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Comparison between frailty index of deficit accumulation and fracture risk assessment tool (FRAX) in prediction of risk of fractures

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Abstract

A frailty index (FI) of deficit accumulation could quantify and predict the risk of fractures based on the degree of frailty in the elderly. We aimed to compare the predictive powers between the FI and the fracture risk assessment tool (FRAX) in predicting risk of major osteoporotic fracture (hip, upper arm or shoulder, spine, or wrist) and hip fracture, using the data from the Global Longitudinal Study of Osteoporosis in Women (GLOW) 3-year Hamilton cohort. There were 3985 women included in the study, with the mean age of 69.4 years (standard deviation [SD] = 8.89). During the follow-up, there were 149 (3.98%) incident major osteoporotic fractures and 18 (0.48%) hip fractures reported. The FRAX and FI were significantly related to each other. Both FRAX and FI significantly predicted risk of major osteoporotic fracture, with a hazard ratio (HR) of 1.03 (95% confidence interval [CI]: 1.02–1.05) and 1.02 (95% CI: 1.01–1.04) for per-0.01 increment for the FRAX and FI respectively. The HRs were 1.37 (95% CI: 1.19–1.58) and 1.26 (95% CI: 1.12–1.42) for an increase of per-0.10 (approximately one SD) in the FRAX and FI respectively. Similar discriminative ability of the models was found: c-index = 0.62 for the FRAX and c-index = 0.61 for the FI. When cut-points were chosen to trichotomize participants into low-risk, medium-risk and high-risk groups, a significant increase in fracture risk was found in the high-risk group (HR = 2.04, 95% CI: 1.36–3.07) but not in the medium-risk group (HR = 1.23, 95% CI: 0.82–1.84) compared with the low-risk women for the FI, while for FRAX the medium-risk (HR = 2.00, 95% CI: 1.09–3.68) and high-risk groups (HR = 2.61, 95% CI: 1.48–4.58) predicted risk of major osteoporotic fracture significantly only when survival time exceeded 18 months (550 days). Similar findings were observed for hip fracture and in sensitivity analyses. In conclusion, the FI is comparable with FRAX in the prediction of risk of future fractures, indicating that measures of frailty status may aid in fracture risk assessment and fracture prevention in the

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Conflict of interest

The authors declare that they have no conflicts of interest.

elderly. Further evidence from randomized controlled trials of osteoporosis medication interventions is needed to support the FI and FRAX as validated measures of fracture risk.

Keywords

FRAX; Frailty index; Hip fracture; Major osteoporotic fracture; Predictive power; GLOW

Introduction

As the population ages worldwide, increasing fractures in the elderly become a greater public health issue [1]. Approximately 340,000 hospitalizations due to hip fractures occurred among persons older than 65 years in USA in 1996 [2], and it is estimated that this annual number of hip fractures will double by the year 2040 [3,4]. Fractures in the elderly are usually followed by impaired quality of life, long-term care, permanent disability and high mortality [5,6].

The fracture risk assessment tool (FRAX) is a recognized computer-based algorithm that uses clinical risk factors to predict absolute 10-year fracture probability in men and women [7,8]. Currently FRAX is being used worldwide with or without femoral neck bone mineral density (BMD) to enhance the prediction of fracture risk [7,8]. Nevertheless, concerns have been expressed about FRAX including that it is difficult to interpret in clinical practice, does not capture many other risk factors (e.g., falls, physical activity, or dose of alcohol, smoking and glucocorticoid use), and has a wide variation and limited discriminative ability in different populations in the prediction of fractures [9–14].

Frailty is defined as a dynamic state of vulnerability which affects an individual in his/her physical, psychological and social functioning and increases the risks of adverse health outcomes [15]. A frailty index (FI) of deficit accumulation is widely used to measure frailty in terms of using a range of health deficits to quantify the cumulative effect [16, 17]. In the elderly, a higher FI was related with higher risk of adverse health outcomes at all ages, despite the deficit accumulation with chronological age across the age spectrum [18,19]. A validated FI was especially useful in evaluating the preventive or therapeutic performance of health and social services provision and policies as a population indication with precise estimates of risks of adverse health outcomes [20–22].

The FI could grade and predict the risk of fractures based on the degree of frailty in the elderly, which had been explored in previous studies [23–26]. However, limited evidence comparing the predictive accuracy of the FI and FRAX in the risk of fractures is available. Therefore, in this study, we aimed to compare the predictive powers between the FI of deficit accumulation and FRAX in predicting risk of fractures, based on the data from the Global Longitudinal Study of Osteoporosis in Women (GLOW) 3-year Hamilton cohort. The primary objective was to compare the predictive accuracy between the FRAX and FI in 3-year risk of major osteoporotic fracture (hip, upper arm or shoulder, spine, or wrist), and the secondary objective aimed at 3-year risk of hip fracture.

Methods

Participants and setting

GLOW is an international longitudinal study which involves 17 sites in 10 countries (Canada, US, Australia, Belgium, France, Germany, Italy, Netherlands, Spain and UK). It has been described previously in detail [27]. GLOW was performed to assess the health consequences of and risk factors for fragility fractures in 60,393 women no less than 55 years old who had consulted their physician in the past 24 months. The participants were stratified according to age strata such that approximately two-thirds of women aged 65 years. Women were eligible to enter the cohort if they had no cognitive impairment or language barriers, and were not institutionalized or too ill to finish the study survey [27].

Our study was a longitudinal analysis of the 3-year GLOW Hamilton, Canada cohort. A sample of about 4000 women were enrolled between May 2008 and March 2009 and followed up every year to complete the survey. Participants were surveyed by mailing questionnaires annually, in which the questionnaires collected data on participant characteristics and risk factors, health care access and use, co-morbidities, perception about fracture risk and osteoporosis, physical activity, medication use, physical function and quality of life [27]. Telephone interviews were conducted if the participant did not return the mailed survey or needed assistance in completing the questionnaire. The study was approved by the Western Institutional Review Board. All participants provided written informed consent before the survey.

The FRAX and the FI of deficit accumulation

The FRAX algorithm aimed to provide an assessment for the prediction of 10-year risks of hip fracture and major osteoporotic fracture (hip, clinical spine, wrist, or proximal humerus fracture) in women and men, using clinical risk factors with or without femoral neck BMD [7,8]. The clinical risk factors included age, gender, weight, height, a history of fragility fracture, parental hip fracture, current smoking, alcohol intake of 3 units daily, use of oral glucocorticoids, diagnosis of rheumatoid arthritis, and secondary osteoporosis [7,28]. Since data on BMD testing was not collected in the GLOW protocol [27], BMD was not included in the FRAX algorithm to predict risks of fractures. We used the Canadian FRAX algorithm [29] to calculate the scores of 10-year fracture risk in this study.

The FI of deficit accumulation was calculated by 34 baseline health deficits including activity of daily living (n = 12), signs and symptoms (n = 6), comorbidities (n = 15) and healthcare utilization (n = 1). The construction of the FI has been described previously based on the GLOW Hamilton cohort [30]. Each deficit was coded by dichotomization or polychotomization to map the interval 0–1 so that the coding could represent the frequency or severity of the deficits. For instance, as regards the question of ‘self-rating of health’, the response of ‘poor’ was coded as 1, ‘fair’ as 0.75, ‘good’ as 0.5, ‘very good’ as 0.25 and ‘Excellent’ as 0. The deficits included in the FI and their individual coding were presented in Supplementary Table 1. To calculate a FI for an individual participant, her values of deficits were summed up and divided by the total number of variables (n = 34) in the FI, with the FI ranging from 0 to 1 [30]. For example, if a women had 4 deficits with each score of 1 point,

2 deficits with each score of 0.5 and the other 28 deficits with each score of 0, then her FI of deficit accumulation would hence be 5 divided by 34 giving a FI = 0.15.

Outcomes

Participants reported fragility fractures that had occurred from age 45 years in baseline questionnaires including spine, clavicle, rib, upper arm or shoulder, wrist, pelvis, hip, upper leg, lower leg or ankle fracture. During the annual follow-up survey, participants documented their incident fractures and the dates in the questionnaires. To directly compare the FI with FRAX, the primary outcome was survival time to first incident major osteoporotic fracture (hip, upper arm or shoulder, spine, or wrist) during the follow-up, while the secondary outcome was time to first incident hip fracture.

Statistical analyses

Data were presented as mean and standard deviation (SD) for continuous variables and frequency and proportion for categorized variables, respectively. Comparison at baseline by the 3-year incident major osteoporotic fracture status was examined using Chi-square tests for the categorical variables and Student's t-test for continuous variables.

To analyze the associations between FRAX or FI and incident fractures during follow-up, Cox proportional hazards models were performed and hazard ratios (HRs) were used to quantify the relationship. Unadjusted HR for FRAX was presented in univariable analyses, whereas results were reported in the age-adjusted model for the FI given that health deficits were all age-associated and age was not included in the FI in the elderly [22,31,32].

Results were presented according to an increase of 0.01 (or 1%) on the FI and FRAX [33]. We also reported the HRs measured by per-0.10 (approximately one SD) increment of the FI and FRAX [26,30]. Moreover, findings from the categorized groups were also displayed using the cut-points of FRAX and FI. For major osteoporotic fracture, participants were categorized into low-risk, medium-risk and high-risk group based on the 10-year fracture risk probability calculated from FRAX, with the cut-points of 10% and 20% for FRAX [34,35]. To directly compare the predictive accuracy between FRAX and FI, we adopted Rockwood's methodology [36] to choose the cut-points of the FI and trichotomize the participants. The cut-points of 0.20 and 0.35 on the FI were identified by overlapping the FI's density distributions of the robust (or low-risk), pre-frail (or medium-risk) and frail (high-risk) women, in which the robust, pre-frail and frail group were defined by the widely used and validated phenotypic frailty model in geriatrics [30,36,37]. The rationale for this methodology was that the frailer a woman was, the greater the likelihood that she would fracture in the future [22,26,38]. On the other hand, for hip fracture, we dichotomized the women into low-risk and high-risk group using the cut-point of 3% for FRAX as recommended [35]. With regard to the FI, we chose its median of 0.22 to categorize participants into low-risk and high-risk group, for the purpose of direct comparison with FRAX in predicting risk of hip fracture.

Survival curves for major osteoporotic fracture were graphed using the Kaplan–Meier (KM) method and compared by the log-rank test between the three groups categorized by the aforementioned cut-points of FRAX and FI, respectively. To assess the proportional hazards

(PH) assumption, both a statistical test and a graphical examination using Schoenfeld residuals were performed. Because evidence was found that the PH assumption was not satisfied for the grouped FRAX (low-risk, medium-risk and high-risk), an extended Cox model was used by splitting the survival time. The goodness of fit of the models was assessed based on the Cox–Snell residuals and the Gronnesby and Borgan test. Model discrimination was assessed with the use of Harrell’s c-index.

We performed two sensitivity analyses to assess the robustness of the findings. First, a sensitivity analysis was conducted using an accelerated failure time model with a Weibull distribution to compare the findings from Cox proportional hazards model analyses. Another sensitivity analysis was performed to assess the impact of missing data. We used multiple imputation approach [39] to impute missing data if the percentage of missing data was more than 10%. If data of <10% on a variable were missing, the median or mean of the variable was used for imputation. Furthermore, we conducted an analysis stratified by the women who were taking and not-taking anti-osteoporotic treatment, calcium and/or vitamin D supplementation at baseline, to investigate the impact of the treatment and/or supplementation on the prediction of the FRAX and FI in fractures in this study.

All tests were two-sided according to a significance level of 0.05. All analyses were performed using STATA Version 12 (Stata Corp., College Station, TX, USA).

Results

There were 3985 women included in the study at baseline (Table 1). The mean age was 69.4 years (SD = 8.89), and the mean body mass index (BMI) was 27.7 (SD = 5.77) kg/m². There were 11% and 49% of participants smoking and drinking respectively. The proportions of the other components include in FRAX by self-report were low: 22% for history of fragility fracture, 16% for parental hip fracture, 12% for diagnosis of rheumatoid arthritis, 4% for use of glucocorticoids and 24% for diagnosis of secondary osteoporosis.

FRAX and FI related to each other significantly, with correlation coefficients of 0.20 for both the continuous values and categorized groups ($p < 0.001$). The baseline FRAX scores of 10-year risk of major osteoporotic fractures had a mean of 0.16 (SD = 0.099), ranging from 0.03 to 0.79. The mean of the FI was 0.24 (SD = 0.13), with a range from 0 to 0.72. Based on the cut-points, there were 41% ($n = 1159$) and 27% ($n = 759$) of the women categorized into medium-risk and high-risk group by FRAX respectively, whereas the proportions were 34% ($n = 1357$) and 22% ($n = 879$) for medium-risk and high-risk group defined by the FI respectively (Table 1).

During the 3-year follow-up, there were 149 (3.98%) incident major osteoporotic fractures (hip, upper arm or shoulder, spine, or wrist) reported. Women with incident fractures were older, had significantly more prior fractures, parental hip fractures, rheumatoid arthritis and the use of glucocorticoids than the participants without incident major osteoporotic fractures (all p -values < 0.05 , Table 1). Women with incident major osteoporotic fractures ($n = 149$) had significantly higher baseline FRAX scores (0.20) and FI (0.28) than those without fractures (FRAX = 0.16; FI = 0.24; $n = 3594$). The 3-year incidence rates for the low-risk,

medium-risk and high-risk group defined by the FRAX were 2.48% (n = 23), 3.81% (n = 44) and 5.80% (n = 44) respectively, while the proportions were 2.86% (n = 50), 3.62% (n = 49) and 5.69% (n = 50) for the FI groups respectively.

Table 2 shows the comparison of prediction and model performances between FRAX and FI in risk of 3-year major osteoporotic fracture. Both the FRAX and FI significantly predicted risk of major osteoporotic fracture, with a HR of 1.03 (95% CI: 1.02–1.05, $p < 0.001$) and 1.02 (95% CI: 1.01–1.04, $p < 0.001$) for per-0.01 increment of the FRAX and FI respectively. The HRs were 1.37 (95% CI: 1.19–1.58) and 1.26 (95% CI: 1.12–1.42) for an increase of per-0.10 (approximately one SD) in the FRAX and FI respectively. No PH assumption violation was observed for the incremental FRAX or FI. The models were both of good fit ($p > 0.05$). The c-indices implied similar discriminative values of the models for major fracture: c-index = 0.62 for the FRAX and c-index = 0.61 for the FI respectively.

Figs. 1 and 2 show the KM survival curves for the participants trichotomized by the FRAX and FI respectively. As shown in Fig. 1, the KM curves crossed approximately at 12 months (365 days) and 18 months (550 days). The statistical test and graphical examination based on Schoenfeld residuals also indicated that the PH assumption was violated for the categorized groups by FRAX. Therefore, an extended Cox model was conducted by splitting survival time into <365 days, 365–550 days and >550 days (Table 2). The relationship between risk of major osteoporotic fracture and the FRAX was significant only when survival time exceeded 550 days, with the HRs of 2.00 (95% CI: 1.09–3.68, $p = 0.026$) and 2.61 (95% CI: 1.48–4.58, $p = 0.001$) for the medium-risk and high-risk group compared with the low-risk group respectively (Table 2). On the other hand, no PH assumption violation was found for the three groups defined by the FI. Log-rank test indicated the significant difference of survival curves between the three groups ($p < 0.001$). Compared with the low-risk group, only the high-risk group presented a significant effect on the major osteoporotic fracture (HR = 2.04, 95% CI: 1.36–3.07, $p = 0.001$). The model for the categorized FI was of good fit ($p = 0.22$) and it had a c-index of 0.61 (Table 2). Moreover, to show the direct comparison between FRAX and FI, we also conducted an extended Cox analysis for the FI by splitting the same survival time spans (<365 days, 365–550 days and >550 days). Similarly, significant associations between risk of major osteoporotic fracture and the FI were only detected when survival time was larger than 550 days: HR = 1.84 (95% CI: 1.16–2.93, $p = 0.009$) for medium-risk group and HR = 2.14 (95% CI: 1.20–3.82, $p = 0.006$) for high-risk group, compared with low-risk women.

There were 18 (0.48%) incident hip fractures reported during the 3-year follow-up (Table 3). Significant associations were found between the per-0.01 increment for FRAX and FI and risk of hip fracture, with a HR of 1.05 (95% CI: 1.02–1.09) and 1.03 (95% CI: 1.00–1.07) for the FRAX and FI respectively. Per-0.10 increase in the FRAX and FI yielded a HR of 1.64 (95% CI: 1.16–2.32) and 1.39 (95% CI: 1.00–1.94) respectively. When the participants were dichotomized into low-risk and high-risk group, nevertheless, only the high-risk group defined by FRAX predicted the risk of hip fracture significantly (HR = 4.05, 95% CI: 1.12–14.72) (Table 3). PH assumption was satisfied for all the models for hip fracture.

A sensitivity analysis using accelerated failure time models with a Weibull distribution yielded similar results to the Cox models for the relationship between the FRAX and FI and risk of major osteoporotic fracture and hip fracture (Table 4). Because approximately 29% (n = 1138) of the women had missing data on the FRAX scores at baseline, models were performed by using multiple imputations to investigate the relationship between FRAX and risk of major osteoporotic fracture and hip fracture, without altering the findings (Supplementary Table 2). Furthermore, to directly compare the prediction of the FRAX and FI in fractures, we restricted the analyses in the same participants whose both baseline FRAX and FI were available (n = 2847). The results remained unchanged from the main analyses (Supplementary Table 3).

Table 5 shows results of the relationship between the 3-year risk of major osteoporotic fracture and FI and FRAX stratified by participants' use of anti-osteoporotic treatment and/or supplementation. During follow-up, there were 108 and 41 incident major osteoporotic fractures reported in the participants receiving anti-osteoporotic treatment, calcium and/or vitamin D supplementation (n = 2912) and the women taking none of these drugs (n = 1073) at baseline, respectively. Similar findings were observed in the women with and without treatment and/or supplementation (Table 5), indicating no significant effect of the treatment and/or supplementation on the prediction of FI and FRAX in major osteoporotic fracture in this population.

Discussion

Main findings

Using the 3-year GLOW Hamilton cohort, the predictive accuracy between the FI of deficit accumulation and FRAX was compared in risk of major osteoporotic fracture and hip fracture. The FRAX and FI related to each other significantly. Similar results were found for the per-0.01 increment of the FRAX and FI in predicting risk of fractures. The high-risk group defined by FRAX predicted 3-year risk of major osteoporotic fracture and hip fracture significantly, while the high-risk group categorized by the FI only showed a significant association with major osteoporotic fracture. The models for FRAX and FI were of good fit and with similar discriminative values. Results from accelerated failure time models and multiple imputations corroborated the robustness of the findings.

In this study, we reported similar results from the continuous FRAX and FI, given that the continuous results could be used as a population indication in evaluating the preventive or therapeutic performance of health [20]. On the other hand, the categorical FRAX was adopted widely in clinical practice to aid in the decisions of further assessment and pharmacologic treatment [12,35]. This was also consistent with the categorical FI, in which the therapeutic or preventive interventions should be specifically directed to the frail or high-risk population [36,40]. The widely-used FRAX consists of clinical risk factors identified from meta-analyses and it has been externally validated and calibrated in specific populations [14]. For the elderly, frailty was a nonspecific state of vulnerability that could be measured and quantified using a FI of deficit accumulation, in which the FI covered a comprehensive domains of deficits related with aging including co-morbidities, signs and symptoms, activities of daily living, healthcare utilization, etc [30,40]. Compared with the

clinical risk factors of FRAX, the FI of deficit accumulation approach predicted the risk of future fractures by quantifying the frailty status. Because participants with more deficits were more likely to be frail and more likely to experience adverse health events [22], measuring their cumulative deficits could contribute to predicting their increased risk of fractures [26]. In this study, comparable findings from continuous and categorical FRAX and FI supported that the frailty approach was not inferior to the recognized FRAX in prediction of fractures (Tables 2, 3).

In this study, comparable results were found in the women who were taking and not-taking anti-osteoporotic treatment and/or supplementation at baseline (Table 5). These findings were also consistent with the main results using the whole population (Table 2), implying no significant effect of the baseline anti-osteoporotic treatment and/or supplementation on the prediction of FRAX and FI in major osteoporotic fracture. Some studies argued that previous falls should be included into FRAX, since previous falls were an independent and significant risk factor for future fractures [12,28]. Nevertheless, evidence showed that models incorporating falls as a risk factor may not be superior to FRAX alone in predicting future risk of fractures [41]. In our study, a post-hoc analysis incorporating baseline falls into the models yielded similar results for both FRAX and FI to the parsimonious models (Table 2), e.g., for the per-0.01 increment the HR was 1.03 and 1.02 and the c-index was 0.61 and 0.61 for FRAX and FI respectively.

Comparison with other studies

Previous studies investigating the relationship between a FI and fractures reported significant results [23–26], which was in line with our findings. For example, the Canadian Multicentre Osteoporosis Study (CaMos) using a 30-item FI to predict 10-year fracture risk reported significant associations between the FI and fractures in adults, with a HR of 1.18 for hip fracture and 1.30 for clinical vertebral fractures (p-values < 0.05) for per-0.10 increase in FI [26]. Nevertheless, no evidence directly comparing the prediction of the FRAX and FI approaches in fractures was available. Besides, there were some suggestions incorporating frailty into FRAX, especially in the previous fallers, to improve the precision of FRAX's predictive power [42]. However, in this study we did not combine the FI and FRAX into the same model, because the FI shared the same three components of FRAX (i.e., use of oral glucocorticoids, rheumatoid arthritis, and secondary osteoporosis) and both prediction tools were significantly associated with each other. Nonetheless, the suggestions did shed some light in that the measures of frailty contributed to the prediction of fractures and the management of frailty could assist in reducing the risk of future fractures [42–44].

Clinical implication

This study yielded similar and comparable relationship between major osteoporotic and hip fracture and the FRAX and FI, indicating that the frailty measure may be as important as FRAX based on clinical risk factors to predict risk of fracture in the elderly. However, compared with the wide-spread application of FRAX in clinical settings, the FI approach may be helpful only as a research tool in population settings, especially given the large amount of information required.

Limitations and strengths

Our study has several limitations. Originally FRAX was designed to predict 10-year risk of fractures, while this study only provided 3-year data. As shown in Fig. 1 and Table 2, the grouped FRAX predicted the risk of major osteoporotic fracture significantly with longer follow-up (i.e., > 550 days), when the medium-risk or high-risk group was compared with the low-risk group. Therefore the short-term observation may compromise the predictive power of both FRAX and FI. Furthermore, since the dates of death were not available in GLOW, the FI could not take into account the competing risk of death for prediction of future fractures, whereas the competing mortality risk was included in the FRAX algorithm. Failing to account for the competing risk of death may bias the prediction of risk of fractures using the FI. Another limitation was due to the inclusion criteria of no cognitive impairment for the participants in GLOW, because cognitive impairment was a significant risk factor for fractures [45]. Moreover, all the data collected in GLOW were only from self-report of participants and could not be validated by medical records. Besides, recall bias was inevitably induced when participants were completing questionnaires. Furthermore, the measures of BMD may assist FRAX with improvement of predictive accuracy in risk of fractures [46], but BMD was not available in GLOW. Even though emerging evidence reported that FRAX with BMD was in good agreement with FRAX alone, and FRAX alone provided the same prediction as FRAX with BMD [47–50], it was unknown whether the FRAX with BMD outperformed the FRAX alone in the elderly in this study. Lastly, the small number of hip fracture ($n = 18$) resulted in imprecise estimates and wide confidence intervals (Tables 3 and 4). Similarly, due to the small proportions of the older participants and small number of fracture events, no analysis was conducted for the very old women. For example, there were only 5 incident major osteoporotic fractures and 4 hip fractures reported in the women aged >85 years ($n = 139$, 3%). Likewise, there were only 13 major osteoporotic fractures and 5 hip fractures found in the participants aged >80 years ($n = 494$, 12%).

This study yielded comparable findings from the FI and FRAX in the prediction of risk of major osteoporotic and hip fractures in the elderly, which may provide some insights into the fracture prevention and risk assessment using the measures of frailty status. The FI approach assisted with the investigation of aging and the prediction of adverse health events including fractures, by quantifying the degree of frailty. This may aid in the decision of intervention plans and evaluations for geriatricians, bone specialists, health researchers and policy-makers. Furthermore, different strategies and sensitivity analyses yielded similar results, which underpinned the robustness of our findings. A third strength was the representative sample because of the unique sampling method in GLOW [27]. Women were enrolled according to the lists provided by their physician practices with few exclusion criteria, which therefore led to the overall participants being representative of the practices [51].

Conclusion

To conclude, both the FI and FRAX significantly predict risk of major osteoporotic and hip fracture significantly using the GLOW 3-year Hamilton cohort. The FI is comparable with FRAX in prediction of risk of future fractures, indicating that measures of frailty status may

aid in the fracture risk assessment and fracture prevention in the elderly. Further evidence from randomized controlled trials of osteoporosis medication interventions is needed to support the FI and FRAX as validated measures of fracture risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

FI	frailty index
FRAX	fracture risk assessment tool
GLOW	Global Longitudinal Study of Osteoporosis in Women
CI	confidence interval
SD	standard deviation
HR	hazard ratio
BMD	bone mineral density
KM	Kaplan–Meier
PH	proportional hazards
BMI	body mass index

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.bone.2015.04.028>.

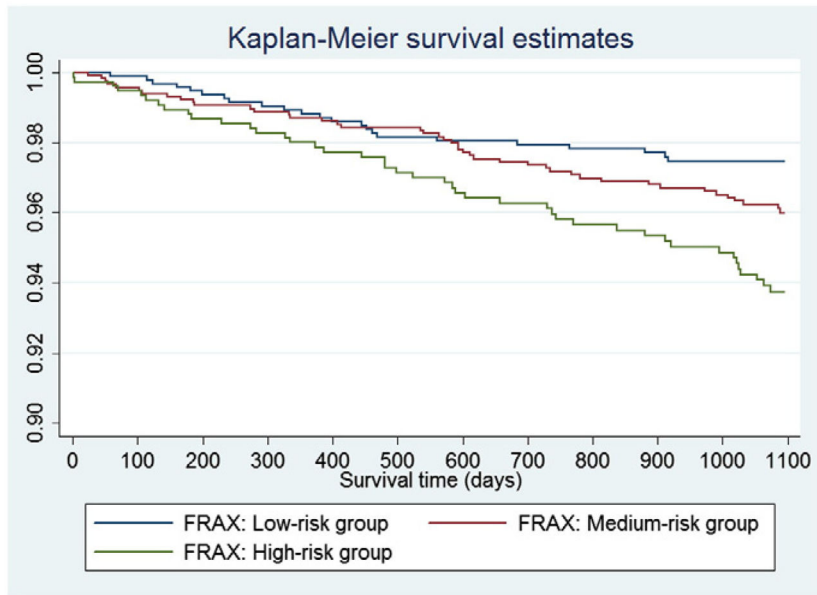


Fig. 1. Kaplan–Meier survival curves in the three groups defined by the FRAX.

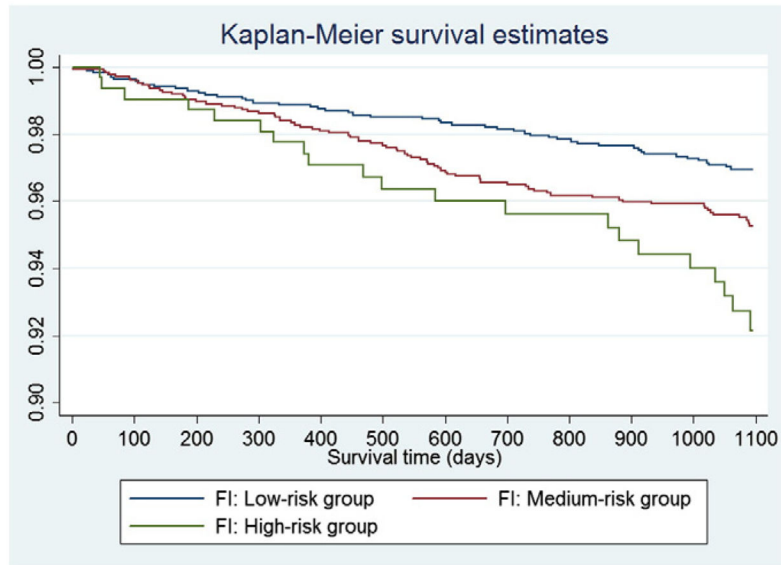


Fig. 2. Kaplan–Meier survival curves in the three groups defined by the FI.

Table 1

Baseline characteristics of participants and comparison by the 3-year incident major osteoporotic fracture status*.

Characteristics	Total participants (n = 3985)	Major osteoporotic fracture ^a		
		No (n = 3594)	Yes (n = 149)	p-Value
Age: mean (SD), years	69.4 (8.89)	69.1 (8.71)	71.3 (9.43)	0.002 ^b
BMI: mean (SD), kg/m ²	27.7 (5.77)	27.7 (5.73)	27.5 (5.74)	0.53 ^b
Smoker, n (%)				
Yes	447 (11.30)	393 (11.01)	15 (10.20)	0.76 ^c
No	3510 (88.70)	3178 (88.99)	132 (89.80)	
Drinking (drinks/week), n (%)				
0	2027 (51.21)	1809 (50.63)	84 (57.14)	0.58 ^d
7	1414 (35.73)	1299 (36.36)	42 (28.57)	
7–13	428 (10.81)	389 (10.89)	16 (10.88)	
14–20	76 (1.92)	66 (1.85)	4 (2.72)	
>20	13 (0.33)	10 (0.28)	1 (0.68)	
Race, n (%)				
White	3717 (93.27)	3374 (93.88)	138 (92.62)	0.53 ^c
Non-white	268 (6.73)	220 (6.12)	11 (7.38)	
Education, n (%)				
High school or less	2509 (64.10)	2239 (63.36)	97 (66.44)	0.45 ^c
More than high school	1405 (35.90)	1295 (36.64)	49 (33.56)	
Prior fractures since 45 years old, n (%)				
Yes	862 (22.31)	737 (21.11)	52 (35.86)	<0.001 ^c
No	3001 (77.69)	2754 (78.89)	93 (64.14)	
Parental hip fracture, n (%)				
Yes	599 (15.88)	534 (15.67)	33 (23.40)	0.014 ^c
No	3173 (84.12)	2874 (84.33)	108 (76.60)	
Rheumatoid arthritis, n (%)				
Yes	447 (11.57)	383 (10.97)	26 (18.06)	0.008 ^c
No	3418 (88.43)	3107 (89.03)	118 (81.94)	
Use of glucocorticoids, n (%)				
Yes	141 (3.63)	121 (3.45)	10 (6.90)	0.029 ^c
No	3748 (96.37)	3387 (96.55)	135 (93.10)	
Secondary osteoporosis, n (%)				
Yes	931 (24.21)	827 (23.83)	43 (30.07)	0.087 ^c
No	2914 (75.79)	2644 (76.17)	100 (69.93)	
FRAX ^e : mean (SD)				
All participants (n = 2847)	0.16 (0.099)	0.16 (0.098)	0.20 (0.11)	<0.001 ^b
Low-risk (n = 929)	0.075 (0.015)	0.075 (0.015)	0.079 (0.015)	–

Characteristics	Total participants (n = 3985)	Major osteoporotic fracture ^a		
		No (n = 3594)	Yes (n = 149)	p-Value
Medium-risk (n = 1159)	0.15 (0.029)	0.14 (0.029)	0.16 (0.028)	–
High-risk (n = 759)	0.29 (0.089)	0.29 (0.089)	0.31 (0.091)	–
FI: mean (SD)				
All participants (n = 3985)	0.24 (0.13)	0.24 (0.13)	0.28 (0.15)	<0.001 ^b
Low-risk (n = 1749)	0.12 (0.047)	0.12 (0.047)	0.13 (0.049)	–
Medium-risk (n = 1357)	0.27 (0.043)	0.27 (0.043)	0.27 (0.044)	–
High-risk (n = 879)	0.44 (0.073)	0.44 (0.072)	0.46 (0.086)	–

SD: standard deviation; BMI: body mass index; FRAX: fracture risk assessment tool; FI: frailty index.

* Mean follow-up = 3.01 years.

^aHip, upper arm or shoulder, spine, or wrist.

^bStudent's t-test.

^cChi-square test.

^dMantel-Haenszel Chi-square test.

^eBaseline FRAX scores of 10-year risk of major osteoporotic fractures.

Table 2

Comparison of prediction and model performances between FI and FRAX in 3-year risk of major osteoporotic fracture.

Model	Major osteoporotic fracture ^a (n = 149)		
	HR (95% CI), p-value	C-index	p-Value for goodness of fit test
<i>Models with per-0.01 increment</i>			
FRAX	1.03 (1.02–1.05), <0.001	0.62	0.15
FI ^b	1.02 (1.01–1.04), <0.001	0.61	0.85
<i>Models with categorized groups</i>			
FRAX ^c			
Medium-risk		N/A ^e	N/A ^e
<365 days	1.33 (0.75–2.38), 0.34		
365–550 days	1.28 (0.62–2.65), 0.51		
>550 days	2.00 (1.09–3.68), 0.026		
High-risk			
<365 days	1.73 (0.78–3.87), 0.18		
365–550 days	1.66 (0.80–3.44), 0.17		
>550 days	2.61 (1.48–4.58), 0.001		
FI ^{b,d}			
Medium-risk	1.23 (0.82–1.84), 0.31	0.61	0.22
<365 days	1.10 (0.69–1.75), 0.70		
365–550 days	1.47 (0.81–2.67), 0.21		
>550 days	1.84 (1.16–2.93), 0.009		
High-risk	2.04 (1.36–3.07), 0.001		
<365 days	1.62 (0.85–3.09), 0.15		
365–550 days	1.27 (0.81–2.01), 0.30		
>550 days	2.14 (1.20–3.82), 0.006		

HR: hazard ratio; CI: confidence interval; FRAX: fracture risk assessment tool; FI: frailty index.

^aHip, upper arm or shoulder, spine, or wrist.

^bAdjusted for age.

^cLow-risk group taken as reference group; the cut-points were 10% and 20% for major osteoporotic fracture; comparisons of high-risk versus low-risk and medium-risk versus low-risk group were within the same follow-up duration strata.

^dLow-risk group taken as reference group; the cut-points were 0.20 and 0.35 for major osteoporotic fracture; comparisons of high-risk versus low-risk and medium-risk versus low-risk group were within the same follow-up duration strata.

^eNo estimation of c index or goodness of fit test conducted due to time-varying variable included in the model.

Table 3

Comparison of prediction and model performances between FI and FRAX in 3-year risk of hip fracture.

Model	Hip fracture (n = 18)		
	HR (95% CI), p-value	C-index	p-Value for goodness of fit test
<i>Models with per-0.01 increment</i>			
FRAX	1.05 (1.02–1.09), 0.004	0.70	0.22
FI ^a	1.03 (1.00–1.07), 0.050	0.72	0.78
<i>Models with categorized groups</i>			
FRAX ^b			
High-risk	4.05 (1.12–14.72), 0.034	0.66	N/A ^d
FI ^c			
High-risk	2.09 (0.72–6.04), 0.18	0.72	N/A ^d

HR: hazard ratio; CI: confidence interval; FRAX: fracture risk assessment tool; FI: frailty index.

^aAdjusted for age.

^bLow-risk group taken as reference group; the cut-point was 3% for the FRAX; comparison of high-risk versus low-risk group was within the same follow-up duration strata.

^cLow-risk group taken as reference group; the cut-point was 0.22 for the FI; comparison of high-risk versus low-risk group was within the same follow-up duration strata.

^dNo goodness of fit test conducted due to small sample size.

Table 4

Results from sensitivity analyses using accelerated failure time models for major osteoporotic fracture and hip fracture.

Model	Major osteoporotic fracture ^a (n = 149)		Hip fracture (n = 18)	
	HR (95% CI) ^e	p-Value	HR (95% CI) ^e	p-Value
<i>Models with per-0.01 increment</i>				
FRAX	1.03 (1.02–1.05)	<0.001	1.05 (1.02–1.09)	0.003
FI ^b	1.03 (1.01–1.04)	<0.001	1.03 (1.00–1.08)	0.049
<i>Models with categorized groups</i>				
FRAX ^c				
Medium-risk			N/A ^f	N/A ^f
<365 days	1.38 (0.80–2.40)	0.25		
365–550 days	1.45 (0.80–2.64)	0.23		
>550 days	1.76 (1.03–3.02)	0.039		
High-risk			4.05 (1.12–14.73)	0.034
<365 days	1.93 (0.97–3.85)	0.062		
365–550 days	2.02 (1.10–3.72)	0.024		
>550 days	2.45 (1.46–4.14)	0.001		
FI ^{b,d}				
Medium-risk	1.23 (0.82–1.85)	0.30	N/A ^f	N/A ^f
High-risk	2.04 (1.36–3.07)	0.001	2.09 (0.72–6.05)	0.17

HR: hazard ratio; CI: confidence interval; FRAX: fracture risk assessment tool; FI: frailty index.

^aHip, upper arm or shoulder, spine, or wrist.

^bAdjusted for age.

^cLow-risk group taken as reference group; the cut-points were 10% and 20% for major osteoporotic fracture, while the cut-point was 3% for hip fracture; comparisons of high-risk versus low-risk and medium-risk versus low-risk group were within the same follow-up duration strata.

^dLow-risk group taken as reference group; the cut-points were 0.20 and 0.35 for major osteoporotic fracture, while the cut-point was 0.22 for hip fracture; comparisons of high-risk versus low-risk and medium-risk versus low-risk group were within the same follow-up duration strata.

^eConverted from accelerated factor.

^fNot applicable for hip fracture due to its dichotomization.

Table 5

Relationship between risk of major osteoporotic fracture and FI and FRAX stratified by participants' use of antiosteoporotic treatment, calcium and/or vitamin D supplementation.

Model	Major osteoporotic fracture ^a			
	Participants with antiosteoporotic treatment and/or supplementation (n = 2912) ^b		Participants without antiosteoporotic treatment or supplementation (n = 1073) ^c	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value
<i>Models with per-0.01 increment</i>				
FRAX	1.03 (1.01–1.05)	<0.001	1.04 (1.01–1.08)	0.019
FI ^d	1.02 (1.01–1.04)	0.001	1.02 (1.00–1.05)	0.033
<i>Models with categorized groups</i>				
FRAX ^e				
Medium-risk				
<365 days	1.54 (0.78–3.08)	0.22	0.92 (0.30–2.78)	0.87
365–550 days	1.52 (0.66–3.53)	0.33	0.62 (0.12–3.29)	0.58
>550 days	1.89 (0.98–3.65)	0.051	2.35 (0.64–8.64)	0.20
High-risk				
<365 days	1.97 (0.76–5.11)	0.17	1.26 (0.26–6.03)	0.77
365–550 days	1.94 (0.84–4.48)	0.12	0.86 (0.16–4.83)	0.87
>550 days	2.42 (1.25–4.71)	0.009	3.26 (1.10–9.67)	0.034
FI ^{d,f}				
Medium-risk	1.21 (0.76–1.93)	0.43	1.29 (0.58–2.88)	0.54
High-risk	2.00 (1.24–3.23)	0.004	2.14 (1.03–4.45)	0.041

HR: hazard ratio; CI: confidence interval; FRAX: fracture risk assessment tool; FI: frailty index.

^aHip, upper arm or shoulder, spine, or wrist.

^bThere were 108 incident major osteoporotic fracture reported.

^cThere were 41 incident major osteoporotic fracture reported.

^dAdjusted for age.

^eLow-risk group taken as reference group; the cut-points were 10% and 20% for major osteoporotic fracture, while the cut-point was 3% for hip fracture; comparisons of high-risk versus low-risk and medium-risk versus low-risk group were within the same follow-up duration strata.

^fLow-risk group taken as reference group; the cut-points were 0.20 and 0.35 for major osteoporotic fracture, while the cut-point was 0.22 for hip fracture; comparisons of high-risk versus low-risk and medium-risk versus low-risk group were within the same follow-up duration strata.