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ORIGINAL ARTICLE

Potential impact of obstetric history on postmenopausal fragility fracture risk: A reassessment of the Fracture Risk Assessment Tool

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Osteoporosis is a prevalent condition among postmenopausal women, significantly contributing to morbidity. The prevention and management of low-energy fractures, which occur due to the decline in bone mineral density (BMD), require a multidisciplinary approach and remain a focus of contemporary research. The reduced cumulative exposure to endogenous estrogen is the most extensively studied factor contributing to BMD loss, with numerous studies linking earlier onset of menopause and delayed menarche to an increased

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ABSTRACT

Objectives: This study aimed to evaluate the impact of integrating obstetric parameters into the Fracture Risk Assessment Tool (FRAX) on the precision of risk assessment.

Patients and methods: In this retrospective study, patients who experienced postmenopausal fragility fractures of the distal radius, proximal femur, or lumbar vertebrae between January 1, 2021, and December 31, 2023, were included. Obstetric histories, along with standard FRAX parameters, were obtained by phone interviews. Based on the FRAX major osteoporotic fracture risk score calculated without bone mineral density, patients were classified into high-, intermediate-, and low-risk group categories. Differences in age at menarche, age at menopause, lactation duration, gravidity, and parity were analyzed across risk categories.

Results: A total of 328 patients (mean age: 64.5±5.8 years; range, 55 to 75 years) were included. The mean FRAX score was 16±8.8 (range, 3 to 58), and 85, 191, and 52 patients were classified as high-, intermediate-, and low-risk, respectively. A positive correlation was observed between FRAX scores and both later age at menarche and earlier menopause ($p<0.001$ and $p=0.008$, respectively). The mean age at menopause was significantly different between the high- and low-risk groups (46.4 *vs*. 49.3 years, $p=0.016$). The intermediate-risk group was also evaluated, showing no significant differences in obstetric parameters compared to the low-risk group ($p>0.05$).

Conclusion: Although late menarche is not explicitly included in FRAX, its association with higher fracture risk was evident. The established influence of early menopause on FRAX scores supports its role in fracture risk estimation. However, the inclusion of additional obstetric parameters did not enhance the predictive accuracy of FRAX in this cohort.

Keywords: Menarche, osteoporosis, osteoporotic fractures, postmenopausal, risk assessment.

risk of fractures.[1-4] Research on such obstetric factors extends beyond menstruation, with parameters such as the gravidity and duration of lactation being explored; however, findings in these areas remain inconsistent.

Assessing the risk of osteoporotic fractures enables a preventative course, ultimately reducing their economic and societal burden.[5-8] One widely utilized method for this risk evaluation is the Fracture Risk Assessment Tool (FRAX), which not only identifies fracture risk but also provides recommendations for preventive measures.[9] While the FRAX has demonstrated utility in numerous studies, it notably lacks consideration of obstetric factors, except for premature menopause (<45 years). Given the ongoing debate regarding the influence of obstetric factors on BMD, their omission from FRAX may potentially limit the tool's accuracy in predicting fracture risk.

In this study, the FRAX score of postmenopausal women who sustained low-energy fractures was calculated, and they were classified according to the intervention thresholds recommended by the UK National Osteoporosis Guideline Group.[10] The study aimed to assess whether patients classified as low risk by these thresholds could be more accurately stratified if factors such as age at menarche, duration of lactation, gravidity, and parity were considered independent risk factors. We hypothesized that patients experiencing osteoporotic fractures despite being classified as low risk of fracture by FRAX would have a late age at menarche, longer durations of lactation, and higher parity.

PATIENTS AND METHODS

The medical records of patients who had sustained postmenopausal distal radius, proximal femur, or lumbar vertebrae fragility fractures between January 1, 2021, and December 31, 2023, treated at the Orthopedics and Traumatology Department of the Aksaray Training and Research Hospital were retrospectively reviewed. Patients were excluded if there was missing data, the patient could not be contacted, or they had a pathological fracture or fracture due to high-energy trauma or multitrauma, history of malignancy, or history of primary amenorrhea. The study protocol was approved by the Aksaray University Clinical Research Ethics Committee (date: 09.11.2023, no: 100-SBKAEK). Written informed consent was obtained from all participants. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Eligible patients were contacted by phone interview, and the necessary parameters for calculating the FRAX major osteoporotic fracture risk score without BMD were collected. These parameters included weight, height, history of fracture, history of parental hip fracture, current smoking, glucocorticoid use, rheumatoid arthritis, secondary osteoporosis, and alcohol use. Additionally, obstetric history, including menarche age, menopause age, lactation duration, gravidity, and parity, was queried. The FRAX score was subsequently calculated using the tool's web interface.[11] Following data collection, patients were categorized into three risk groups (high, intermediate, and low risk) based on the National Osteoporosis Guideline Group intervention thresholds.[10] Differences in obstetric history between patients classified as low risk and those classified as high risk were evaluated.

Statistical analysis

Statistical analysis was performed using the Jamovi software (www.jamovi.org).[12] The normality of data was assessed using the Kolmogorov-Smirnov test, which indicated that the data did not follow a normal distribution. Consequently, the Kruskal-Wallis test was applied to compare obstetric parameters across the low-, intermediate-, and high-risk categories. Further analysis was conducted using the FRAX score as a continuous variable, and correlation analysis was performed for obstetric parameters. Thresholds for early and late menarche were defined as ≤11 years and ≥15 years, respectively. Additionally, comparisons were made between nulliparity, primiparity, multiparity, and grand multiparity (>5 births) using the Kruskal-Wallis test. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 328 patients (mean age: 64.5±5.8 years; range, 55 to 75 years) were included in the study (Figure 1). Following the calculation of the FRAX score, 85, 191, and 52 patients were classified as high-, intermediate-, and low-risk, respectively. The demographic characteristics of the patients are summarized in Table I. When comparing the risk groups, no significant differences were found in obstetric parameters, except for a younger mean age at menopause in the high-risk group, with 49.3±4.8, 48.2±5.2, and 46.4±5.6 years in the low-, intermediate-, and high-risk groups, respectively (p=0.012; Table I).

When correlation analyses were conducted without risk categories, older age at menarche and

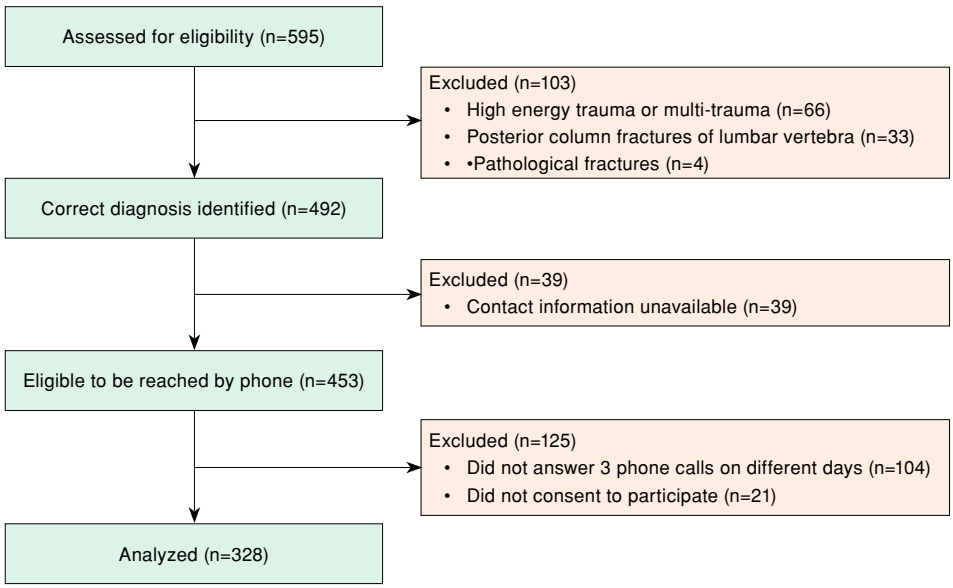

FIGURE 1. Flowchart showing patient exclusions in the retrospective analysis.

TABLE I
Patient demographics and obstetric parameters classified under fracture risk groups

	Low-risk (n=52)	Intermediate-risk (n=191)	High-risk (n=85)	Total (n=328)
	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Age (year)	63.5±5.3	64.4±5.9	65.4±5.9	64.5±5.8
Body mass index (kg/m^2)	31.9±6.1	31±5.9	28.5±4.8	30.5±5.8
Age at menarche (year)	13.2±1.4	13.3±1.5	13.5±1.5	13.4±1.5
Age at menopause (year)	49.3±4.8[a]	48.2±5.2[b]	46.4±5.6[a,b]	47.9±5.4
Duration of lactation (month)	73±29	73.3±46.5	76.2±34.2	74±41.1
Gravidity	4.2±1.5	4±1.9	4.3±1.8	4.1±1.8
Parity	3.9±1.5	3.8±1.7	4.1±1.7	3.9±1.7

SD: Standard deviation; a: Statistical significance in post-hoc analysis between groups, p=0.016; b: Statistical significance in post-hoc analysis between groups, p=0.048.

TABLE II
Correlation analysis of FRAX scores and obstetric parameters

Parameter correlated to FRAX® score	Correlation coefficient	*p*
Age at menarche	0.497	<0.001
Age at menopause	-0.145	0.008
Duration of lactation	0.011	0.840
Gravidity	0.027	0.623
Parity	0.007	0.897

FRAX: Fracture Risk Assessment Tool.

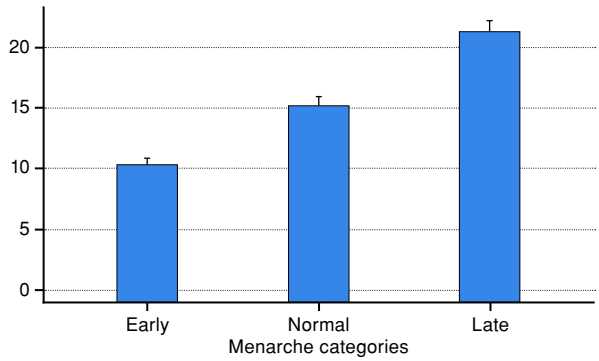

FIGURE 2. Bar plot shows FRAX scores for menarche ages classified as early, normal, and late.
FRAX: Fracture Risk Assessment Tool.

younger age at menopause were both positively correlated with the higher fracture risk scores ($p<0.001$ and $p=0.008$, respectively; Table II). However, no significant correlations were found between the FRAX scores and the duration of lactation and gravidity and parity (Table II). Further analysis after categorizing menarche age and parity revealed that the late menarche group had double the mean FRAX score compared to the early menarche group ($p<0.001$; Figure 2). However, parity did not have a significant influence on FRAX scores (Figure 3).

DISCUSSION

Considering that all patients included in the study had sustained postmenopausal osteoporotic fractures, we initially hypothesized that those classified as low risk by FRAX would be more accurately categorized as high risk if unaccounted factors, such as certain obstetric parameters, were introduced. However, the results from current study contradicted our hypothesis. The FRAX score effectively stratified the increased risk in women with a late age at menarche, despite not including menarche age as a parameter. This was unexpected, as FRAX managed to classify women with late menarche age as higher risk, presumably based on the other parameters already included in the model.[13] Additionally, longer durations of lactation, higher gravidity, and higher parity did not appear to effect risk estimation. This finding suggests that these obstetric factors may not play as significant a role in fracture risk as previously speculated. As expected, early menopause, a parameter already included in FRAX, was associated with a higher calculated fracture risk. This reinforces the validity of FRAX in identifying well-established risk factors such as early menopause in postmenopausal women.

Recent evidence on parameters reflecting cumulative endogenous estrogen exposure, derived from large population studies and Mendelian

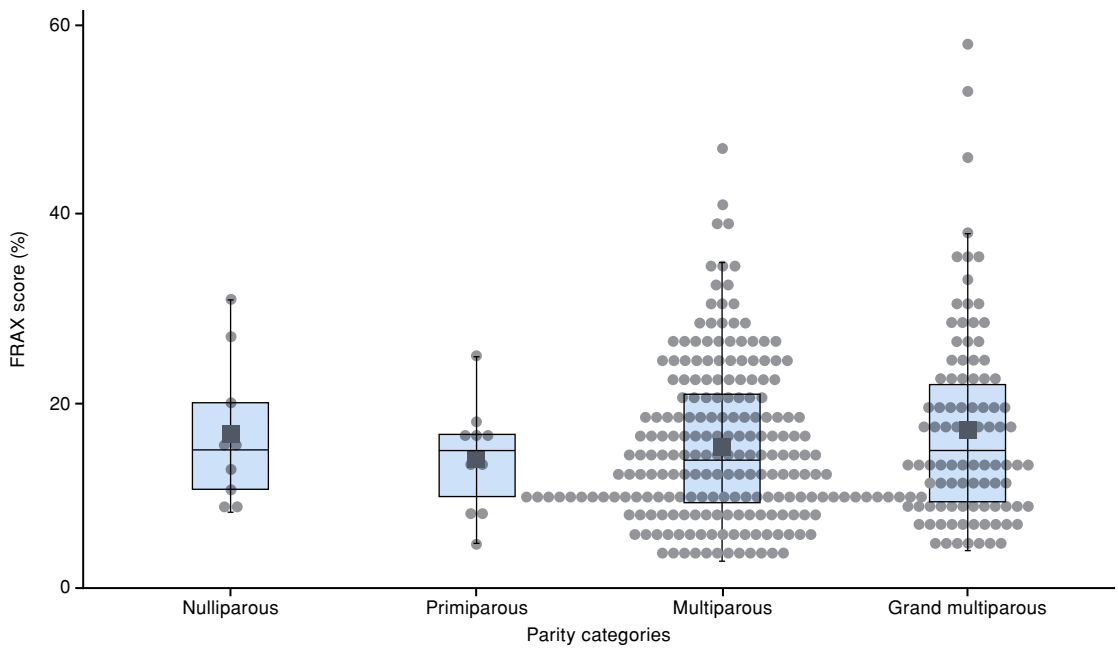

FIGURE 3. Stacked box plot shows FRAX scores for parity classified as nulliparous, primiparous, multiparous, and grand multiparous. Notice that the first two groups make up only 5.8% of all patients.
FRAX: Fracture Risk Assessment Tool.

randomization studies, appears robust.[2-4,14] The evidence supports the theory that estrogen loss increases bone resorption while impairing new bone formation, thereby reducing BMD.[15] A 2021 study by Yoo et al.[2] including over 1 million postmenopausal Korean women reported that shorter estrogen exposure and nulliparity were associated with an increased risk of fracture. Notably, the most prominent protective factors were an early menarche (12 years or younger) and a later menopause (55 years and older). Similarly, in their Mendelian randomization study, Zhang et al.[4] identified a modestly decreased BMD for each additional year in age at menarche. Furthermore, both a recent meta-analysis and a registry-based study also support that shorter estrogen exposure is associated with increased risk of postmenopausal osteoporotic fractures of any type.[3,14] In their 2023 meta-analysis on predictors of osteoporotic fracture in postmenopausal women, Long et al.[3] reported increased risk related to an age at menarche of 15 years or older and age at menopause of 40 years or younger, based on data from over 1 million patients. Yang et al.[14] also highlighted a threshold of 16 years age at menarche for increased risk of lower BMD. Although we did not evaluate risk factors based on fracture endpoint, we also observed that FRAX estimated higher fracture risk in patients with an age at menarche of 15 years or older.

Nulliparity did not appear to differ significantly among the FRAX risk groups in our study. However, it is important to note that only 2.7% of the women included were nulliparous, while 94.2% were multiparous, limiting the ability to make an optimal comparison. The long-term risk of osteoporotic fractures in multiparous women remains a subject of debate. Some hypothesize that multiparity may lead to decreased bone mass due to the increased calcium demands during pregnancy and lactation, potentially raising the risk of fractures later in life.[3,16,17] In their population-based cohort study with women aged 60 years or older, Panahi et al.[16] showed that parity of four and above was associated with significantly lower femoral neck and lumbar spine BMD. Yang et al.,[17] in a similarly designed study, also reported that six and above parity was associated with significantly lower lumbar spine BMD. Conversely, there are many studies reporting increased bone loading and elevated estrogen levels during pregnancy acting as protective factors against bone loss or no significant correlation between multiparity and fracture risk.[18-22] A similar debate surrounds the impact of lactation on bone health. While a considerable number of studies suggest that it can be associated with a transient bone loss, which possibly restores to original bone composition within 6 to 12 months,[2] the data on fracture risk remain inconsistent. Lactation has been associated with both reduced risk of hip fracture and increased risk of other fractures.[2,23-25] Moreover, several preclinical studies suggest an anabolic effect in the post-lactation period, which may increase the mechanical properties of the cortical bone.[26,27]

This study had several limitations. First, while restricting the study to postmenopausal women with fractures made the retrospective assessment of FRAX more feasible, it also limited our ability to conduct a genuine risk analysis, as fracture incidence could not be evaluated on a large scale. Second, FRAX scores were calculated based on data obtained through telephone interviews prone to a recall bias, which could have been mitigated with prospective collection of data. Not including further confounding factors of osteoporosis, such as dietary habits or physical activity, also limited our ability to make a more complete analysis. Moreover, being the most up-to-date recommendation, we employed risk categorization based on intervention thresholds in a British cohort.[10] A more reliable analysis might have been achieved if a contemporary risk stratification system specific to the Turkish population had been used.[28] Finally, considering that the patients were included from a single city, the population diversity was not optimal, with limited number of nulliparous and primiparous women; thus, the results may not be fully applicable to other demographics or regions.

In conclusion, late menarche, despite being an unaccounted factor, was associated with higher risk in the FRAX, while other obstetric parameters showed similar risk profiles. Considering the increased risk in relation to shorter endogenous estrogen exposure, analyzing larger data on this aspect can be worthwhile during a future update of the FRAX. However, based on these findings, we are not able to strongly recommend the inclusion of obstetric parameters for improving the accuracy of risk assessment using the FRAX.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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