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Development and Validation of Osteoporosis Risk-Assessment Model for Korean Men

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Purpose: The aim of the present study was to develop an osteoporosis risk-assessment model to identify high-risk individuals among Korean men.

Materials and Methods: The study used data from 1340 and 1110 men ≥50 years who participated in the 2009 and 2010 Korean National Health and Nutrition Examination Survey, respectively, for development and validation of an osteoporosis risk-assessment model. Osteoporosis was defined as T score ≤-2.5 at either the femoral neck or lumbar spine. Performance of the candidate models and the Osteoporosis Self-assessment Tool for Asian (OSTA) was compared with sensitivity, specificity, and area under the receiver operating characteristics curve (AUC). A net reclassification improvement was further calculated to compare the developed Korean Osteoporosis Risk-Assessment Model for Men (KORAM-M) with OSTA.

Results: In the development dataset, the prevalence of osteoporosis was 8.1%. KORAM-M, consisting of age and body weight, had a sensitivity of 90.8%, a specificity of 42.4%, and an AUC of 0.666 with a cut-off score of -9. In the validation dataset, similar results were shown: sensitivity 87.9%, specificity 39.7%, and AUC 0.638. Additionally, risk categorization with KORAM-M showed improved reclassification over that of OSTA up to 22.8%.

Conclusion: KORAM-M can be simply used as a pre-screening tool to identify candidates for dual energy X-ray absorptiometry tests.

Key Words: Osteoporosis, risk assessment, men, Korea

INTRODUCTION

Osteoporosis is a disease characterized by low bone mass and structural deterioration of bone tissue, leading to bone fragility and an increased vulnerability to fractures.[1] As osteoporosis and related fractures occur primarily due to aging, they are a increasing health care burden in the aging population.[2] According to the 2009 Korean Health Statistics, the prevalence of osteoporosis was 8.1% in men aged 50 years or older.[3] However, osteoporosis is presently under-diagnosed and under-treated. Among men with osteoporosis, 6.4% were diagnosed with osteoporosis by a physician, and only 4.3% reported being treated.[3] Although men have a relatively lower risk of having osteoporosis compared to women, men with osteoporotic fracture demonstrated a higher rate of mortality and correspondingly a greater economic impact.[4-6] Thus, earlier intervention of osteoporosis is needed in men.[7] It is, therefore, crucial that effort is given to finding more effective methods for prevention and early detection of osteoporosis for men.

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Currently, dual-energy X-ray absorptiometry (DXA) is the most commonly used method of diagnosing osteoporosis and of monitoring changes in bone density over time.[8] However, DXA is not recommended as a routine screening test for the general population because of its relatively high cost.[9] Most guidelines limit the use of DXA for men aged 70 years or older, with the exception of younger adults with known risk factors.[10] Therefore, some osteoporosis risk-assessment models have been developed for pre-screening, using simple variables. However, most tools have been developed and validated for women.[11-15] In a nationwide dataset of Korean postmenopausal women, we recently developed and validated an osteoporosis risk-assessment model. Details of the study have previously been published.[16] For men, relatively fewer osteoporosis risk-assessment models are available. The Male Osteoporosis Screening Tool with body weight and quantitative ultrasound index was developed in Hong Kong Chinese men.[17] It provides a sensitivity of 94% and a specificity of 46%. Mscore with age, body weight, gastrectomy, emphysema, and prior fracture and a reduced $Mscore_{age\text{-}weight}$ were developed in Caucasian and African American men.[18] Mscore and $Mscore_{age\text{-}weight}$ had a sensitivity of 88% and 100%, and a specificity of 57% and 73%, respectively. The Male Osteoporosis Risk Estimation Score (MORES) with age, body weight, and history of chronic obstructive pulmonary disease was developed in the US men.[19] MORES had a sensitivity of 93% and a specificity of 59%.

In addition, the Osteoporosis Self-assessment Tool, similar to the Osteoporosis Self-assessment Tool for Asian (OSTA), has also been widely validated in American men,[20] African American men,[21] American and Hong Kong Chinese men,[22] Filipino men,[23] and Korean men.[24] However, the subjects used in the Korean OSTA studies were limited to patients at a few clinics. Meanwhile, the Korea National Health and Nutrition Examination Survey (KNHANES) included DXA tests since the middle of 2008,[25] which is the first nationwide bone mineral density (BMD) dataset for the Korean population.

Therefore, we aimed to develop and validate an osteoporosis risk-assessment model, based on a nationwide dataset to identify high-risk Korean men who may benefit from further evaluation of osteoporosis.

MATERIALS AND METHODS

Study participants

The study is based on the data acquired in the KNHANES, which is conducted by the Korea Centers for Disease Control and Prevention and the Ministry of Health and Welfare. The KNHANES is a nationwide survey to assess the health and nutritional status of a non-institutionalized representative sample of the Korean population. A stratified, multi-stage, clustered probability sampling design was used to select participants from residential districts throughout; for the 2009 survey (KNHANES IV-3), household units were selected using the 2005 census in Korea.[3] For the 2010 survey (KNHANES V-1), sampling was either based on the registered market value of apartment building complexes or a registered database of the Korean government system that includes all registered citizens.[26] For development of the osteoporosis risk-assessment model, 1592 men aged 50 years or older who participated in the 2009 KNHANES were included. Of them, 252 men were excluded from the current analysis because of at least one of the following reasons: absence of BMD measurement (n=149), previously diagnosed osteoporosis or treatment for osteoporosis (n=34), missing blood tests (n=144), and being in a bed-ridden state (n=14). Finally, data from 1340 men were used for this study. For validation of the developed model, the 2010 KNHANES dataset was used. Of 1353 men aged 50 years or older, 243 men were excluded in the same manner as the development dataset: absence of BMD measurement (n=112) and missing blood tests (n=147). Finally, 1110 participants were eligible for validation of the model developed. This study was approved by the Institutional Review Board of Korea Centers for Diseases Control and Prevention (2009-01CON-03-2C, 2010-02CON-21-C) and Yonsei University Health System (4-2011-0222) and was monitored by the Human Research Protection Center of Severance Hospital, Yonsei University Health System. All participants provided written informed consent.

Measurement

The survey consisted of a health interview survey, a health behavior survey, a nutrition survey, and a health examination survey. Household interviews and self-reported questionnaires were used to acquire information about their health behavior, past or current history of disease, and family history. Smoking status was classified as current smokers or current nonsmokers (past smokers or never smokers). Alcohol intake was classified as current alcohol drinkers or current non-alcohol drinkers (past alcohol drinkers or never-alcohol drinkers). Physical activity was measured by the International Physical Activity Questionnaires-short form. Moderate activity refers to the activity to make individuals breathe somewhat harder than normal, and high activity refers to the activity to make individuals breathe much harder than normal. Regular exercise was defined as moderate-to-high intensity of physical activity at least three times per week. Trained examiners in specially equipped mobile examination centers performed anthropometrics, blood tests, and BMD measurements. Standing height and body weight were obtained using standardized techniques and equipment. Body mass index (BMI) was calculated as body weight in kilograms divided by standing height in meters squared (kg/m^2). Blood samples were collected after a minimum fasting time of 8 h and handled according to standard procedures. All samples were properly processed, immediately refrigerated, and transported in cold storage to the Central Testing Institute in Seoul, Korea. Blood samples were analyzed

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within 24 h after transportation. Serum 25-hydroxyvitamin D [25(OH)D] concentrations were assessed using a gamma counter (1470 Wizard, Perkin-Elmevr, Turku, Finland) with a radioimmunossay (Diasorin, Stillwater, MN, USA).[27] Low vitamin D was defined as a serum 25(OH)D concentration of less than 20 ng/mL.[27] Serum parathyroid hormone (PTH) concentrations were measured using a chemiluminescence assay (Diasorin) for the measurement of intact PTH. Elevated PTH was operationally defined as a serum PTH concentration of 80 pg/mL or greater. Elevated alkaline phosphatase (ALP) was operationally defined as a serum ALP concentration of 300 IU/L or greater. BMD (g/cm^2) was measured at total femur, femoral neck, and L1–4 spine using a QDR Discovery fan beam densitometer (Hologic Inc., Bedford, MA, USA) equipment located in the mobile examination centers. We analyzed the results of the DXA using industry standard techniques at the Korean Society of Osteoporosis and performed analysis using Hologic Discovery software (version 13.1; Hologic Inc., Bedford, MA, USA).[28] The stability of the DXA measurements was maintained by daily calibration.[29] T scores were calculated using gender-specific normal values for young Japanese men; the reference means (standard deviations) of BMD at the femoral neck and lumbar were 0.846 (0.124) and 1.024 (0.120), respectively. Osteoporosis and low BMD were defined as a T score less than or equal to -2.5 and -2.0, respectively, at either the femoral neck or lumbar spine.

Statistical analyses

We selected potential risk and protective factors for osteoporosis based on previous studies and statistical investigation of the development dataset. Age,[18-24] body weight,[17-24] quantitative ultrasound index,[17,22] gastrectomy,[18] emphysema,[18] previous (low impact) fracture,[18] and history of chronic obstructive pulmonary disease[19] were evaluated because they were components of previously developed osteoporosis risk-assessment models.[17-24] Additionally, all components of the World Health Organization Fracture Risk Assessment Tool (FRAX®)[30] except corticosteroid use, secondary osteoporosis, and parent fractured hip were evaluated. There were no relevant data available to evaluate these variables in the KNHANES. In addition, regular exercise,[31] history of type 2 diabetes,[32] depression,[33] and biomarkers[34,35] including 25(OH)D, PTH, and ALP were evaluated. Simple linear regression analyses were performed to detect variables that achieved borderline statistical significance (p<0.15). Among the identified potential risk factors, covariates for the multiple linear regression model were selected by 10-fold cross-validation.[36] In detail, the development dataset was randomly divided into 10 subsamples. Nine subsamples were used to select significant covariates using stepwise addition and deletion (p<0.15), and the remaining one subsample was used for validation. This process was repeated ten times with different subsamples to determine the optimal number of covariates. Variables that did not reach a statistical signifi-

Table 1. Baseline Characteristics of Participants in the Development and the Validation Dataset

Variables	Development dataset (n=1340)	Validation dataset (n=1110)
Age (yrs)	63.4±8.9	63.5±8.3
50–54	278 (20.8)	193 (17.4)
55–59	228 (17.0)	212 (19.1)
60–64	253 (18.9)	223 (20.1)
65–69	229 (17.1)	197 (17.8)
70–74	190 (14.2)	161 (14.5)
≥75	162 (12.1)	124 (11.2)
Weight (kg)	66.1±9.7	66.1±9.3
<50	175 (13.1)	131 (11.8)
50–54	185 (13.8)	154 (13.9)
55–59	229 (17.1)	232 (20.9)
60–64	300 (22.4)	224 (20.2)
65–69	215 (16.0)	187 (16.9)
≥70	236 (17.6)	182 (16.4)
Height (cm)	166.6±5.9	166.6±5.8
Body mass index (kg/m^2)	23.8±3.0	23.7±2.8
Current smoking	452 (33.7)	317 (28.6)
Current drinking	1001 (74.7)	842 (75.9)
Regular exercise (≥3 time/wk)	480 (35.8)	353 (31.8)
History of rheumatoid arthritis	11 (0.8)	18 (1.6)
Diabetes	249 (18.6)	208 (18.7)
Depression	20 (1.5)	12 (1.1)
Serum 25-OH vitamin D (ng/mL)	20.4 [15.7, 31.2]	20.2 [15.8, 25.0]
Serum alkaline phosphatase (IU/L)	230 [194, 276]	232 [195, 278]
Serum parathyroid hormone (pg/mL)	64.7 [50.9, 79.3]	62.6 [50.1, 79.0]
BMD at femoral neck (g/cm^2)	0.75±0.12	0.75±0.12
T-score at femoral neck	-0.79±0.98	-0.81±0.94
T-score<-1.0	568 (42.4)	479 (43.2)
T-score<-2.0	133 (9.9)	112 (10.1)
T-score<-2.5	44 (3.3)	35 (3.2)
BMD at lumbar spine (g/cm^2)	0.94±0.16	0.94±0.15
T-score at lumbar spine	-0.70±1.30	-0.67±1.28
T-score<-1.0	561 (41.9)	471 (42.4)
T-score<-2.0	199 (14.9)	153 (13.8)
T-score<-2.5	91 (6.8)	73 (6.6)
Lower BMD at any site (g/cm^2)*	0.75±0.12	0.74±0.12
Lower T-score at any site*	-1.14±1.03	-1.14±0.99
T-score<-1.0	747 (55.8)	630 (56.8)
T-score<-2.0	255 (19.0)	210 (18.9)
T-score<-2.5	109 (8.1)	91 (8.2)

BMD, bone mineral density.
Data are expressed as mean±standard error or number (%) or median [interquartile range].
*Lower at either femoral neck or lumbar spine T-score.

cance (p≥0.05) were excluded based on the results of the multiple linear regression analysis with the selected covariates. Multicollinearity among the investigated variables was assessed using a variance inflation factor. Then, a final multiple linear regression model with the selected covariates was computed. The regression coefficient of each covariate was used to calculate its index weight. To standardize the effect of each variable, a ratio using a coefficient for each covariate divided by the reference value, the absolute value of the coefficient for age (per 10 years), was calculated. Each standardized coefficient was then multiplied by an integer that was able to discriminate the effect of each variable and the final value was rounded off as an integer.

Three candidate models were tested to develop a simple and effective model; Model 1 included age and body weight, Model 2 added health behavior, and Model 3 added blood test(s). In addition, these three models were compared to OSTA, which was a model available in the Korean population. Correlations of the scores from the three candidate models and OSTA with actual BMD T scores (lower values at either the femoral neck or lumbar spine) were evaluated using Spearman's correlation analyses. The goodness of fit of each model was assessed using the Hosmer-Lemeshow test.[37] The ability of each model to discriminate those with osteoporosis from those without osteoporosis was compared using receiver operating characteristic curves and the area under the curves (AUC) with sensitivity on the y-axis and (1-specificity) on the x-axis for all possible cut-off values. Next, a cut-off score was chosen which yielded 90% sensitivity or greater for detecting those with osteoporosis in each model. The cut-off score was applied for each model and the final model was selected based on sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio, and negative likelihood ratio with their exact binomial confidence intervals (CIs). Additionally, the number of missed cases that represents the number of undetected osteoporotic subjects per 1000 subjects (i.e., false negatives), the number of unnecessary DXA tests that represents the number of subjects without osteoporosis referred for DXA testing per 1000 subjects (i.e., false positives), and AUC were compared. The model that showed the best performance using the fewest variables was selected and named as the Korean Osteoporosis Risk-Assessment Model for Men (KORAM-M). KORAM-M was then validated using an independent dataset, KNAHNES V-1. Sensitivity analyses were performed with an outcome of low BMD T score of -2.0 or lower at either the femoral neck or lumbar spine.

Three risk categories were created operationally according to the KORAM-M scores: low, intermediate, and high risk of having osteoporosis. Low risk was defined as having a less than 10% probability of osteoporosis, high risk was defined as having more than 70% probability, and intermediate risk was defined as in between these values. The net reclassification improvement (NRI)[38] was then calculated to assess whether the KORAM-M risk categories provided a benefit in discriminating participants with osteoporosis from those without osteoporosis over the risk categories of OSTA. NRI was calculated by constructing 3×3 tables according to the risk categories of KORAM-M and OSTA, separately in participants with or without osteoporosis. Any upward movement in categories for participants with osteoporosis meant improved reclassification, and any downward movement implied poor reclassification. For participants without osteoporosis, the interpretation was opposite.[38]

NRI=[P(up|D=1)-P(down|D=1)]-[P(up|D=0)-P(down|D=0)] (where D represents osteoporosis, 1 for osteoporosis, and 0 for normal)

All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA), and statistical significance was defined as a two-sided p value less than 0.05.

RESULTS

Characteristics of study participants

Table 1 presents the baseline characteristics of Korean men in the development dataset (2009 KNHANES) and the validation dataset (2010 KNHANES). A total of 1340 and 1110 men in the development dataset and the validation dataset, respectively, were eligible for the current study. The mean age was 63.4 years in the development dataset and 63.5 years in the validation dataset. The prevalence of osteoporosis was 8.1% in the development dataset and 8.2% in the validation dataset. Old age, low body weight, short height, current smoking, diabetes, depression, low serum 25(OH)D, elevated ALP, and elevated PTH were selected as potential risk factors of osteoporosis. Meanwhile, protective factors were current alcohol drinking and regular exercise.

Table 2. Regression Coefficients and Index Weights in the Final Multiple Regression Model

Variable	Regression coefficient	Standard error	p value	Index weight
Intercept	-2.847	0.299	<0.0001	–
Age (10 yrs)	-0.161	0.029	<0.0001	-3
Weight (10 kg)	0.441	0.027	<0.0001	8
No regular exercise	-0.112	0.051	0.027	-2
Low vitamin D*	-0.119	0.049	0.015	-2
Elevated ALP†	-0.320	0.067	<0.0001	-6

*Serum 25(OH)vitD <20 ng/mL, †Serum alkaline phosphatase ≥300 IU/L.

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Table 3. Discriminatory Performance of OSTA and the Candidate Models to Identify Men with Osteoporosis and Low BMD

	Sensitivity	Specificity	PPV	NPV	NMC	NUDT	LR (+)	LR (-)	ROC			
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)			(95% CI)	(95% CI)	AUC (SE)	Statistical difference		
Osteoporosis (T_{FN}≤-2.5 or T_{LS}≤-2.5)												
Development dataset												
OSTA (≤0)	86.2 (78.3, 92.1)	49.7 (46.9, 52.6)	13.2 (10.8, 15.9)	97.6 (96.1, 98.7)	138	503	1.72 (1.56, 1.88)	0.28 (0.17, 0.44)	0.680 (0.018)			
OSTA (≤1)	90.8 (83.8, 95.5)	36.9 (34.2, 39.7)	11.3 (9.3, 13.6)	97.8 (96.1, 99.0)	92	632	1.44 (1.34, 1.55)	0.25 (0.14, 0.45)	0.639 (0.016)	(ref)		
Model 1 (≤-9)	90.8 (83.8, 95.5)	42.4 (39.6, 45.2)	12.3 (10.1, 14.7)	98.1 (96.6, 99.1)	92	576	1.58 (1.46, 1.70)	0.22 (0.12, 0.39)	0.666 (0.016)	<0.001	(ref)	
Model 2 (≤-10)	91.7 (84.9, 96.2)	41.2 (38.4, 44.0)	12.1 (10.0, 14.6)	98.3 (96.7, 99.2)	83	589	1.56 (1.45, 1.68)	0.20 (0.11, 0.38)	0.665 (0.015)	0.004	0.780	(ref)
Model 3 (≤-12)	90.8 (83.8, 95.5)	43.3 (40.5, 46.1)	12.4 (10.2, 14.9)	98.2 (96.6, 99.1)	92	567	1.60 (1.48, 1.73)	0.21 (0.12, 0.38)	0.671 (0.016)	<0.001	0.559	0.311
Validation dataset												
OSTA (≤0)	84.6 (75.5, 91.3)	48.4 (45.3, 51.5)	12.8 (10.2, 15.7)	97.2 (95.4, 98.5)	154	517	1.64 (1.47, 1.82)	0.32 (0.20, 0.52)	0.665 (0.021)	(ref)		
OSTA (≤1)	92.3 (84.8, 96.9)	33.2 (30.3, 36.2)	11.0 (8.9, 13.4)	98.0 (95.9, 99.2)	77	669	1.38 (1.28, 1.49)	0.23 (0.11, 0.48)	0.627 (0.016)	(ref)		
Model 1 (≤-9)	87.9 (79.4, 93.8)	39.7 (36.7, 42.8)	11.5 (9.3, 14.1)	97.4 (95.3, 98.7)	121	603	1.46 (1.33, 1.60)	0.30 (0.17, 0.53)	0.638 (0.019)	0.365	(ref)	
Model 2 (≤-10)	85.7 (76.8, 92.2)	37.9 (34.9, 40.9)	11.0 (8.8, 13.5)	96.7 (94.5, 98.3)	143	622	1.38 (1.25, 1.52)	0.38 (0.23, 0.63)	0.618 (0.020)	0.506	0.017	(ref)
Model 3 (≤-12)	89.0 (80.7, 94.6)	39.5 (36.4, 42.5)	11.6 (9.3, 14.2)	97.6 (95.6, 98.8)	110	606	1.47 (1.35, 1.60)	0.28 (0.15, 0.50)	0.642 (0.018)	0.272	0.703	0.017
Low BMD (T_{FN}≤-2.0 or T_{LS}≤-2.0)												
Development dataset												
OSTA (≤0)	80.0 (74.6, 84.7)	53.1 (50.1, 56.1)	28.6 (25.3, 32.1)	91.9 (89.4, 93.9)	200	470	1.71 (1.56, 1.86)	0.38 (0.29, 0.48)	0.665 (0.015)	(ref)		
OSTA (≤1)	88.2 (83.6, 91.9)	40.0 (37.1, 43.0)	25.7 (22.8, 28.7)	93.5 (90.9, 95.6)	118	600	1.47 (1.38, 1.57)	0.29 (0.21, 0.41)	0.642 (0.013)	(ref)		
Model 1 (≤-9)	85.5 (80.6, 89.6)	45.6 (42.6, 48.6)	27.0 (24.0, 30.2)	93.1 (90.5, 95.1)	146	544	1.57 (1.46, 1.69)	0.32 (0.23, 0.43)	0.656 (0.013)	0.091	(ref)	
Model 2 (≤-10)	85.5 (80.6, 89.6)	44.2 (41.2, 47.2)	26.5 (23.5, 29.6)	92.8 (90.3, 94.9)	146	559	1.53 (1.42, 1.65)	0.33 (0.24, 0.45)	0.648 (0.013)	0.434	0.142	(ref)
Model 3 (≤-12)	85.1 (80.1, 89.2)	46.5 (43.5, 49.6)	27.2 (24.2, 30.5)	93.0 (90.5, 95.0)	149	535	1.59 (1.48, 1.71)	0.32 (0.24, 0.43)	0.658 (0.014)	0.071	0.749	0.160
Validation dataset												
OSTA (≤0)	77.1 (70.1, 82.6)	51.0 (47.7, 54.3)	26.9 (23.4, 30.1)	90.5 (88.0, 92.9)	229	490	1.57 (1.43, 1.74)	0.45 (0.35, 0.58)	0.641 (0.017)	(ref)		
OSTA (≤1)	86.7 (81.3, 91.0)	35.2 (32.1, 38.4)	23.8 (20.8, 27.0)	91.9 (88.5, 94.5)	134	648	1.34 (1.25, 1.44)	0.38 (0.27, 0.54)	0.609 (0.014)	(ref)		
Model 1 (≤-9)	84.8 (79.2, 89.3)	42.7 (39.4, 46.0)	25.7 (22.4, 29.1)	92.3 (89.3, 94.7)	153	574	1.48 (1.36, 1.60)	0.36 (0.26, 0.50)	0.637 (0.015)	0.004	(ref)	
Model 2 (≤-10)	86.2 (80.8, 90.6)	41.1 (37.9, 44.4)	25.5 (22.3, 28.8)	92.7 (89.7, 95.1)	139	589	1.46 (1.36, 1.58)	0.34 (0.24, 0.48)	0.636 (0.015)	0.009	0.931	(ref)
Model 3 (≤-12)	86.7 (81.3, 91.0)	42.7 (39.4, 46.0)	26.1 (22.9, 29.5)	93.2 (90.3, 95.4)	134	574	1.50 (1.39, 1.63)	0.32 (0.23, 0.46)	0.647 (0.014)	0.001	0.287	0.218

OSTA, Osteoporosis Self-assessment Tool for Asians; BMD, bone mineral density; PPV, positive predictive value; NPV, negative predictive value; NMC, the number of missed cases which represents the number of undetected osteoporotic subjects (i.e., false negatives) per 1000 subjects; NUDT, the number of unnecessary DXA tests which represents the number of subjects referred for DXA testing (i.e., false positives) per 1000 subjects; ROC, receiver operation characteristics; AUC, area under the curve; SE, standard error; T_{FN}, T-score at femoral neck; T_{LS}, T-score at lumbar spine; DXA, dual-energy X-ray absorptiometry; ALP, alkaline phosphatase.
Model 1 included age and weight, model 2 added regular exercise, and model 3 added low vitamin D and an elevated ALP.

Development and validation of KORAM-M

Five variables associated with BMD T scores were selected according to 10-fold cross-validation: age, body weight, regular exercise, low serum 25(OH)D, and serum ALP concentrations. After adjustment for covariates, all variables had significant and independent associations with BMD T scores. Multicollinearity among those variables was not significant. Table 2 presents regression coefficient, standard error, and index weight of each variable in the final multiple regression model. Based on the selected variables and their index weights, three candidate models were developed as follows:

- Model 1=[(age in years/10)×(-3)+(weight in kilograms/10)×8]
- Model 2=[(age in years/10)×(-3)+(weight in kilograms/10)×8+(if no regular exercise)×(-2)]
- Model 3=[(age in years/10)×(-3)+(weight in kilograms/10)×8+(if no regular exercise)×(-2)+(if low vitamin D)× (-2)+(if elevated ALP)×(-6)]

The ranges of scores in Model 1, Model 2, and Model 3 in men were from 6 to 61 (median 34), from 4 to 61 (median 33), and from -2 to 59 (median 31), respectively. The range of scores in the candidate models in men (-2 to 59) was different from that in postmenopausal women's candidate models (-27 to 9) previously published.[16] Therefore, the scores for the models used for men were adjusted by subtracting 45 from the scores for the men's models:

- Model 1=[(age in years/10)×(-3)+(weight in kilograms/10)×8-45]
- Model 2=[(age in years/10)×(-3)+(weight in kilograms/10)×8+(if no regular exercise)×(-2)-45]
- Model 3=[(age in years/10)×(-3)+(weight in kilograms/10)×8+(if no regular exercise)×(-2)+(if low vitamin D)×(-2)+(if elevated ALP)×(-6)-45]

In the development dataset, all models for men showed reasonable fitness according to the Hosmer-Lemeshow test (p for OSTA=0.969, p for Model 1=0.776, p for Model 2=0.717, and p for Model 3=0.630). In correlation analysis between the predicted scores and actual BMD T scores, Spearman's correlation coefficients were 0.320 for OSTA, 0.480 for Model 1, 0.482 for Model 2, and 0.494 for Model 3 (p for all <0.001). In terms of discriminative performance, Model 1 and Model 2 demonstrated significantly higher values of AUC compared to that of OSTA. Additionally, Model 2 showed a significantly higher value than that of Model 1, but comparable to that of Model 3. However in the validation dataset, AUC of each model was not significantly different. For sensitivity analysis, model fitness, correlation, and AUC were also evaluated with outcome of low BMD.

Table 3 presents the discriminatory performance of OSTA and the candidate models with the selected cut-off scores to yield 90% or greater sensitivity based on sensitivity, specificity, PPV, NPV, false negative, false positive, positive likelihood ratio, negative likelihood ratio, and AUC. In the case of OSTA, the predefined cut-off score of 0 showed a relatively low sensitivity (86.2%). Therefore, a cut-off score of 1 to yield 90% or greater sensitivity was used as a reference. Model 1 showed an improved specificity, PPV, NPV comparable to OSTA, but comparable to Model 2 and Model 3. Additionally, the AUC of Model 1 was significantly higher than that of OSTA, with a cut-off score of 1, but comparable to that of Model 2, with a cut-off score of -10, and Model 3, with a cut-off score of -12. Therefore, Model 1, only based on age and body weight, with a cut-off score of -9 was finally selected and named as the KORAM-M.

Performance of KORAM-M by risk category

Table 4 presents the performance of KORAM-M to predict osteoporosis according to its risk categories. To define the clinical implications of KORAM-M, three risk categories were formed with cut-off values of -9 and -27: greater than -9 for low risk, between -27 and -9 for intermediate risk, and less than -27 for high risk. In the development dataset, 39.7, 56.1, and 4.2% were classified into low-, intermediate-, and high-risk categories, respectively. Among the participants in the low-, intermediate-, and high-risk categories, 1.9, 9.7, and 46.4%, respectively, had osteoporosis. In the validation dataset, the percentage of men in the low-, intermediate-, and high-risk categories was 37.5, 60.4, and 2.2%, respectively. The prevalence of osteoporosis was 2.6, 10.1, and 50.0% in the low-, intermediate-, and high-risk categories, respectively. We additionally analyzed men aged less than 70 years and those at 70 or more separately. In the development dataset, in men aged less than 70 years, 50.5, 48.9, and 0.6% were classified into low-, intermediate-, and high-risk categories, respectively. Among men in the low-, intermediate-, and high-risk categories, 2.0, 7.9, and 66.7%, respectively, had osteoporosis. In men aged 70 years or older, 9.4, 76.4, and 14.2% were classified into low-, intermediate-, and high-risk categories, respectively. Among men in the low-, intermediate-, and high-risk categories, 0.0, 13.0, and 44.0%, re-

Table 4. Performance of KORAM-M to Predict Osteoporosis According to Its Risk Categories

Risk category	Development dataset		Validation dataset	
	Total, n (column %)	Osteoporosis, n (row %)	Total, n (column %)	Osteoporosis, n (row %)
High (<-27)	56 (4.2)	26 (46.4)	24 (2.2)	12 (50.0)
Intermediate (-27– -9)	752 (56.1)	73 (9.7)	670 (60.4)	68 (10.1)
Low (>-9)	532 (39.7)	10 (1.9)	416 (37.5)	11 (2.6)
Total	1340 (100.0)	109 (8.1)	1110 (100.0)	91 (8.2)

KORAM-M, Korean Osteoporosis Risk-Assessment Model for Men.

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spectively, had osteoporosis (Supplementary Table 1, only online).

The net improvement of KORAM-M compared to OSTA with the suggested cut-off scores (-4 and -1) was 0.9% (1 out of 109) for participants with osteoporosis, 6.3% (78 out of 1231) for those without osteoporosis, and 7.3% (95% CI 0.5–14.0) overall. Furthermore, the NRIs of KORAM-M showed improved classification up to 22.8%, compared to OSTA, across the different cut-off scores of OSTA: -3 and 1, -4 and 1, -5 and 1, and -6 and 1 (Table 5).

Comparison of KORAM-M with the current Korean NHIC guidelines

At present, Korean National Health Insurance Corporation (NHIC) guidelines for osteoporosis screening using DXA tests are limited to men aged 70 years or older with exceptions being younger men with low BMI (<18.5), past history or family history of non-traumatic fracture. KORAM-M was developed using each individual's age and body weight; thus, it may provide an efficient targeting guideline for the use of DXA tests. The number of recommended DXA tests of KORAM-M would be more than double that of the NHIC guidelines; 60.3% vs. 27.8% of men, respectively. KORAM-M could identify 90.8% of men with osteoporosis, but the NHIC guidelines classify only 60.0% of men with osteoporosis as screening targets. Accordingly, false negative rate of KORAM-M was 9.2%, which is much lower than the rate of the NHIC guidelines, 39.4%. However, KORAM-M was inferior to NHIC guidelines in terms of specificity. According to the NHIC guidelines, 24.9% of men without osteoporosis are recommended to screen for the disease. On the other hand, when we apply KORAM-M, 57.6% of men without osteoporosis are recommended to screen. Both PPV and NPV were similar between KORAM-M and NHIC guidelines (Table 6). We repeated these analyses separately for men aged less than 70 years and for those at 70 or more. In a subgroup analysis of men aged less than 70 years, KORAM-M clas-

Table 5. Net Reclassification Improvement of KORAM-M Compared to OSTA Risk Categories with the Different Cut-Off Values

OSTA risk category	Total	Osteoporosis	Participants with osteoporosis, %		Participants without osteoporosis, %		NRI (95% CI)
	n (column %)	n (row %)	Up	Down	Up	Down	
Cut-off: -3, 1							-0.5 (-8.2, 7.2)
High (<-3)	117 (8.7)	37 (31.6)	0.0	11.9	0.0	4.1	
Intermediate (1– -3)	759 (56.6)	62 (8.2)	1.8	0.9	0.0	7.7	
Low (>1)	464 (34.6)	10 (2.2)	0.9	0.0	2.2	0.0	
Cut-off: -4, 1							7.3 (0.5, 14.0)
High (<-4)	65 (4.9)	25 (38.5)	0.0	4.6	0.0	1.1	
Intermediate (1– -4)	811 (60.5)	74 (9.1)	5.5	0.9	0.3	7.7	
Low (>1)	464 (34.6)	10 (2.2)	0.9	0.0	2.2	0.0	
Cut-off: -5, 1							16.2 (8.9, 23.4)
High (<-5)	27 (2.0)	13 (48.1)	0.0	0.0	0.0	0.0	
Intermediate (1– -5)	849 (63.4)	86 (10.1)	11.9	0.9	1.3	7.7	
Low (>1)	464 (34.6)	10 (2.2)	0.9	0.0	2.2	0.0	
Cut-off: -6, 1							22.8 (13.9, 31.6)
High (<-6)	10 (0.7)	5 (50.0)	0.0	0.0	0.0	0.0	
Intermediate (1– -6)	866 (64.6)	94 (10.9)	19.3	0.9	2.0	7.7	
Low (>1)	464 (34.6)	10 (2.2)	0.9	0.0	2.2	0.0	

KORAM-M, Korean Osteoporosis Risk-Assessment Model for Men; OSTA, Osteoporosis Self-assessment Tool for Asians; NRI, net reclassification improvement; CI, confidence interval.

Table 6. Comparison between the Current NHIC Guideline and the KORAM-M

	NHIC guideline (%)	KORAM-M (%)
No. of subjects recommended for DXA testing	373/1340 (27.8)	808/1340 (60.3)
Sensitivity	66/109 (60.6)	99/109 (90.8)
Specificity	924/1231 (75.1)	522/1231 (42.4)
Positive predictive value	66/373 (17.7)	99/808 (12.3)
Negative predictive value	924/967 (95.6)	522/532 (98.1)
False negative rate	43/109 (39.4)	10/109 (9.2)
False positive rate	307/1231 (24.9)	709/1231 (57.6)

NHIC, National Health Insurance Corporation; KORAM-M, Korean Osteoporosis Risk-Assessment Model for Men; DXA, dual-energy X-ray absorptiometry.

sified 80.8% of men with osteoporosis as screening targets, while the NHIC guidelines recommended only 17.3% of them to screen. Accordingly, false negative rate of KORAM-M was estimated to be 19.2%, which is much lower than that of NHIC guidelines, 82.7% (Supplementary Table 2, only online).

DISCUSSION

In the present study, the Korean osteoporosis risk-assessment model for men was developed and validated in a Korean population based on a nationally representative BMD and health examination dataset: KORAM-M=[(age in years/10)×(-3)+(weight in kilograms/10)×8-45].

To develop KORAM-M, we examined clinically or statistically significant factors that were associated with BMD: age, body weight, height, current smoking status, currently alcohol drinking status, regular exercise, diabetes, depression, low serum 25(OH)D, elevated ALP, and elevated PTH. Of these factors, five variables were selected as potential components of the risk-assessment models including age, body weight, regular exercise, serum 25(OH)D, and serum ALP concentrations. To develop a simple and effective model, we first defined a baseline model for age and body weight, which were fundamental factors in the previously developed models.[18-24] We then investigated the incremental effect of adding regular exercise to predict osteoporosis. The effect of regular exercise on BMD is still controversial. In the present study, a positive association between regular exercise and BMD was shown. Although only a few studies are available, our findings are consistent with previous studies that found positive effects of exercise on BMD in men.[39,40] Therefore, we assessed regular exercise as a component of osteoporosis risk-assessment model, even though it has never been used in previous models. Additionally, in this study, serum ALP concentrations were negatively correlated with BMD, and vitamin D concentrations were positively correlated to BMD. Vitamin D deficiency is known to exacerbate osteoporosis[41] and osteoporotic fracture.[42] Thus, we evaluated whether an invasive laboratory test further improved the prediction of osteoporosis. As evaluating performance of each model using sensitivity, specificity, PPV, NPV, false positive, false negative, positive likelihood ratio, negative likelihood ratio, and AUC, the baseline model with age and body weight was comparable to other models adding regular exercise and laboratory tests. Therefore, KORAM-M was developed based on simple variables including age and body weight. KORAM-M can be easily used in a primary care setting for pre-screening to decide whether to use DXA testing as well as in the general population for self-screening purposes.

In this study, we assessed both linear and logistic regression models to calculate an index weight of each variable to make a scoring system to predict osteoporosis. However, when we compared the performance of the models, the scoring system using the weights from linear regression analyses slightly outperformed those from logistic regression analyses (data not shown).

In addition, all candidate models were compared with OSTA, which has been validated in many countries.[21,22,24] Overall, KORAM-M indicated better performance for the detection of osteoporosis than OSTA. The discriminative performance of KORAM-M was significantly superior to that of OSTA (AUC= 0.666 and 0.639, respectively, $p<0.001$). Additionally, KORAM-M showed improved net reclassification up to 22.8% over OSTA across different cut-off scores. Furthermore, KORAM-M showed higher sensitivity than the current Korean NHIC guidelines (90.8% vs. 60.6%). The difference of sensitivity was more prominent among men younger than 70 years: 80.8% for KORMA-M vs. 17.3% for NHIC guidelines. Thus, we can propose a combined strategy. Screening with DXA can be recommended to men 70 years or older, and to men younger than 70 years at high risk according to KORAM-M. Osteoporosis itself presents no specific symptoms, but the burden of osteoporotic fracture continues to grow with age. Accordingly, the potential risks and benefits of DXA testing should be assessed. However, no clinical trials are available to investigate the effectiveness of osteoporosis screening or any potential risks that can result from screening.[9] In false-negative cases, a diagnosis of osteoporosis can be overlooked and further treatment can be delayed. In opposition, false-positive cases can lead to unnecessary DXA tests, unnecessary exposure to radiation, and increased health care costs. However, even though participants who underwent DXA testing did not have osteoporosis (false-positive cases), the result of the DXA test will still evaluate the status of their bone health and help obtain the proper interval for BMD testing.

The study has several limitations that warrant consideration. First, the cost-effectiveness of KORAM-M was not considered. Although KORAM-M could identify more than 90% of people with osteoporosis, the false positive rate was approximately 50%. Therefore, to use KORAM-M in clinical practice, its potential benefits and shortcomings should be further investigated. Second, in spite of using a nationwide representative dataset, the KNHANES is a cross-sectional study. Therefore, KORAM-M is limited to estimating prevalent cases of osteoporosis. Considering that the eventual goal for improving bone health is to prevent osteoporotic fracture, and that BMD scores provide only a marginal benefit for predicting osteoporotic fracture,[43] the role of KORAM-M in preventing osteoporotic fracture should be further evaluated. At present, the Korean version of FRAX® to predict the 10-year probability of hip fracture and major osteoporotic fracture (clinical spine, humerus, or wrist fracture) is available. Because KORAM-M and FRAX share two major factors, age and body weight, studies on correlations of a calculated risk of osteoporosis by KORAM-M with an estimated risk of osteoporotic fracture by FRAX and prevalent cases of osteoporotic fracture are needed in well-designed cohort

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studies with the Korean population. Lastly, to estimate gender-specific T scores at the femoral neck and lumbar spine, site and gender-specific reference means and standard deviations were adopted from the Japanese data because no Korean reference data are currently available. Thus, KORAM-M should be additionally adjusted when Korean reference BMD data are available.

To our knowledge, the current study is the first to develop an osteoporosis risk-assessment model for Korean men using a nationally representative dataset that includes BMD measurements and other relevant risk factors of osteoporosis. Our findings suggest that KORAM-M is a useful pre-screening tool for screening osteoporosis by DXA in the Korean men. Since KORAM-M is easy to calculate with simple variables, it can be used in either a primary care setting or in general use as a self-screening tool. However, prior to using KORAM-M in these settings, its cost-effectiveness, especially compared to current NHIC guidelines, should be investigated. Additionally, replication studies using other Korean BMD datasets are recommended. Finally, further adjustment of KORAM-M using BMD data as a reference in the Korean population is necessary.

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