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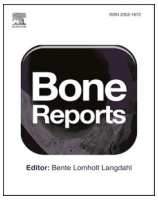

The effect of fracture recency on observed 5-year fracture probability: A study based on the FRISBEE cohort

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ABSTRACT

Introduction: Prediction models, especially the FRAX®, are largely used to estimate the fracture risk at ten years, but the current algorithm does not take into account the time elapsed after a fracture. Kanis et al. recently proposed correction factors allowing to adjust the FRAX® score for fracture recency. The objective of this work was to analyze the effect of fracture recency in the FRISBEE cohort.

Methods: We identified in the FRISBEE cohort subjects who sustained a validated fracture during the first 5 years following an incident MOF. We calculated their estimated 5-year risk of fracture using FRAX® uncorrected, adjusted for recency and further adjusted for the MOF/hip ratios calibration factors previously derived for the Belgian FRAX®. We compared the fracture risk estimated by FRAX® before and after these corrections to the observed incidence of validated fractures in our cohort.

Results: In our ongoing cohort, 376 subjects had a first non-traumatic incident validated MOF after inclusion; 81 had a secondary fracture during the 5 years follow-up period after this index fracture. The FRAX® score significantly under-evaluated the observed incidence of fractures in our cohort by 54.7 % (fracture rate of 9.7 %; 95 % CI, 6.8–12.9 %) if uncorrected ($p < 0.001$) and by 32.6 % after correction for recency (14.5 %; 95 % CI, 11.1–18.2 %) ($p = 0.01$). The calibration for MOF/hip ratios improved the prediction (17.5 %; 95 % CI: 13.7–21.4 %) ($p = 0.2$). After correcting for recency and for calibration, the predicted value was over-evaluated by 22 % (fracture rate of 26.1 %; 95 % CI, 21.6–30.5 %) but this over-evaluation was not significant ($p = 0.1$).

Conclusion: Our data indicate that the correction of the FRAX® score for fracture recency improves fracture prediction. However, correction for calibration and recency tends to overestimate fracture risk in this population of elderly women.

1. Introduction

Prediction models, especially the FRAX®, are largely used to estimate the fracture risk at ten years, but the current algorithm does not take into account the site of a previous fracture nor the time elapsed after a fracture. Kanis et al. recently proposed correction factors allowing to adjust the FRAX® score for fracture recency (McCloskey et al., 2021; Kanis et al., 2020; Kanis et al., 2021). These correction factors decrease with age and vary according to the site of the sentinel fracture, with higher ratios for hip and vertebral fractures than for humerus and forearm fractures. Leslie and colleagues recently examined in the Manitoba Bone Mineral Density Program registry the effect of fracture recency on fracture risk prediction using FRAX® with or without these correction factors (Leslie et al., 2022). They found that the effect of fracture recency was less than previously reported, especially in elderly women. In women aged 40 to 64 years, a recent vertebral and humerus fracture increased the observed 10-year probability of major osteoporotic fracture (MOF) by a factor of 1.61 and 1.48, respectively, over the FRAX® prediction. These factors are lower than the multipliers recently proposed by Kanis et al. (2.32 and 1.67, respectively). For

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women above 65 years of age, the only significant time dependency was for a prior hip fracture and for hip fracture occurrence after the index fracture.

In this work, we examined the effect of fracture recency in our ongoing cohort of postmenopausal women (Fracture Risk Brussels Epidemiological Enquiry, FRISBEE) (Cappelle et al., 2017; Iconaru et al., 2019).

2. Materials and methods

We used for this study data from the FRISBEE cohort. This prospective cohort study comprises 3560 post-menopausal women who are surveyed yearly since their inclusion (2007–2013) for the occurrence of fragility fractures (Cappelle et al., 2017). Participating individuals, randomly selected from population lists of six districts of Brussels, were recruited by postal mailing. The invitation letter explained the issue of osteoporosis with its clinical significance and the goals of the study. Free screening by DXA was offered to participants and performed in one of the centers involved in the study. A reminder letter was sent after 1 month to non-responders. Informed consent was obtained from each woman by return mail. The participation rate was 25 % (20 % after the first letter + 5 % after the reminder letter).

For all participants, BMD at the lumbar spine level (L1-L4) and at the hip (femoral neck, trochanter, and total hip) was measured at baseline by DXA (Hologic). Participants are followed yearly by phone calls and all data were systematically encoded in a specific database. Multiple validated clinical risk factors (CRFs) and medications intake were systematically registered at baseline and during follow-up, without any intervention in the treatment of study participants. We systematically registered the CRFs included in the FRAX® prediction tool: age, body mass index (BMI), history of a prior fragility fracture, parental history of hip fracture, ever use of oral glucocorticoids during a cumulative period of three months or longer, rheumatoid arthritis, current smoking and excessive alcohol intake. The following additional risk factors not included in the FRAX® model were also registered: early non-substituted menopause (occurring before the age 45 years), a sedentary lifestyle (corresponding to the lowest activity level, which was evaluated according to a 6-level scale, adapted from the International Physical Activity Questionnaire (IPAQ) WHO score), Proton Pump Inhibitors (PPI) or Selective Serotonin Reuptake Inhibitors (SSRI) use, education level and comorbidities as chronic obstructive pulmonary disorder, chronic liver disease, inflammatory bowel diseases, chronic malnutrition, anorexia, type 2 diabetes (Cappelle et al., 2017; Iconaru et al., 2019; Iconaru et al., 2022).

Incident non-traumatic or low-traumatic (falls from standing height or less) fractures were systematically registered during follow-up. To be considered, any fracture reported by the study participants had to be validated by written radiological and/or surgical reports. We also registered fractures that were not reported by study participants but found in their medical files and validated by radiological reports (Baleanu et al., 2020a; Baleanu et al., 2020b). For vertebral fractures, we used for this analysis only “clinical fractures”, with symptoms declared by the participants and fractures validated by radiological reports, as well as fractures that were not reported by study participants and found in their medical files, but only if the radiological exam was requested for clinical symptoms. Fractures of the skull, face, fingers, toes and traumatic or pathological fractures, i.e., caused by metastatic cancer, were not considered in this report.

The protocol was accepted by the Ethics Committee of all participating sites (approval number B07720072493).

For this study, we identified in the FRISBEE cohort those patients who had a first incident validated MOF after study inclusion and who were followed for 5 years after the incident fracture.

The 10-year fracture risk was calculated by the Belgian FRAX® on the basis of the CRFs at the time of the incident fracture, except for BMD which was measured at baseline only. The 5-year risk was derived on the basis of previously published FRAX linearity (Leslie et al., 2017). Because in our Brussels cohort, MOFs/hip ratios were 1.7–1.8 times those observed in Sweden currently used for MOFs prediction in the Belgian FRAX® version (Mugisha et al., 2021), resulting in an under-evaluation of MOFs risk (Mugisha et al., 2021; Johansson et al., 2011), the calculated risk was adjusted for this calibration factor. Probability ratios to adjust 5-year FRAX® probabilities of a MOF for fracture recency, according to the index fracture site and age, were applied using recommendations of Kanis et al. (Kanis et al., 2021).

We used the Pearson's chi squared test to compare the estimated fracture risks versus the observed incidence of fractures in our cohort.

3. Results

In our ongoing cohort of 3560 postmenopausal women, 376 subjects had a first non-traumatic incident validated MOF after inclusion (135 clinical spine, 51 hip fractures, 61 proximal humerus and 129 wrist fractures). Eighty-one had a secondary fracture during the 5 years follow-up period after this index fracture (21.5 %; 95 % CI, 17.3–25.7 %): 33 clinical spine, 19 hip fractures, 15 proximal humerus and 14 wrist fractures. 58 of them (15.4 %) had a diagnostic of osteoporosis at DXA evaluation (study inclusion) and there were comorbidities or drugs affecting bone health in 72 women (19.1 %). At the time of the incident fracture, 105 subjects (27.9 %) were treated by a pharmacological therapy against osteoporosis. Patients who were treated were initially prescribed oral bisphosphonates (70/105, 66.7 %), iv bisphosphonates (11/105, 10.5 %), denosumab (13/105, 12.4 %), strontium ranelate (5/105, 4.7 %) or a selective estrogen receptor modulator (SERM) (6/105, 5.7 %). The most commonly prescribed oral bisphosphonate was alendronate (46/70, 65.7 %), followed by ibandronate (12/70, 17.1 %) and risedronate (9/70, 12.9 %).

The mean (±SD) age of the women at the time of the first incident fracture was 76.5 ± 6.8 years and 96.3 % were older than 65 years (“elderly”). The mean time to first fracture after inclusion was 3.6 ± 2.2 years.

The predicted 5-year risk calculated by the FRAX®, uncorrected, adjusted for recency using the age and site-specific multipliers derived by Kanis et al. (2021), corrected for our calibration factor for the MOF/hip ratios (Mugisha et al., 2021), and adjusted for both recency and our calibration factor were compared to the rate of observed validated fractures during the 5-year period following the index fracture (Fig. 1).

If not corrected for the MOF/hip ratio, the Belgian FRAX® tool under-evaluated the observed incidence of fractures by 54.7 % (estimated fracture risk = 9.7 %; 95 % CI, 6.8–12.9 %) ($p < 0.001$). This under-evaluation was attenuated at 32.6 % when the correction for recency was applied but remained significant (estimated fracture risk =14.5 %; 95 % CI, 11.1–18.2 %) ($p = 0.01$). After re-calibration for the MOF/hip ratios (Mugisha et al., 2021) without correction for recency, the estimated rate risk remained non-significantly lower (estimated fracture risk = 17.5 %; 95 % CI: 13.7–21.4 %) ($p = 0.2$) than the observed fracture rate, but the correction for recency then led to a non-significant over-evaluation of the risk (estimated fracture risk =26.1 %; 95 % CI, 21.6–30.5 %) ($p = 0.1$).

4. Discussion

The objective of this work was to analyze the effect of fracture recency in the FRISBEE cohort.

Adjustment of the FRAX® for time since a previous fracture was recently proposed by Kanis et al. (Kanis et al., 2020; Kanis et al., 2021) who calculated probability ratios associated with fracture recency according to the index fracture site and age. These recent fracture multipliers have not yet been directly validated in populations with complete information on all FRAX® risk factors.

A recent analysis was performed by Leslie and colleagues (Leslie et al., 2022) in the Manitoba Bone Mineral Density Program registry to

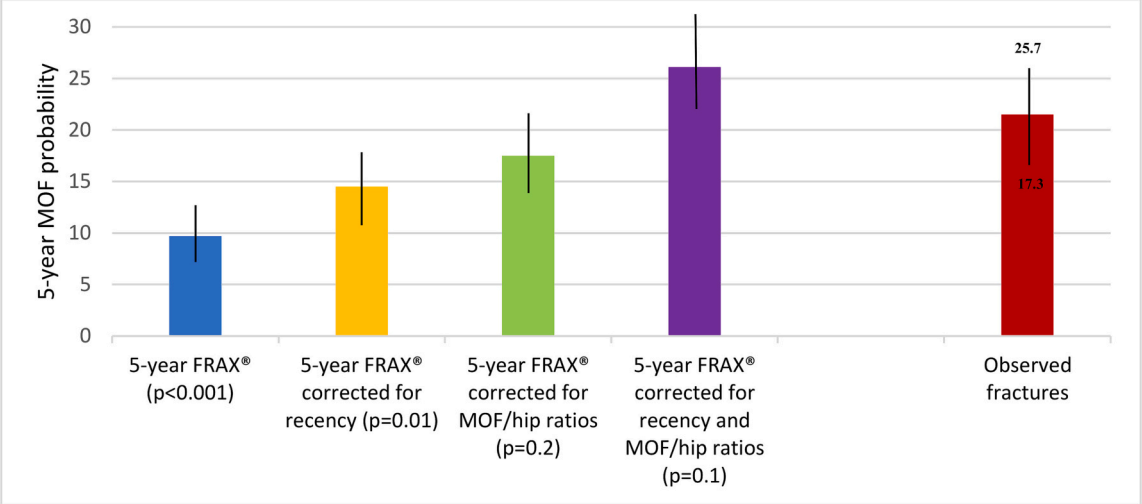

Fig. 1. Five-year probability of MOFs calculated with the FRAX® score, uncorrected, corrected for recency, for MOF/hip ratios, or for both, compared to the rate of observed validated fractures in the FRISBEE cohort.
Blue column: 5-year probability of MOFs calculated with the current Belgian FRAX®.
Yellow column: 5-year probability of MOFs calculated with the Belgian FRAX® corrected for recency using the age and site-specific multipliers derived by Kanis et al. (Kanis et al., 2021).
Green column: 5-year probability of MOFs calculated with the Belgian FRAX® corrected by a factor of 1.8 for MOF/hip ratios (Baleanu et al., 2020b).
Purple column: 5-year probability of MOFs calculated with the FRAX® corrected for recency and for MOF/hip ratios.
Red column: rate of observed validated fractures during the 5-year period following the index fracture.
Bars show the 95 % confidence intervals.
The 5-year probabilities of MOFs calculated with the Belgian FRAX®, corrected or not are compared to the rate of observed fractures using Pearson's chi squared test.

characterize the effects of a previous fracture, stratified as recent (<2 years) versus remote (≥2 years), on fracture risk, performance of FRAX®, and the utility of recent-fracture multipliers. This effect was confirmed for incident MOFs in women aged 40 to 64 years after a recent MOF. Time dependency was also observed for an incident hip fracture within the next 2 years in women aged 65 years or older after a recent MOF, with stronger effects for a recent hip fracture or humerus fracture. However, these differences were attenuated in elderly women (Leslie et al., 2022). We thus studied the effect of fracture recency in our ongoing cohort of postmenopausal women, most of whom (96.3 %) older than 65 years of age.

In a previous study, we analyzed the importance of a recent fracture as a CRF for occurrence of a new fracture independently of other classical CRFs (Iconaru et al., 2021). We showed that a recent fracture increased by a factor of 3 to 4 the risk of a recurrent fracture. These findings are in line with the recent demonstration that a recent fracture has a marked impact on the probability of future fracture, providing a rationale to adjust for recency the FRAX® score.

In this work, we compared the predicted 5-year risk calculated by the FRAX® score, uncorrected, adjusted for recency using the age and site-specific multipliers derived by Kanis et al. (Kanis et al., 2021), and corrected for our calibration factor (Mugisha et al., 2021) to the actual rate of observed validated fractures during the 5-year period following the index fracture. Our data confirm that the FRAX® underestimates the probability of fractures in our cohort. They also show that the correction for recency tends to overestimate fracture risk in this population of women above 65 years of age. Thus the correction of the FRAX® for calibration, with or without an adjustment for recency, improves fracture prediction, with values not significantly different of the observed rate, showing that the effect of recency is indeed attenuated in an older population.

Even if our results showed that the effect of recency is attenuated in an older population, a first fracture should continue to be regarded as a major risk factor for a second fracture and needs a clinical evaluation and an appropriate treatment. We sustain the recent studies showing that these patients are at very high risk for an imminent fracture, providing a rationale to adjust for recency the conventional FRAX® score. Nevertheless, our data indicate, in agreement with Leslie et al., that the recency multipliers should be validated in additional cohorts of elderly women in order to refine their role in fracture risk assessment before using them in everyday practice. Additionally these adjustments should be defined also in men.

The study has strengths and limitations. The strengths lie in a large longitudinal study cohort, its prospective design, and the validation by radiological reports of all considered fractures, reported or not by study participants. The main limitation of our study could be an insufficient power due to the relatively small number of fractures.

In summary, our data show that the correction for fracture recency tends to overestimate 5- year fracture risk in elderly subjects. The effect of recency is thus attenuated in an older population.

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CRediT authorship contribution statement

L. Iconaru: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **A. Charles:** Data curation. **F. Baleanu:** Conceptualization, Methodology, Writing – review & editing. **M. Moreau:** Formal analysis. **M. Surquin:** Conceptualization, Methodology, Writing – review & editing, Supervision. **F. Benoit:** Conceptualization, Methodology, Writing – review & editing, Supervision. **J.J. Body:** Conceptualization, Methodology, Writing – review & editing, Supervision. **P. Bergmann:** Conceptualization, Methodology, Writing – review & editing, Supervision.

Declaration of competing interest

We wish to declare that there are no known conflicts of interest associated with this publication that could be perceived as prejudicing

the impartiality of the research reported.

Data availability

Data will be made available on request.

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