Estimation of fracture risk by the FRAX tool in patients with systemic lupus erythematosus: a 10-year longitudinal validation study

Chi Chiu Mok, Sau Mei Tse, Kar Li Chan and Ling Yin Ho

Abstract

Background: The fracture risk assessment tool has been widely used to stratify the 10-year fracture risk to guide therapy. Using the actual fracture data of a 10-year longitudinal cohort of older patients with systemic lupus erythematosus, we reported an underestimation of the tool in predicting major symptomatic osteoporotic fractures. Treatment of osteoporosis in systemic lupus erythematosus should not be based on fracture risk estimation alone. Relevant time-dependent risk factors should be taken into account for an individualized decision.

Objective: To compare the observed fracture incidence in a 10-year longitudinal cohort of patients with systemic lupus erythematosus (SLE) with the fracture risk prediction from the fracture risk assessment (FRAX) tool.

Methods: Adult patients (≥40 years) with SLE who had a first DEXA scan performed in 2005–2009 were studied. The 10-year rates of major osteoporotic and hip fractures were estimated by FRAX using clinical data at DEXA with adjustment for prednisolone dosage. The actual incidence of clinical fractures at 10 years was compared with the estimated rates. Factors associated with new fractures were studied by logistic regression.

Results: A total of 229 SLE patients were studied (age: 50.2 ± 6.6 years, 93% women). Glucocorticoid was used in 148 (65%) patients at baseline (mean dose: 7.3 ± 6.9 mg/day; 34% ≥ 7.5 mg/day). Osteoporosis (bone mineral density T score ≤ –2.5) at the hip, femoral neck, or spine was present in 61 (27%) patients. The estimated 10-year risk of major osteoporotic and hip fractures by FRAX was 3.4 ± 4.5% and 0.95 ± 2.3%, respectively. After 10 years, three patients developed hip fracture, 6 patients had limb fractures and 20 patients had symptomatic vertebral fractures (major osteoporotic fracture 12.7%, hip fracture 1.3%). The actual major osteoporotic fracture rate was significantly higher than the FRAX estimation (12.7% vs 3.4%; p < 0.001). Logistic regression revealed that osteoporosis (odds ratio [OR]: 4.07 [1.51–10.9]), previous fragility fracture (OR: 3.18 [1.02–9.90]), and a parental history of fracture (OR: 4.44 [1.16–17.0]) were independently associated with new clinical fractures at 10 years.

Conclusion: The FRAX tool underestimates the major clinical fracture risk at 10 years in patients with SLE.

Keywords: fracture, glucocorticoid, lupus, osteoporosis, risk

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include glucocorticoid (GC) treatment, vitamin D deficiency due to sun protection and renal insufficiency, arthritis and myopathy, early menopause, failure to achieve a peak bone mass during adolescence, and the use of other medications, such as anticonvulsants and anticoagulants. The prevalence of osteoporosis and symptomatic fractures reported in various Asian and non-Asian studies ranges from 1.4% to 6.8% and 4.4% to 18.8%, respectively, depending on study design, patient selection, ethnicity, ongoing treatment, and method of identification of osteoporosis. Population-based studies have demonstrated a 1.2- to 4.7-fold increased incidence of all symptomatic fractures in SLE patients compared with matched healthy controls. A meta-analysis reported a two-fold increased risk of vertebral fractures in SLE patients relative to controls. Thus, recent European and Asian treatment recommendations emphasize on managing bone health in patients with SLE. As most patients with SLE are receiving GCs for disease control, the American College of Rheumatology (ACR) recommends patients receiving ≥3 months of prednisolone (≥2.5 mg/day) should receive intervention to prevent osteoporosis. Patients should be stratified into different risk levels (low, moderate, and high) by a fracture estimation tool and reassessed annually to decide on pharmacological therapies. Periodic assessment of bone mineral density (BMD) is also recommended for older individuals and younger patients with significant risk factors.

The fracture risk assessment (FRAX) tool was developed in the year 2008 to evaluate the fracture risk of individual patients according to 10 clinical factors with or without the BMD of the femoral neck. The FRAX prediction models were established from epidemiological studies of fractures and mortality within countries and, in some cases, within ethnicities. The FRAX is a computer-based tool that calculates the 10-year probability of a major osteoporotic fracture (distal forearm, proximal humerus, clinical spine, and hip) and hip fracture alone. Currently, there are more than 50 models available for fracture risk prediction. Among various fracture risk tools available, the FRAX has been incorporated in many clinical guidelines to assess for the intervention threshold.

As SLE patients are generally younger and the disease is not regarded as a risk factor in the FRAX formula, whether the tool accurately predicts future fractures in SLE is unclear. The objective of this study is to validate the fracture risk estimation of the FRAX tool by comparing with the actual fracture incidence in a longitudinal cohort of patients with SLE.

Patients and methods
All patients who fulfilled the 1997 ACR criteria for SLE and attended our out-patient rheumatology clinics in the year 2021 were reviewed. Inclusion criteria for this study were: (1) patients who have had a first dual-energy X-ray absorptiometry (DEXA) scan performed between years 2005 and 2009 (baseline); and (2) age ≥ 40 years at the time of DEXA examination. Subjects were excluded if they were lost to follow-up or succumbed due to any reasons in less than 10 years after DEXA unless fractures had developed.

The predicted rates of major osteoporotic and hip fractures were estimated retrospectively using the FRAX formula (data from Hong Kong, China) based on the clinical data at the time of DEXA, with adjustment when the daily dose of prednisolone was ≥7.5 mg (multiply by 1.15 for major osteoporotic and 1.20 for hip fracture) according to the recommendations from the ACR. The actual observed incidence of symptomatic vertebral and non-vertebral fractures at 10 years (i.e. in the years 2015–2019) of the included patients was retrieved by a retrospective review of the medical records. All new fractures developed over time were confirmed by radiological examination and documented by attending physicians or orthopedic surgeons. Vertebral fracture was defined on plain radiograph as deformities with a loss of least 25% of the height of the vertebral bone. Limb fractures referred to those that occurred with a low-energy impact (eg. fall from a standing height). Fractures that occurred beyond 10 years from DEXA examination were not included for analysis.

Comparison was made between the actual observed fracture incidence and that estimated by the FRAX tool from clinical data at DEXA examination. Factors associated with new symptomatic clinical fractures at 10 years were studied by statistical analyses. This study was approved by the Research and Ethics committee of Tuen Mun Hospital, Hong Kong (NTWC/REC/21137). Informed consent for publication of this study was not obtained from the participants because data were collected retrospectively. All patient details have been de-identified during data
The reporting of this study conforms to the checklist recommended by EULAR for reporting longitudinal observational registry studies in rheumatology derived from an extension of the STROBE guidelines.\(^\text{13}\)

**Measurement of BMD and assessment of vertebral fracture**

BMD at the lumbar spine [L2-4], non-dominant hip and femoral neck was measured by the DEXA technique using a Discovery\textsuperscript{TM} W densitometer (Hologic, Bedford, USA). For patients with avascular bone necrosis of the hip or joint replacement, the BMD of the other hip was used. When avascular necrosis or hip replacement occurred on both sides, the hip data were not used. Spine data were also excluded from analysis in patients who had collapse/severe scoliosis/deformity of the lumbar spine or significant aortic calcification. The reference ranges for the \(T\)-scores were derived from the third National Health and Nutrition Examination Survey (NHANES III) database (hip) and the device manufacturer’s data set (lumbar spine).\(^\text{14}\)

**Statistical analyses**

Unless otherwise stated, values in this study were expressed as mean ± standard deviation (SD). Comparison of two groups was performed by the independent Student’s \(t\)-test for continuous variables and chi-square test for categorical variables. Multivariate logistic regression was used to study the association of the clinical factors at baseline with the occurrence of new osteoporotic fractures at 10 years’ follow-up. Covariates considered in the regression model included age, sex, personal, and parental history of fracture, premature menopause, current smoking, habitual drinking, body mass index (BMI), daily dose of prednisolone, osteoporosis at any site by DEXA scan, concomitant medical illnesses, and the use of anti-osteoporotic or other medications that may affect BMD. Statistical significance was defined as a \(p\) value of <0.05, two-tailed. All statistical analyses were performed using the SPSS program (version 18.0 for Windows 10).

**Results**

**Study population**

A total of 263 patients fulfilled the inclusion criteria, but 34 were excluded because of less than 10 years’ follow-up (16 died, 18 were lost for follow-up; none had a fragility fracture before their last clinic visits or hospital admissions). Finally, 229 patients were studied (age 50.2 ± 6.6 years at DEXA examination; 93% women). All were ethnic Chinese. One hundred and forty-eight (65%) patients were receiving prednisolone, and the mean dose was 7.3 ± 6.9 mg/day; 34% ≥ 7.5 mg/day. A personal history of fragility fracture was present in 23 (10.0%) patients, and 17.3% of female patients had menopause before the age of 45 years. The mean BMI was 23.5 ± 3.8 kg/m\(^2\) (5.7% patients had BMI \(\leq\) 18 kg/m\(^2\)). Table 1 shows the cumulative clinical manifestations of the SLE patients studied, and Table 2 shows the risk factors for osteoporosis in these patients. Fourteen (6.1%) patients were receiving anti-osteoporotic treatment at the time of DEXA examination (oral bisphosphonates in 8 and raloxifene in 6 patients). Sixty-two (27%) patients were receiving medications that may adversely affect BMD within 6 months prior to DEXA scan. Nineteen patients had chronic kidney disease (estimated glomerular filtration rate \(\leq\) 60 mL/min/1.73 m\(^2\)), six patients had concomitant thyroid disorders, and one patient had overlapped rheumatoid arthritis.

**BMD and fracture risk estimation**

Osteoporosis (BMD; \(T\) score \(\leq\) –2.5) of the hip, femoral neck, and lumbar spine occurred at a frequency of 9.0%, 11.3%, and 23.4%, respectively at baseline (27% at any of these three sites; Table 3).

The estimated mean 10-year risk of major osteoporotic and hip fractures using the BMD data and other risk factors in the FRAX formula, adjusted for prednisolone dosage, was 3.4 ± 4.5% and 0.95 ± 2.3%, respectively. Ten (4.4%) patients were estimated to have moderate (10–20%) or high risk (>20%) of having a major osteoporotic fracture, while 51 (22.3%) patients were predicted to have moderate risk (1–3%) or high risk (\(\geq\)3%) of having a hip fracture.

**Actual fracture rate at 10 years**

After a follow-up of 10 years, three patients had a hip fracture, six patients had non-hip limb fractures (humerus, tibia, or radius), and 20 patients had symptomatic vertebral fractures. The actual observed major osteoporotic and hip fracture incidence was 12.7% and 1.3%, respectively.
The observed major osteoporotic fracture rate was significantly higher than that estimated by FRAX (12.7% vs 3.4%; \( p < 0.001 \)). However, the observed hip fracture incidence was not significantly higher than the estimation by FRAX (1.3% vs 0.95%; \( p = 0.69 \)).

Table 4 shows the number of patients who had major osteoporotic fractures at 10 years stratified by the fracture risk estimated by FRAX at baseline. Twenty-eight patients (12.8%) developed fractures in the low-risk group by FRAX (12.7% vs 3.4%; \( p < 0.001 \)). However, the observed hip fracture incidence was not significantly higher than the estimation by FRAX (1.3% vs 0.95%; \( p = 0.69 \)).

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FRAX estimation at baseline. The estimated risk of major fractures by FRAX was non-significantly higher in those who had actual fractures at 10 years than those who did not (4.2 ± 2.5% vs 3.3 ± 4.7%; p = 0.14).

Factors associated with actual major osteoporotic fractures at 10 years
Logistic regression was performed to evaluate the factors associated with new fractures at 10 years (Table 5). As there were no fractures occurring in male patients and there was only one habitual drinker, the odds ratios (ORs) showed extreme values on univariate analysis. These two factors were not put into the multivariate regression model. Results of analysis revealed that BMD T-score ≤ −2.5 at spine, hip, or femoral neck (OR: 4.07 (1.51–10.9); p = 0.005), previous fragility fracture (OR: 3.18 (1.02–9.90); p = 0.045) and a parental history of fracture (OR: 4.44 (1.16–17.0); p = 0.03) were independently associated with major osteoporotic fractures at 10 years. Age, BMI, daily dose of prednisolone, current smoking, concomitant medical illnesses, and the use of anti-osteoporotic and other medications at baseline were not significantly associated with new fractures.

Discussion
This is a longitudinal study to validate the accuracy of the FRAX tool in predicting clinical fractures at 10 years in a cohort of Chinese patients with SLE. Although the fracture risk estimation was performed retrospectively using clinical information at the time of DEXA examination, data were complete as they were routinely collected for BMD evaluation. This study revealed that despite adjustment for the daily dose of GCs, the FRAX tool underestimated the risk for major osteoporotic fractures in patients with SLE at 10 years. Under-estimation of the fracture risk was more serious in the low-risk group stratified by the FRAX formula. As there was no significant difference between the observed and FRAX-estimated incidence of hip fracture, the underestimation was mainly confined to symptomatic vertebral and non-hip limb fractures.

GC use is the most important cause of secondary osteoporosis. GCs adversely affect the trabecular bone more than the cortical bones of the skeleton. The much higher incidence of vertebral than non-vertebral fractures at 10 years in this study is

| Table 3. Baseline DEXA results and fracture risk estimation by FRAX. |
|-----------------|----------|----------|
| **DEXA results and estimated fracture risk** | **Mean ± SD; number (%)** |
| **BMD values, g/cm²** |           |           |
| Lumbar spine (L2-4) | 0.908 ± 0.138 |           |
| Femoral neck (non-dominant) | 0.708 ± 0.109 |           |
| Total hip (non-dominant) | 0.808 ± 0.121 |           |
| **BMD T score < −2.5** |           |           |
| Lumbar spine | 53 (23.4) |           |
| Femoral neck | 25 (11.3) |           |
| Total hip | 20 (9.0) |           |
| Any of the above sites | 61 (27.0) |           |
| **FRAX-estimated and GC-dose-adjusted major osteoporotic fracture risk at 10 years** |           |           |
| <10% | 219 (95.6) |           |
| 10–20% | 8 (3.5) |           |
| >20% | 2 (0.9) |           |
| **FRAX-estimated and GC-dose-adjusted hip fracture risk at 10 years** |           |           |
| <1% | 178 (77.7) |           |
| ≥1–3% | 35 (15.3) |           |
| ≥3% | 16 (7.0) |           |

BMD, bone mineral density; DEXA, dual-energy X-ray absorptiometry; FRAX, fracture risk assessment; GC, glucocorticoid.

| Table 4. Actual rate of major osteoporotic fractures at 10 years stratified by FRAX estimation or BMD at baseline. |
|-----------------|--------|--------|
| **Actual rate of major fractures at 10 years** |           |           |
| **Major osteoporotic fracture risk by FRAX formula at baseline** |           |           |
| Low-risk (<10%) | 28/219 (12.8%) |           |
| Moderate/high-risk (≥10%) | 1/10 (10.0%) |           |
| **Bone mineral density at baseline** |           |           |
| Osteopenia at any site (but not osteoporotic) | 12/108 (11.1%) |           |
| Osteoporosis at any site | 16/61 (26.2%) |           |

FRAX, fracture risk assessment. T-score between −1.0 and ≥ −2.5. T-score ≤ −2.5.
consistent with the effects of GCs on BMD as almost two-third of our patients were using long-term GCs. On the other hand, GCs also exhibit negative effects on bone microarchitecture, which may be better reflected by the trabecular bone score (TBS) and quantitative CT (qCT) examination.\textsuperscript{15,16} The failure of the FRAX tool to take into account the decline of bone quality and the cumulative doses of GCs administered over time may have contributed to the underestimation of osteoporotic fractures in our patients. The risk of fracture in continuous GC users is proportional to the daily dose of GCs according to a general practice research database in the United Kingdom.\textsuperscript{17} This is consistent with our study in which the fracture risk at 10 years increased with daily dose of prednisolone in the regression model, although statistical significance could not be achieved. As the FRAX tool did not consider the effect of additional GC doses used for SLE flares over time, its prediction power for new fractures might be undermined despite adjustment for the risk in users of higher daily doses of prednisone.\textsuperscript{7}

Table 5. Logistic regression for factors associated with new major osteoporotic fractures at 10 years.

| Covariates at DEXA scan | Odds ratio (95% confidence interval) | p value |
|-------------------------|-------------------------------------|---------|
| Age, per year           | 0.99 (0.92–1.07)                    | 0.87    |
| BMI, per kg/m\(^2\)     | 1.07 (0.96–1.18)                    | 0.22    |
| Current smoking         | 0.28 (0.03–2.37)                    | 0.24    |
| Menopause before age of 45 years | 0.67 (0.20–2.30)          | 0.53    |
| T-score < −2.5 at any site (total hip, femoral neck, or lumbar spine) | 4.07 (1.51–10.9) | 0.005 |
| Personal history of fragility fracture | 3.18 (1.02–9.90) | 0.045 |
| Parental history of fragility fracture | 4.44 (1.16–17.0) | 0.03 |
| Prednisolone dose, per mg/day | 1.04 (0.99–1.10) | 0.14 |
| Use of anti-osteoporotic medications\textsuperscript{a} | 0.86 (0.16–4.75) | 0.86 |
| Use of medications that may adversely affect BMD\textsuperscript{b} | 1.71 (0.69–4.25) | 0.25 |
| Concomitant medical illnesses\textsuperscript{c} | 0.38 (0.07–2.11) | 0.27 |

BMD, bone mineral density; BMI, body mass index; DEXA, dual-energy X-ray absorptiometry.
\textsuperscript{a}Bisphosphonates or raloxifene.
\textsuperscript{b}Anticonvulsants, proton pump inhibitors, calcineurin inhibitors, loop diuretics, selective serotonin reuptake inhibitors, glitazones, aromatase inhibitors, and anticoagulants.
\textsuperscript{c}Thyroid, parathyroid, and other endocrine disorders, overlap syndrome with rheumatoid arthritis, and renal insufficiency.

There are additional osteoporosis risk factors not considered in the FRAX formula. Activity of SLE, driven by elevation of pro-inflammatory cytokines, such as tumor necrosis factor (TNF), interleukin (IL)-1, IL6, and IL17, may promote osteoclastogenesis while inhibiting osteoblast activity.\textsuperscript{18–22} SLE itself is not given additional weighting in the prediction model. Menopause that develops over time and the use of other non-GC drugs, such as anticonvulsants, calcineurin inhibitors, heparin, loop diuretics, proton pump inhibitors, selective serotonin reuptake inhibitors, and the thiazolidinediones are also not incorporated in the FRAX model.

The strength of our study is the long-term longitudinal follow-up and the availability of the actual fragility fracture data for comparison with the FRAX tool. All the required data including BMD assessment for fracture risk estimation at baseline were available. However, our study is limited by the small number of hip fracture events, which may not be powered to compare the estimated and observed hip fracture rates at 10 years. Moreover, time-dependent factors such as change in menopausal status, cumulative disease activity of SLE, and the cumulative exposure to GCs were unavailable for multivariate analysis. Nevertheless, the reliance on the cumulative disease activity and GC dose exposure to decide on the fracture risk estimation and osteoporosis treatment does not seem to be pragmatic in daily practice. Finally, the limited sample size of our study did not allow for comparison of the accuracy of prediction of fractures by BMD per se or the FRAX formula based on a new prediction model generated from our SLE patients.

In conclusion, our study showed that despite adjustment for baseline prednisolone dosage as recommended by the ACR, the FRAX formula underestimates the major clinical fracture risk, particularly symptomatic vertebral fracture, in our Hong Kong Chinese patients with SLE. As the data used in the establishment of the FRAX formula differ across localities, our observation cannot be generalized to other ethnic groups. Our observation suggests that the threshold for pharmacological therapy in SLE patients should not be solely determined by the fracture risk prediction per se. In patients estimated to have fracture
risk not meeting the threshold of therapy as stated in guidelines,7,10,11 individualized decision on treatment should be considered based on the presence of extra and relevant time-dependent risk factors, such as frequent disease flares and additional GC therapies. Future research should focus on the role of these additional risk factors and bone quality assessment, such as TBS, in the fracture prediction models. Validation studies in large longitudinal cohorts of SLE patients using various immunosuppressive regimens are needed.

Author contributions
Chi-Chiu Mok: Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing.
Sau Mei Tse: Conceptualization, Data curation, Methodology, Writing – review & editing.
Kar Li Chan: Conceptualization, Data curation, Methodology, Writing – review & editing.
Ling Yin Ho: Conceptualization, Data curation, Methodology, Writing – review & editing.

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