Predicting 10-Year Risk of Osteoporosis in Pre- and Perimenopausal Women

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INTRODUCTION: Osteoporosis may not have clinical manifestations prior to the onset of a fragility fracture, which poses challenges for prevention and early detection. Women undergoing menopause are at particularly elevated risk of developing osteoporosis. While several known risk factors for osteoporosis exist in clinical practice, a combined predictive model incorporating these factors to provide an individualized assessment of long-term osteoporosis risk does not exist. Using advanced statistical techniques, assessing osteoporosis risk with superior predictive performance is possible. The purpose of this study was to incorporate clinical risk factors, serum biomarker levels, and bone mineral density (BMD) measurements to predict 10-year risk of osteoporosis in pre- and perimenopausal women.

METHODS: This is a secondary analysis of 3,302 patients using baseline and 10-year follow-up data from the Study of Women's Health Across the Nation (SWAN). A total of 1,617 participants had incomplete baseline data or did not have 10-year follow-up and were excluded from this analysis. Of the remaining 1,685 participants, 337 (20%) were randomly selected as a holdout set for model validation, while a generalized additive model with pairwise interactions (GA^2M) was trained on the other 1,348 (80%). The primary outcome was whether participants had been told they had a diagnosis of osteoporosis by a doctor or other health care provider at 10-year follow-up. There were 14 risk factors included at baseline: age, height, weight, body mass index (BMI), waist circumference, race, menopausal status, maternal osteoporosis history, maternal spine fracture history, serum estradiol level, serum dehydroepiandrosterone (DHEAS) level, serum thyroid-stimulating hormone (TSH) level, total spine BMD, and total hip BMD. The GA^2M also considered six pairwise interaction effects among the 14 risk factors. Importance scores were calculated as the average of the absolute predicted value of each feature for the training dataset. Confidence intervals were calculated using bootstrapping by resampling the validation dataset 200 times with replacement.

RESULTS: The model predicted 10-year risk of osteoporosis with an area under the receiver-operating characteristic (AUROC) of 0.85 (95% confidence interval [CI], 0.77-0.92) (**Figure 1**). Brier score for the model was 0.052 (95% CI, 0.033-0.072). Importance scores for each of the 14 risk factors and 6 pairwise interaction effects are shown in **Table 1**. Total spine BMD and total hip BMD had the two highest scores at 0.012 and 0.010, respectively, and age had the third-highest score at 0.005. The pairwise partial dependence plot for the interaction between age and total spine BMD is shown in **Figure 2**. In addition, a calibration curve for the model is shown in **Figure 3**. Using a probability of 0.066 as the threshold for predicting a diagnosis of osteoporosis, sensitivity was 0.81, specificity 0.78, accuracy 78%, and kappa 0.22. Alternatively, using 0.136 as the threshold, sensitivity was 0.52, specificity 0.93, accuracy 90%, and kappa 0.35.

DISCUSSION AND CONCLUSION: The clinical prediction model developed in this analysis integrated clinical risk factors, serum biomarker levels, and BMD measurements to predict 10-year risk of osteoporosis in this population with good performance. Total spine BMD and total hip BMD were the two features with the highest predictive power. Moreover, in women with total spine BMD values below 0.9 g/cm^2, absolute 10-year risk of osteoporosis was greater at a younger age. These data suggest a potential benefit for bone densitometry screening in women before the age of 65, which is currently the standard of care. However, BMD may not fully reveal the osteoporosis picture, as there are multifactorial contributions to risk including metabolic profiles. In addition, these findings provide a framework for highly accurate risk stratification. Using the high-risk threshold of 0.136, the model has few false positives, with a specificity of 0.93. Using a lower threshold of 0.066, there are fewer false negatives, with the model correctly identifying 81% of patients who will be diagnosed in the next decade. Stratifying patients by risk could improve population-wide outcomes by (1) helping physicians diagnose osteoporosis before fractures occur and (2) establishing a rationale for the investigation of prophylactic management strategies.

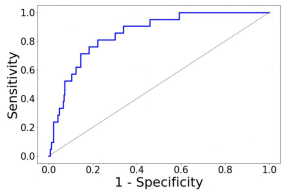

Figure 1. Receiver-operating characteristic curve.

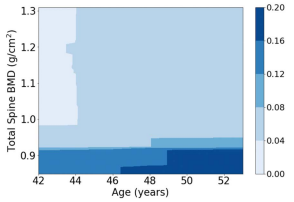

Figure 2. Partial dependence plot computed by GA²M showing the pairwise interaction effect on 10-year osteoporosis risk of age and total spine bone mineral density (BMD).

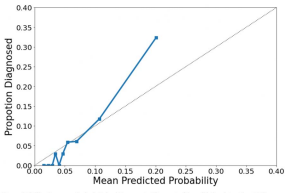

Figure 3. Calibration curve. Each plotted point represents 10 percent of the validation dataset (n = 337).

Table 1. Importance scores of each predictor as computed by GA^2M.

Predictor	Importance Score
Total spine BMD	0.012205
Total hip BMD	0.009899
Age	0.004935
Menopausal status	0.004119
Weight	0.004118
Waist circumference	0.003925
Total hip BMD x total spine BMD	0.003185
Total spine BMD x serum TSH level	0.003124
Serum estradiol level	0.003065
Total spine BMD x serum estradiol level	0.003049
BMI	0.003042
Serum DHEAS level	0.003017
Age x total spine BMD	0.003002
Total spine BMD x menopausal status	0.002970
Age x total hip BMD	0.002729
Race	0.002492
Maternal osteoporosis history	0.002376
Serum TSH level	0.002323
Height	0.001990
Maternal spine fracture history	0.000713