAX.[14] Required inputs included age, sex, weight (kg), and height (cm). Additional variables—except for BMD—were binary (yes/no) and included: personal history of fragility fracture in adulthood (including radiographic vertebral fractures), parental history of hip fracture, current smoking, prolonged glucocorticoid use ($\geq$3 months at $\geq$5 mg/day), diagnosis of rheumatoid arthritis, presence of secondary osteoporosis (e.g., untreated hypogonadism, early menopause, osteogenesis imperfecta, chronic malnutrition or malabsorption, prolonged immobility, organ transplantation, insulin-dependent diabetes, untreated long-term hyperthyroidism, chronic liver disease), and alcohol intake of three or more units per day.

To estimate the number of expected fractures in the cohort, the individual MOFR and HFR values were multiplied by 837 and divided by 100.

Fracture risk was stratified as low, medium, or high according to the criteria established by the Canadian Association of Radiologists and Osteoporosis Canada (CAROC).[15] According to the European recommendations for the diagnosis and treatment of postmenopausal osteoporosis, two FRAX thresholds are defined to guide clinical decisions: below the low-risk threshold, only general bone health measures are recommended; above the high-risk

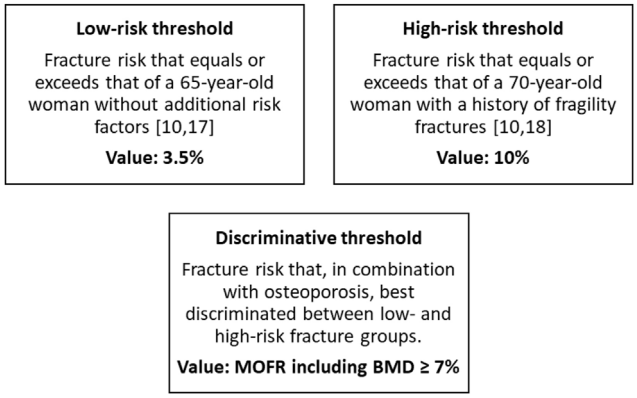

Fig. 1. Definition of FRAX intervention thresholds.

threshold, pharmacological treatment is indicated. In the intermediate zone, performing a BD is advised to refine risk classification.[16]

MOFR thresholds

The underestimation of MOFR by FRAX in Spain[7–9] advises against applying the high-risk thresholds used in other populations. In 2013, based on data from 643 of the 853 women in our cohort who had not received antiresorptive or bone formation agents (BA), we proposed specific high and low MOFR thresholds to improve risk stratification and guide the indication for BD in women at intermediate risk.[10]

The low-risk threshold was established using the criteria of the U.S. Preventive Services Task Force (USPSTF) for osteoporosis screening.[17] According to USPSTF, BD is indicated in women under 65 when their fracture risk equals or exceeds that of a 65-year-old woman without additional risk factors. For a Caucasian woman in the U.S., this corresponds to an MOFR of 9.3%, whereas the equivalent figure for a Spanish woman is 3.6%, reflecting Spain's lower background fracture incidence. For simplicity, this threshold was rounded to 3.5% in our model.

The high-risk threshold was set at 10%, based on the MOFR of a 70-year-old Spanish woman with a history of fragility fractures. This value is comparable to the 20% MOFR used by the U.S. National Osteoporosis Foundation (NOF) to define high risk in women with osteopenia,[18] and reflects proportional calibration to national fracture risk levels.

These thresholds and subsequent reclassification criteria are presented in Fig. 1.

Fracture identification

In the final two months of 2018, the electronic primary care medical records were reviewed to identify all fractures sustained by the women included in the 2008 cohort over the 10-year period following baseline bone densitometry. For the purposes of this study, no participants were contacted directly.

Fracture identification encompassed both coded entries recorded by primary care physicians and events documented solely in the free-text sections. In cases of uncertainty regarding the occurrence, location, or mechanism of a reported fracture, the corresponding emergency department report and/or radiographic images were reviewed for confirmation.

Vertebral fractures were radiologically confirmed in all cases. However, as no baseline spine radiographs were available from 2008, the possibility that some fractures were already present but undiagnosed at that time cannot be entirely excluded. When accessible, earlier spinal images were reviewed to reduce the risk of misclassification.

The duration of treatment with calcium, vitamin D, and bone-active agents (BA) was recorded for each patient.

Clinical records could not be retrieved for 16 women, due to a change in the hospital's electronic medical record system in 2010. This change altered patient identification numbers, and errors in the tax identification or patient codes in the original dataset prevented linkage to the updated files.

Statistical analyses

Descriptive results are presented as absolute numbers (percentages), means (standard deviations), or medians (interquartile ranges and 95% confidence intervals), as appropriate.

Comparisons between groups were performed using the Chi-squared test for categorical variables, analysis of variance (ANOVA) for normally distributed continuous variables, and the Mann–Whitney or Kruskal–Wallis tests for non-normally distributed variables, depending on the number of groups.

The discriminative ability of FRAX for fracture prediction was assessed using the area under the receiver operating characteristic (ROC) curve. The negative predictive value for fracture was also calculated for the high MOFR threshold.

To determine the threshold after re-evaluating fracture risk once BMD results were included, we selected the FRAX value that, in combination with the presence of osteoporosis, best discriminated between low- and high-risk groups. The selected threshold corresponded to the value at which the 95% confidence intervals for fracture incidence in these groups showed minimal or no overlap, indicating a meaningful separation in clinical risk.

Time to first MOF was analyzed using Kaplan–Meier survival curves. Statistical significance was defined as a two-tailed α level of 0.05.

All statistical analyses were performed using SPSS software (version 15.0 for Windows; IBM Corp.).

Results

The final study sample consisted of 837 women. Follow-up was incomplete in 10 cases due to relocation outside Catalonia or loss of contact with primary care. Fifty-eight women died during the follow-up period.

At baseline (2008), the mean age was 62 ± 9 years. Eighty percent of participants had at least one fracture risk factor. BMD was normal in 20%, osteopenic in 55%, and osteoporotic in 25%. Detailed baseline characteristics are shown in Table 1.

The mean MOFR was $6.21\% \pm 5.39$, with a median of 4.23% (IQR 2.56–8.00), and the mean HFR was $2.08\% \pm 3.20$, with a median of 0.90% (IQR 0.40–2.40). Both estimates were lower when BMD was included in the FRAX calculation.

More than 80% of women received calcium and/or vitamin D supplementation, and 25% (n: 209) received BA. Among the latter, 91% were treated with bisphosphonates, 14% with selective estrogen receptor modulators, 14% with denosumab, 11% with strontium ranelate, and 5% with teriparatide.

A total of 251 fractures were identified in 207 women: 169 due to fragility, 80 traumatic, and 2 pathological (Table 2). Thirty-five women experienced two fractures, eight had three, and one patient had four, including a hip fracture as the final event. Among the pathological cases, one woman developed jaw osteonecrosis following radiotherapy for a tongue-base neoplasm (rheumatoid arthritis, low-dose glucocorticoids, methotrexate, leflunomide, no BA in prior 5 years); another sustained a pelvic fracture during the course of multiple myeloma.

Table 1
Basal demographic and clinical parameters of the 837 women included in the study.

Age	61.95 (8.61) years
Age ≥ 65 years	320 (38%)
Body mass index (BMI)	27.04 (4.17) kg/m^2
BMI < 20 kg/m^2	21 (3%)
Previous fracture	216 (26%)
Parental hip fracture	121 (15%)
Active smoker	92 (11%)
Glucocorticoid treatment	80 (10%)
Rheumatoid arthritis	81 (10%)
Secondary osteoporosis[a]	303 (36%)
Excessive alcohol consumption	2 (1%)
Number of risk factors for fracture[b]	1.5 (1.1)
Bone mineral density	
Lumbar spine	0.874 (0.127) g/cm^2
T-score	−1.50 (1.20)
Femoral neck	0.705 (0.104) g/cm^2
T-score	−1.24 (0.96)
Total hip	0.819 (0.106) g/cm^2
T-score	−1.04 (1.09)
Treatment with BA[c]	209 (25%)

[a] The main cause (282/303) was menopause before age 45.
[b] Eighty percent of the women had some fracture risk.
[c] BA: antiresorptive or formation bone agents.

Table 2
Number of fractures identified in the 10 years of follow-up by location and mechanism of production.

Location	Fragility	Trauma
Face	0	4
Spine	74	5
Ribs	8	5
Pelvis	9	0
Coccyx	0	1
Clavicle	1	1
Trochanter	0	1
Humerus	10	1
Distal forearm	50	0
Carpus/Metacarpus/Fingers	0	12
Hip	12	0
Patela	0	3
Tibia/Fibula	1	2
Ankle	4	6
Tarsus/Metatarsus/Toes	0	38
Polytrauma	0	1
	169	80

A hundred and forty-four women experienced a MOF (66 vertebral, 39 distal forearm, 10 hip, 9 humerus). The median time to first MOF was 64 ± 36 months (range 0–119). Notably, 64% of these women did not meet densitometric criteria for osteoporosis. Based on baseline MOFR values from 2008, the expected number of MOF was 52 (or 44 when BMD was included in the calculation), underscoring the underestimation by FRAX.

Women who sustained a MOF were significantly older (mean 65 vs. 61 years; $p < 0.001$), had more fracture risk factors (age > 65, previous fracture), lower BMD at all sites, and higher MOFR at baseline. They also received BA more frequently during follow-up (101/118 vs. 407/704; $p < 0.001$).

Among the 58 women who died, eight had experienced a MOF (including two hip fractures), with no significant differences compared to the rest of the cohort.

Twelve women sustained a hip fracture, with a median time to event of 82 months (IQR 46–112). The number of expected hip fractures based on 2008 HFR was 17 (or 12 with BMD included).

The area under the ROC curve (AUC) for MOFR in predicting MOF was 0.643 (95% CI 0.592–0.694), indicating low discriminative ability. For hip fracture prediction, the AUC for HFR was 0.740 (95% CI 0.632–0.849), indicating moderate accuracy. BMD alone had no predictive value at any site (AUC < 0.5). The negative predictive value for hip fracture in women with HFR < 3% was 99%.

Applying the proposed MOFR thresholds, 331 women (40%) were classified as low risk (31 MOFR; incidence 9.36%, 95% CI 6.22–12.5), 357 (42%) as intermediate (58 MOF; incidence 16.25%, 95% CI 12.42–20.07), and 149 (18%) as high risk (35 MOF; incidence 23.49%, 95% CI 16.68–30.30).

A FRAX value of 7% or the presence of osteoporosis was identified as the most discriminative threshold for differentiating between low- and high-risk groups. After reclassification of the intermediate group, 574 women (69%) were categorized as low risk (63 MOF; incidence 10.98%, 95% CI 8.42–13.53), and 263 (31%) as high risk (61 MOF; incidence 23.19%, 95% CI 18.09–28.29).

The proposed algorithm is shown in Fig. 2.

The negative predictive value for fracture in women classified as low risk by the algorithm was 89%.

Kaplan–Meier curves for time to first MOF by risk category are shown in Fig. 3.

Discussion

This study assessed the clinical performance of a FRAX-based classification algorithm adapted to the Spanish population. Using prospectively collected data and a 10-year follow-up, we evaluated its ability to stratify fracture risk and guide decision-making in a real-world setting.

Our results confirm that the Spanish version of FRAX predicts HFR with acceptable discriminative power and high negative predictive value, particularly when the HFR is below 3%. However, its usefulness is limited in younger women, where hip fracture risk is generally low despite the possibility of other major fractures.

Consistent with previous observations, FRAX underestimates MOFR in this population. Nevertheless, applying the proposed thresholds—3.5% for low risk and 10% for high risk—allowed effective stratification into clinically meaningful categories. Rather than quantifying precise risk, the algorithm helps classify patients as low, intermediate, or high risk, and supports the indication for densitometry or treatment. Reclassification of intermediate-risk women using BMD further refines this process, particularly in identifying additional candidates for intervention. Although it may also be applied after a fracture, the algorithm is intended for primary prevention. Therefore, in the absence of fracture risk factors, it would be advisable to apply it periodically in postmenopausal women and in men over the age of 50.

To date, only one study has proposed FRAX-based thresholds for low (5%) and high (7.5%) MOFR in Spain. This was published by Azagra et al.,[19] based on a retrospective 10-year follow-up of 816 women from the FRIDEX cohort, in whom 76 MOF were identified. Only 8.9% of the women fell into the intermediate-risk category, and thus had an indication for BD. The high-risk group comprised 70 women (8.6% of the cohort), among whom 15 MOF occurred. The authors proposed that BD should also be performed in these high-risk women, bringing the total percentage of candidates for densitometry to 17.5%. This strategy was considered cost-effective when compared with a model assuming BD in all women and treatment of all osteoporotic patients—an approach that no longer aligns with current clinical guidelines.

Validation of these thresholds in the FROCAT cohort,[20] confirmed the distribution into low (67.8%), medium (11.9%) and high (20.3%) MOFR categories, although BMD was only available in 21.5% of subjects, limiting further analysis.

Compared with the FRIDEX cohort, our study population showed a higher incidence of MOF. Although the mean age of our

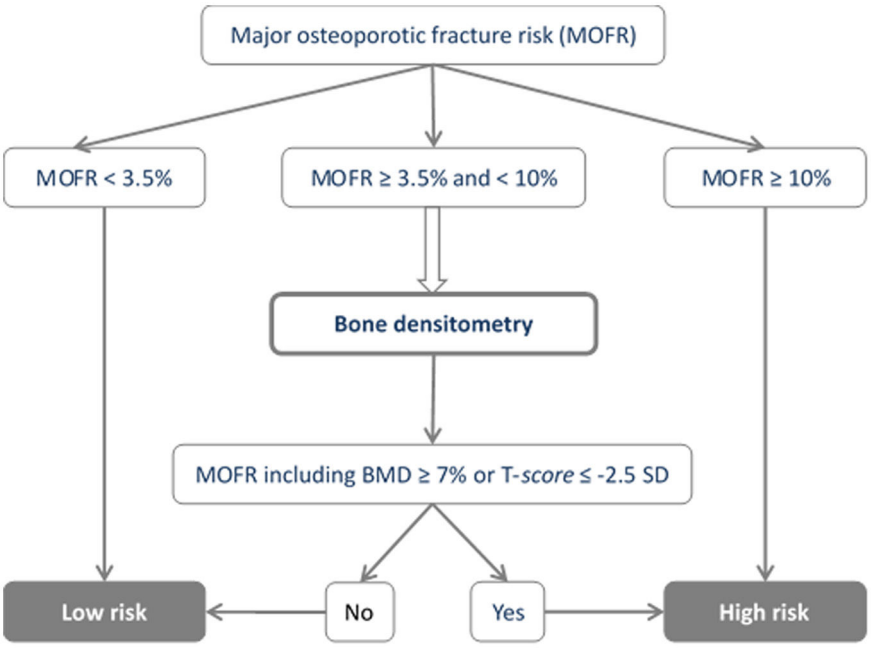

Fig. 2. Classification algorithm.

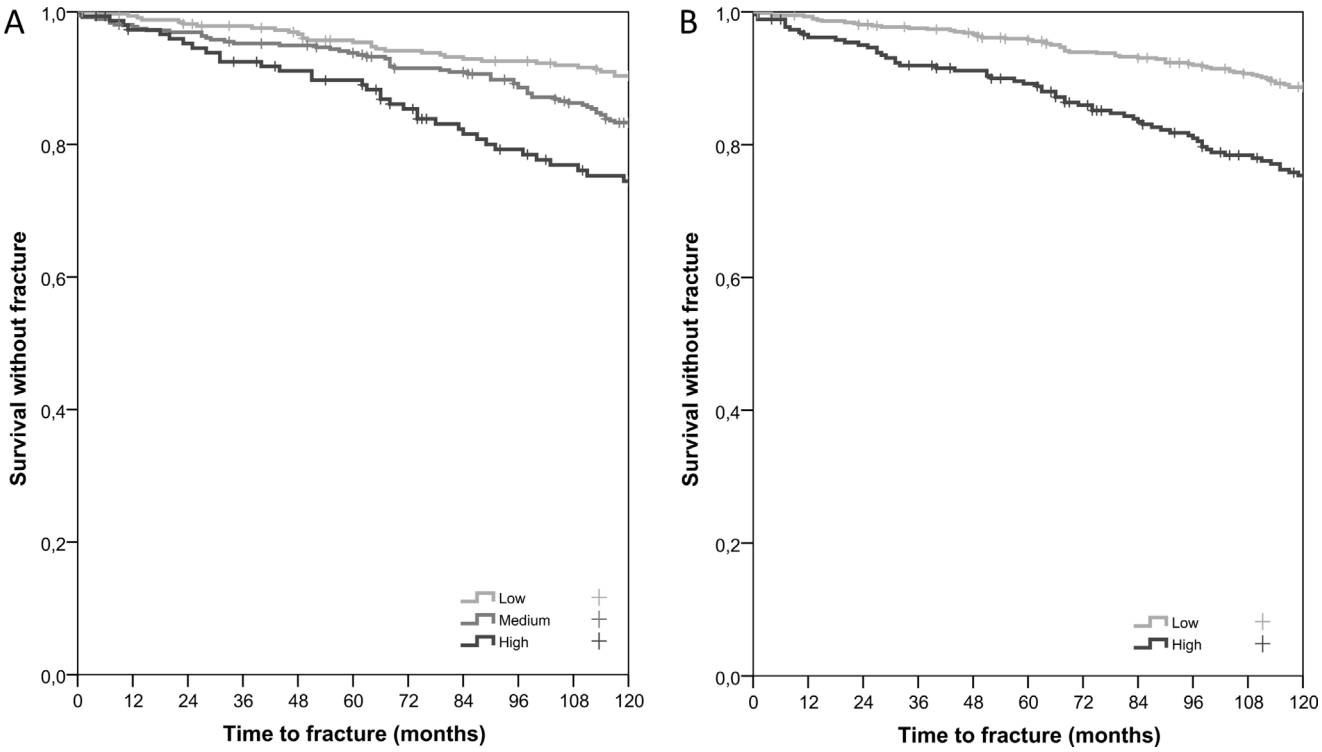

Fig. 3. Time until first MOF for the initial classification of MOFR (A) and after reclassification with BMD results (B) for low, medium and high MOFR.

participants was higher (62 vs. 57 years, with 38% vs. 18% aged ≥65), the main reason likely lies in our inclusion of women who received BA either before or after study entry. Theoretically, these patients would have been treated due to high risk or high fracture incidence. In contrast, the FRIDEX cohort had a greater proportion of women with previous fractures (49% vs. 26%), many of whom had not received treatment despite being at higher risk.

The recommendations from the Spanish Society of Rheumatology,[21] advise performing BD in patients with a fragility fracture, two or more major risk factors, or an MOFR ≥ 5%. However, data from EPISER2016[22]—the first study to evaluate FRAX in a representative Spanish population—showed that only 10–13% of women fell within the 5–10% MOFR range, depending on the threshold used. This suggests that using 5% as a lower limit may be overly restrictive, limiting the identification of women who could benefit from further assessment.

One of the key contributions of Azagra et al.[19,20] was to show that the high MOFR threshold in Spain is far below the 20% proposed by the NOF. Nonetheless, applying their algorithm strictly would substantially reduce the number of BDs performed and may con-

tradict the widely accepted principle of treating high-risk patients directly, as is common in cardiovascular risk models. Recommending BD even in clearly high-risk individuals could delay necessary treatment.

The 10% MOFR threshold, as adopted by the Spanish Society of Rheumatology,[21] is more conservative than the 7.5% proposed by Azagra et al.,[19] but more compatible with clinical practice. It increases the proportion of women classified as intermediate risk—where BMD is most informative—while allowing direct treatment in those exceeding 10%, even without densitometry.

Data from EPISER2016 further support the use of a 10% MOFR threshold in Spain. Among women aged ≥65, all those with MOFR ≥10% also had HFR ≥3%—a value considered valid in the Spanish FRAX model. In contrast, 8% of those with MOFR ≥7.5% had HFR values below 3%, suggesting potential overestimation of risk at that lower threshold. Moreover, 13% of women in the 7.5–10% range would reasonably undergo BD and could then be reclassified based on BMD.

Establishing a high-risk threshold inevitably raises the question of how many older women would qualify for treatment. In EPISER2016, applying a 10% MOFR threshold would categorize most women over the age of 75 as high risk. Nonetheless, pharmacological intervention in this age group is considered cost-effective.[23] Moreover, clinical evidence in women aged 65 years or older with osteopenia has shown that treatment with zoledronic acid significantly reduces both vertebral and non-vertebral fractures.[24] Therefore, in older adults with osteopenia and high fracture risk, initiating treatment—even in the absence of densitometric osteoporosis—appears reasonable and appropriate when guided by individualized clinical judgment.

The main limitations of this study relate to the recruitment of patients from a BD unit and the inclusion of women treated with BA, factors that may limit generalizability. However, by including only referrals from primary care, we likely excluded patients with secondary osteoporosis due to severe comorbidities, and the population studied closely reflects the clinical setting where the algorithm would be applied. Excluding treated women would have led to a lower-risk sample, less representative of routine practice. Regarding the influence of BA during follow-up on fracture outcomes, previous research involving over 35,000 women aged ≥50 years −65% of whom received BA- showed that FRAX predictions remained well-calibrated in both treated and untreated individuals, with similar observed and predicted fracture rates.[25] Since the only FRAX variable affected by treatment is BMD, and the model incorporates only femoral neck BMD (which tends to change modestly compared to spinal BMD), the overall impact of treatment on FRAX-based fracture risk estimation appears limited. Although baseline spine radiographs were not available, all recorded vertebral fractures were clinically relevant, suggesting they represent true incident or progressive events. Lastly, the results cannot be extrapolated to men.

Importantly, the study has several notable strengths. It was conducted in a real-world clinical setting, without interference in therapeutic decisions. Fracture identification was exhaustive, combining diagnostic codes and free-text searches, and confirmed through radiology or emergency reports when necessary. The age distribution of the cohort—mean age 62 years, with over one-third aged ≥65—enhances external validity, better reflecting the profile of women at increased fracture risk. As highlighted in EPISER2016, age is a key determinant of fracture incidence and high-risk classification. Finally, the exceptionally low loss to follow-up over a 10-year period (<2%) provides a robust foundation for the longitudinal analyses.

In conclusion, our results support the use of the Spanish version of FRAX to estimate hip fracture risk, applying the internationally accepted 3% threshold to identify high-risk individuals. To assess overall osteoporotic fracture risk, we propose a validated classification algorithm based on adapted MOFR thresholds (3.5% and 10%) that allows effective stratification of Spanish women into low, intermediate, and high-risk categories. This model offers a pragmatic approach to guide the use of bone densitometry and treatment decisions in routine clinical practice. By improving the alignment between estimated risk and observed fracture incidence, it contributes to more efficient resource allocation and optimized patient care in the management of osteoporosis.

The proposed algorithm may be particularly valuable in primary care settings and in contexts with limited access to bone densitometry. It facilitates clinical decision-making, especially for physicians who are not experts in osteoporosis, by providing a structured and evidence-based framework for risk assessment. A frequently underestimated strength of FRAX is that it prompts clinicians to systematically evaluate fracture risk factors, thereby improving the quality of risk stratification. Furthermore, in areas where DXA availability is restricted or subject to long waiting times, our findings support the appropriateness of initiating treatment in high-risk individuals based solely on FRAX estimates.

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No funding was received for this study.

Conflicts of interest

None.

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