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ORIGINAL ARTICLE

A nomogram for predicting osteoporosis risk based on age, weight and quantitative ultrasound measurement

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Abstract
Introduction Quantitative ultrasound measurement (QUS) or clinical risk index alone are not reliable tools for the identification of women with osteoporosis. This study examined the prognostic value of combined QUS and clinical risk index for predicting osteoporosis risk in Thai women.
Methods The study was designed as a cross-sectional investigation with 300 women of Thai background, aged between 38 and 85 years (mean age: 58). Femoral neck bone mineral density (BMD) was measured by DXA (Hologic QDR-4500; Bedford, MA, USA). A femoral neck BMD T-scores ≤ -2.5 was defined as "osteoporosis"; otherwise, "non-osteoporosis". QUS was measured by Achilles+ (GE Lunar, Madison, WI, USA) and converted to T-score. Three models for predicting osteoporosis were considered: model I included age, weight and QUS, model II included age and weight, and model III included only QUS. The prognostic performance among the models was assessed by the area under the receiver operating characteristic curve (AUC).
Results The prevalence of osteoporosis was 12.7% (n=38/300) by femoral neck BMD. Age, weight and QUS were each significantly associated with osteoporosis risk. The AUC±SE value for model I was 0.86±0.03, which was significantly higher (p=0.02) than that for model II (AUC=0.80±0.04) or model III (AUC=0.79±0.04). Based on the estimated parameters of model I, a nomogram was constructed for predicting osteoporosis.
Conclusion These data suggest that the combination of QUS and age and weight could significantly improve the prognosis of osteoporosis in Asian women, and that the nomogram can assist primary care physicians in the identification of high-risk women.

Keywords Bone mineral density · Epidemiology · Nomogram · Osteoporosis · Quantitative ultrasound measurement

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Introduction

One of the priorities in osteoporosis research is the development of diagnostic tools for identifying high-risk individuals for intervention [1]. Because individuals with low bone mineral density (BMD) are at high risk of fracture [2–4], it has been recommended that individuals with low BMD should be considered for treatment [5–7]. However, this would require measurement of BMD in all individuals in the general population, which is not cost-effective [8, 9]. Furthermore, the DXA instrument for measuring BMD is

relatively expensive, and is not widely available in most developing countries, including Thailand. Therefore, using DXA for mass screening in postmenopausal women is at present impractical without some selection of the target population [5, 6, 10–14].

Effort to use clinical risk indices to identify subjects likely to have low BMD is regarded as an attractive and cost-effective approach to the prevention of osteoporosis. For postmenopausal women of Asian background, the Osteoporosis Self-Assessment Tools for Asians (OSTA) [15] and the Khon Kaen Osteoporosis Study score (KKOS) [16] have been suggested as a tool for identifying individuals with osteoporosis. These instruments are actually based on a linear combination of age and weight, and then further dichotomized into high-risk versus low-risk scores. One potential weakness of these tools is that the dichotomization could result in loss of information, which leads to reduced sensitivity or specificity. Indeed, the OSTA score had high sensitivity but low specificity and low positive predictive value (PPV) in the identification of osteoporotic Thai women [17], and can result in a high false positive rate when using in general population. KKOS, a Thai-specific clinical risk score, is more sensitive and specific, but had modest PPV and requires further research and evaluation [16].

Quantitative ultrasound (QUS) calcaneus measurement—a portable, less expensive, less time-consuming radiation-free technique—has been developed as an alternative method for assessment of BMD. It has been shown in previous studies that QUS was an independent predictor of fracture risk in the elderly population [18, 19]. However, the diagnostic performance of QUS for identifying osteoporosis was equivocal [20–22]. In Thai postmenopausal women, the diagnostic performance of QUS calcaneus measurement in case-finding for osteoporosis had a low sensitivity but high specificity [23]. A recent meta-analysis of the accuracy of QUS concluded that "the current available literature suggests that results of calcaneal quantitative ultrasound at commonly used cut-off thresholds do not definitely exclude or confirm DXA-determined osteoporosis" [24]. It is hypothesized that a model with QUS and anthropometric variables can improve the accuracy of prediction.

In a primary clinical setting, the use of a non-invasive and simple instrument such as QUS calcaneus measurement, together with readily available demographic information such as age and weight, is potentially a useful approach for identifying individuals with high risk of osteoporosis. It is hypothesized that the combination of QUS and age and weight can improve accuracy in the identification of high-risk women. This study was therefore designed to determine the diagnostic performance when using age and weight combined with QUS of the calcaneus for identifying osteoporosis in Thai postmenopausal women.

Study design and methods

Setting and subjects

The present study was designed as a cross-sectional investigation in 300 consecutive newly postmenopausal women (defined by no menstruation normally for at least 1 year) who came to evaluate possible osteoporosis at the outpatient clinics of the Nuclear Medicine Division, Phramongkutklao Hospital, Bangkok, Thailand, between June 2002 and November 2002. All women were of Thai background, and were excluded from analysis if they had a history of metabolic bone disorders (other than postmenopausal bone loss), presence of cancer(s) with known metastasis to bone, history of previous hip or calcaneal fracture, history of hip or knee prosthesis, abnormal features of bone at the calcaneus on physical examination, or history of calcification at the calcanal bone from disease of the calcaneus, i.e., plantar fasciitis, plantar fibroma, retro-calcaneal bursitis or ankle sprain/strain. This study was approved by the Ethics Committee of Phramongkutklao College of Medicine, and informed consent was obtained from all subjects. The study was conducted in accordance with the 1975 Helsinski Declaration, as revised in 2000 (Edinburgh).

Measurements

Subjects were invited to meet with a research nurse who completed a questionnaire and an informed consent form. Body weight (including light indoor clothing) was measured using an electronic balance scale (accuracy 0.1 kg) and standing height (without shoes) with a stadiometer (nearest 0.1 cm).

QUS of the calcaneus was measured using an Achilles express ultrasound device (Lunar, Madison, WI, USA). In this study, the QUS was measured twice for test–retest reliability by the same technologist. The first was carried out before the DXA, and the second after the DXA was carried out. The duration of both measurements did not exceed 30 minutes. The QUS measurement was expressed in T-score, which is the number of standard deviations further from the peak level. The T-score was provided by the instrument.

Bone mineral density (g/cm^2) was measured at the femoral neck by DXA using a Hologic QDR-4500 densitometer (Hologic, Bedford, MA, USA). The BMD measurement was expressed in T-score, and used as a gold standard. The classification was based on a previously published reference data base for Thai women, in which peak BMD was estimated at 0.814 g/cm^2, with standard deviation being 0.10 g/cm^2 [25]. Each woman was classified as having "osteoporosis" if her femoral neck

BMD T-score was equal to or less than −2.5; otherwise the woman was classified as "non-osteoporosis".

Statistical analyses

In order to develop an optimal model for predicting osteoporosis risk, three linear logistic regression models were considered: model I included age, weight and QUS T-scores, model II included age and weight, and model III included only QUS T-scores. The prognostic performance of each model was assessed by the area under the receiver operating characteristic curve (AUC) [26]. Differences in AUC among the models were evaluated by non-parametric test [27]. Based on the test, an optimal model was selected, and parameter estimates of this model were then used for constructing a nomogram using the Design library [28]. The bootstrap method was applied to examine the predictive accuracy of the nomogram in new settings. In this method, subsamples, each with 150 women, were repeatedly resampled (with replacement) from the original entire dataset, and parameter estimates were computed for each subsample and were used for the calibration of predictive accuracy [29].

Results

A total of 300 Thai women, aged between 38 and 85 years (mean age: 58 years) were included in this study; of those, 21.7% (n=46) aged 65 years or older. The average duration of menopause was 11 years. The prevalence of osteoporosis (BMD T-scores ≤ -2.5) was 12.7% (n=38/300). As expected, osteoporotic women were, on average, older, and had shorter height and lower body weight than those without osteoporosis. Furthermore, all QUS measurement was significantly lower in the osteoporosis group than in the non-osteoporosis group (Table 1). The differences persisted even after adjusting for age (data not shown).

Table 1 Characteristics of study subjects

Variable	Non-osteoporosis	Osteoporosis	*P*-value
N	262	38	
Age	56.8 (8.1)	65.7 (9.4)	<0.0001
Weight	58.3 (8.9)	51.7 (8.5)	<0.0001
Height	155.5 (5.8)	151.3 (6.6)	0.0002
Body mass index	24.1 (3.4)	22.5 (3.0)	0.0065
Femoral neck BMD	0.72 (0.10)	0.51 (0.06)	<0.0001
Femoral neck T-score	−1.00 (1.01)	-3.10 (0.58)	<0.0001
QUS T-score	−1.06 (1.49)	−2.59 (1.24)	<0.0001

Notes: Values are mean (SD). *P*-values were derived from the unpaired *t*-test for difference between osteoporosis and non-osteoporosis group

Advancing age, lower weight and lower QUS T-scores were each significantly and independently associated with an increased risk of osteoporosis (Table 2). The odds of having osteoporosis were increased by 1.5 (95% CI: 1.2–1.9) for each 5-year increase in age, 1.6 (95% CI: 1.2–2.0) for each 5-kg reduction in weight, and 1.9 (95% CI: 1.4–2.7) for each unit of decrease of QUS T-score. The AUC for the model II (with age and weight) was virtually identical to that for the model III (with QUS only). However, the model I with all three factors had the highest AUC value (0.86± 0.03), which represented a significant improvement over either model II or model III (p<0.02) (Table 3 and Fig. 1).

Based on the parameter estimates of model I, the probability of having osteoporosis (denoted by p) was estimated by the following equation: $p = e^x/(1+e^x)$, where x=–3.24+0.0822×*Age*–0.0883×*Weight*–0.6535×*QUS*. If a probability of osteoporosis of at least 0.3 is considered high-risk, then according to this model, virtually all women weighing 40 kg or less, aged 65+ and with QUS T-scores less than or equal to -1 are in the high-risk group. Moreover, most women weighing 40 kg, aged 50+ years and with QUS T-scores less than -2 are in the high-risk group (Table 4).

A nomogram for predicting osteoporosis risk was constructed from the model, and is shown in Fig. 2. For example, a woman aged 70 years, weighing 50 kg, with a QUS T-score=-2, (population average) is predicted to have a 36% chance of having osteoporosis. However, with the same QUS level and the same weight, a woman aged 85 years would have a probability of osteoporosis of approximately 65%.

The internal validity of the nomogram was evaluated for its ability to determine a patient's risk of osteoporosis, as measured by the concordance index (which is similar to the area under the curve of a ROC curve). Results of boostrapping validation suggested that the nomogram discriminated well, with a bootstrap-corrected concordance index of 0.80 (P<0.001), with an "optimism index" of 1.07% (i.e., the model over-estimates the concordance index by approximately 1.1%). The nomogram-based predicted probability of osteoporosis was compared to the

Table 2 Models for predicting osteoporosis

Model	Odds ratio (95% CI) for predictor[1]		
	Age	Weight	QUS
I	1.51 (1.20–1.89)	0.64 (0.50–0.83)	0.52 (0.37–0.73)
II	1.71 (1.39–2.12)	0.63 (0.48–0.81)	
III			0.42 (0.31–0.58)

[1]: Odds ratio and 95% confidence interval were estimated per 5-year increase in age, 5-kg increase in weight, and 1-unit increase in QUS T-score.

Table 3 Comparison of models for predicting osteoporosis

Model	Predictor	Area under the curve (AUC±SE)	Change in AUC±SE from model I	*P*-value
I	Age+weight+QUS	0.860±0.032		
II	Age+weight	0.797±0.041	0.063±0.025	0.012
III	QUS	0.785±0.041	0.075±0.010	0.023

actual probability, and the result suggested that the predictions calculated with the nomogram approximated the actual outcomes (Fig. 3).

Discussion

Osteoporosis is increasingly becoming a major public health concern in Asia, as the population is progressively aging. Ideally, all postmenopausal women who are at high risk of fracture should be screened by BMD measurement and follow-up treatment. However, as the DXA densitometer is not widely available in Asian countries due to high cost, such a screening program is impractical and perhaps not cost-effective. Thus, simple clinical risk indices (i.e., OSTA and KKOS) have been developed for identifying individuals who are at high risk of having osteoporosis [15, 16]. However, these tools have relatively low sensitivity and specificity, due partly to the arbitrary cut-off values which often lead to information loss. Recently, QUS has been proposed as a screening tool, but recent study has suggested that QUS, too, has low sensitivity in terms of osteoporosis prediction. This study suggested that the combination of QUS and age and weight could significantly improve the accuracy of prediction.

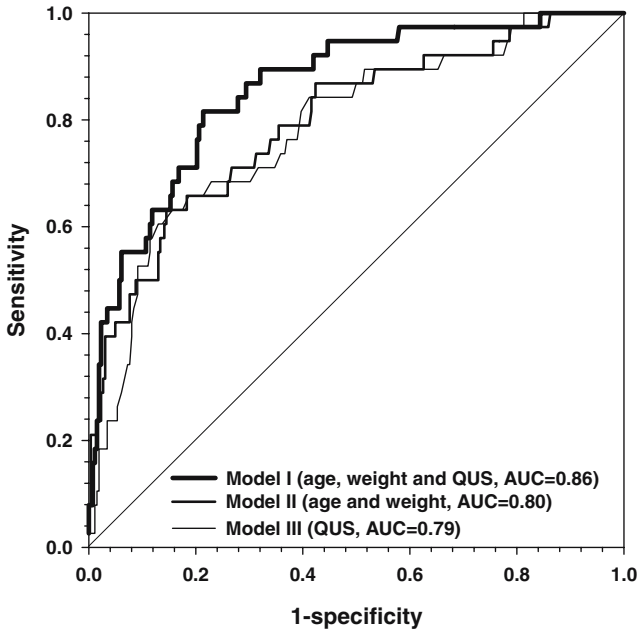

Fig. 1 Receiver operating characteristic curves for the three models. The AUC of model I was 0.86, which was significantly higher than that of models II (AUC=0.80) or model III (AUC=0.79)

Table 4 Predicted probability of having osteoporosis for a given age, weight and QUS

Weight	Age	QUS T-score				
		−4	−3	−2	−1	0
40 kg	50	**0.49**	**0.33**	0.20	0.12	0.07
	55	**0.59**	**0.43**	0.28	0.17	0.10
	60	**0.68**	**0.53**	**0.37**	0.23	0.14
	65	**0.77**	**0.63**	**0.47**	**0.32**	0.19
	70	**0.83**	**0.72**	**0.57**	**0.41**	0.27
	75	**0.88**	**0.79**	**0.67**	**0.51**	**0.35**
	80	**0.92**	**0.85**	**0.75**	**0.61**	**0.45**
	85	**0.94**	**0.90**	**0.82**	**0.70**	**0.55**
50 kg	50	0.28	0.17	0.10	0.05	0.03
	55	**0.37**	0.24	0.14	0.08	0.04
	60	**0.47**	**0.32**	0.20	0.11	0.06
	65	**0.57**	**0.41**	0.27	0.16	0.09
	70	**0.67**	**0.51**	**0.36**	0.22	0.13
	75	**0.75**	**0.62**	**0.45**	0.30	0.18
	80	**0.82**	**0.71**	**0.56**	**0.40**	0.25
	85	**0.87**	**0.78**	**0.65**	**0.50**	**0.34**
60 kg	50	0.14	0.08	0.04	0.02	0.01
	55	0.20	0.11	0.06	0.03	0.02
	60	0.27	0.16	0.09	0.05	0.03
	65	**0.36**	0.23	0.13	0.07	0.04
	70	**0.46**	0.30	0.19	0.11	0.06
	75	**0.56**	**0.40**	0.26	0.15	0.09
	80	**0.66**	**0.50**	**0.34**	0.21	0.12
	85	**0.74**	**0.60**	**0.44**	0.29	0.17

Notes: Probabilities of at least 0.3 were bold

The lack of sensitivity of QUS in the prediction of osteoporosis is perhaps not surprising, because the correlation between QUS and BMD by DXA is modest. For example, the correlation between broadband ultrasound attenuation (BUA) and lumbar spine BMD ranged from 0.3 to 0.5 [30]. However, the site-matched correlations between QUS and BMD were significantly higher than those for non-matched sites, with the correlation ranging from 0.6 to 0.8 [22, 31, 32], but less with BMD of the lumbar spine (r= 0.50–0.54) or the hip (0.47–0.52), or the wrist (0.63) [33]. In other words, at most QUS can account for only 50% of the variance in BMD. Nevertheless, the present study indicated that a simple linear combination of QUS, age and body weight could significantly improve the prognostic sensitivity over and above either QUS or anthropometric factors.

The use of QUS and anthropometric factors has a number of obvious advantages: low cost, no radiation, non-invasiveness and flexibility. The use of QUS to assess bone

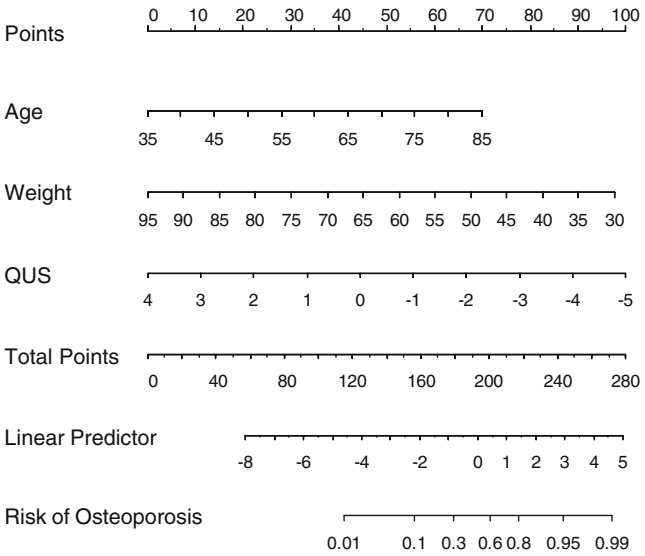

Fig. 2 Nomogram for predicting osteoporosis. Mark an individual's age on the "Age" axis, and draw a vertical line to the "Point" axis to determine the number of points the individual receives for her age. Repeat this process for the weight and QUS T-score. Add the number of points from each predictor. Mark this sum on the "Total Points" axis, and draw a vertical line down to meet the "Risk of Osteoporosis" axis, to find the woman's probability of having osteoporosis. Example: Mrs X, 70 years old, weighs 50 kg and has a QUS T-score of -2; her score for age is approximately 50, her weight score is 67; and QUS score is 66. Her total score is therefore 50+67+66=183, and her probability of having osteoporosis is around 0.36. In other words, in 100 women like her, one would expect 36 of them have osteoporosis

properties has several advantages over DXA. Firstly, QUS measurement is noninvasive, and can be provided by easily portable scanners at relatively low cost. Moreover, QUS requires less operator skill than DXA, and is becoming more common in primary care centers and smaller clinics. Compared with DXA, QUS involves no ionizing radiation, and is therefore suitable for regular use.

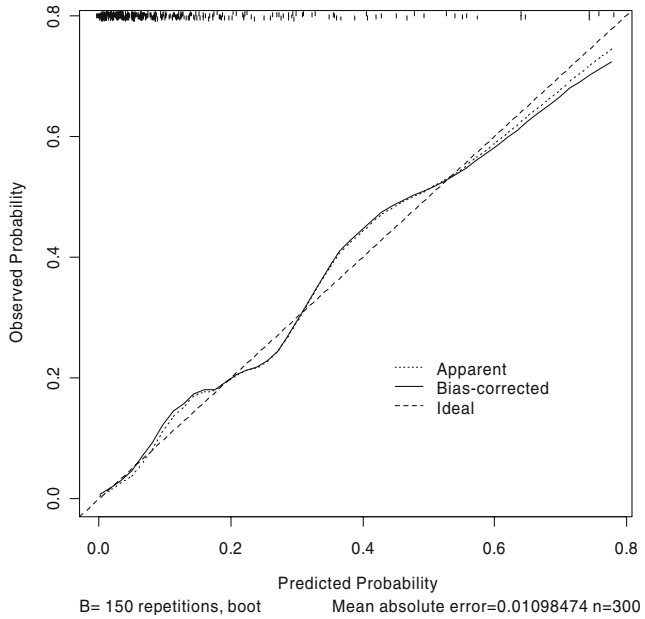

Fig. 3 Calibration of nomogram: plot of predicted probability against the observed probability of having osteoporosis. *Points* represent bootstrap-corrected estimates of accuracy

QUS measurements are temperature-dependent [34–36], and the temperature of the bone and soft tissue at the measured skeletal site is the main cause of seasonal variation in QUS measurement. The temperature at the measurement site was associated with lower SOS measurements [37]. On the other hand, the association between variation of BUA and temperature has been inconsistent, perhaps because BUA is dependent on the core temperature of the bone; therefore, temperature of the skin or room temperature alone would not represent the true temperature of BUA, causing an inconsistent finding [37]. Although the true effect of temperature on BUA is not completely understood, the seasonal variation in QUS measurements has been well-documented [35]. This seasonal dependence can potentially limit the long-term precision of the QUS as a diagnostic tool.

Osteoporosis or low bone mineral density is the primary risk factor for fracture [2–4], and women with osteoporosis are recommended for treatment to reduce their risk of fracture [5]. The purpose of a model for predicting osteoporosis risk is, therefore, to suggest a prognosis or therapeutic action, and to reduce the burden of fracture in the general population. Traditional models for predicting osteoporosis were largely based on some cut-off values of predictors, which were in turn determined from a validated functional relationship between the predictors and osteoporosis. Although this approach of model development has the appeal of simplicity, it is prone to misclassification (false positive and false negative). For example, a woman aged 60 years may have comparable risk with a woman aged 61 years, but the artificial cut-off at the age of 60 can separate the two women into two different risk groups. Furthermore, such a categorization of risk is usually applicable to a group of patients, not to an individual patient. The present study considered all predictor variables in their continuous scales, and took the position that the risk of osteoporosis is a continuum. Therefore, the nomogram as shown in this study is a useful means for communicating risk to an individual patient, because it is based on a combination of any characteristics of the individual patient. It has been demonstrated that a nomogram has a better performance than risk-grouping categorization [38, 39], because the nomogram estimates a continuous probability of osteoporosis, which provides a more accurate prediction than models based on risk grouping.

The present findings must be interpreted within the context of a number of potential strengths and weaknesses. A major strength of this study lies in its validity and

sampling scheme. The measurement of BMD in this study was based on the DXA instrument, which is considered to be one of the most accurate and valid methods of measurement. The sample size was reasonably large, to allow for a stable estimation of relations between risk factors and osteoporosis. The subjects in this study were Thai, among whom body size, lifestyles, cultural backgrounds and environmental living conditions are different from other populations. Thus, care should be taken when extrapolating these results to other populations. Although the present model is encouraging, it must be validated in independent populations before it can be implemented in a clinical setting. It is important to note that the outcome of this study was osteoporosis, not fracture which is perhaps the ultimately relevant outcome. Previous studies have shown that clinical indices could predict the risk of osteoporosis with good sensitivity and specificity, but could not predict fracture risk [40]. The present nomogram has not been validated in an independent population for the prediction of fracture, and thus its external validity remains to be established. Nevertheless, since individuals with osteoporosis are considered for therapeutic intervention, the present model is still useful in clinical practice.

In summary, this study has shown that a linear combination of QUS, age and body weight, represented by a nomogram, could improve the accuracy of osteoporosis prediction, compared with either QUS alone or age and weight. Identification of high-risk individuals for intervention is one of the priorities in osteoporosis research [1]. It is hoped that the approach presented in this study represents a step in that direction.

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