Pre-screening for Osteoporosis with Calcaneus Quantitative Ultrasound and Dual-energy X-ray Absorptiometry Bone Density

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Abstract

Calcaneal quantitative ultrasonography (QUS) is a useful prescreening tool for osteoporosis, but the advantages of QUS and dual-energy X-ray absorptiometry (DXA) remain unclear. We evaluated the correlation between QUS and DXA in a Taiwanese population. A total of 772 patients were enrolled and demographic data were recorded with the QUS and DXA T-score over the hip and spine. The correlation coefficient of QUS with the DXA-hip was 0.171. For DXA-spine, it was 0.135 overall, 0.237 in females, and 0.255 in males. The logistic regression model using DXA-spine as a dependent variable was established, and the classification table showed 66.2% accuracy. ROC analyses with Youden's Index revealed the optimal cut-off point of QUS for predicting osteoporosis to be 2.72. This study showed a meaningful correlation between QUS and DXA in a Taiwanese population. Thus, it is important to pre-screen for osteoporosis with calcaneus QUS.

1. Introduction

Fractures related to osteoporosis are widely recognized as an important health problem because of their significant morbidity among patients, elevated risk for mortality, and increasing medical, financial, and social costs. Globally, nearly 9 million estimated osteoporosis-related fractures occur annually [1]. In Taiwan, the prevalence of osteoporosis is estimated to be 1.6 million and is quickly increasing. In addition, it is twice as common in women over the age of 50 than in men [2]. According to the WHO, osteoporosis is defined as "a systemic disease characterized by low bone mass and deterioration of micro-architecture of bone tissue, leading to bone fragility and eventually elevated fracture risk" [3]. The current gold standard for measuring bone mineral density (BMD) is dual X-ray absorptiometry (DXA)[4,5]. The diagnostic criteria of osteoporosis is based on the BMD compared to a reference of Caucasian women aged 20–29, commonly called T-scores, which must be lower than 2.5 standard deviations (SDs) [6]. However, this method is costly, instrument-based, involves ionizing radiation, and requires highly trained operators to minimize error, possibly leading to the low use of DXA assessment as a screening tool [7]. These disadvantages may explain the underdiagnosis of osteoporosis in Taiwan and globally[8].

Calcaneal quantitative ultrasound (QUS) is an alternative approach for assessing bone health and identifying osteoporosis. Since its introduction in 1984, QUS has gained popularity in recent years for being cheaper, portable, free of ionizing radiation, and easier to handle [9]. QUS assesses bone health by measuring the propagation of ultrasound waves, a frequency that exceeds the normal auditory range of humans (>20 kHz), at varying frequencies. Two parameters are commonly generated by QUS, namely, the speed of sound (SOS) and the velocity of sound (VOS) and broadband ultrasound attenuation (BUA) [10]. The SOS refers to the transmission time of the wave through the length of body parts. Broadband attenuation occurs when sound waves pass through soft tissue and bone and energy is absorbed. There is a combined score called the Stiffness Index (SI), which combines the velocity and attenuation using different algorithms. Calcaneus is the most studied and only recognized skeletal site for QUS assessment because of the high percentage of trabecular bone and two lateral surfaces that facilitate ultrasound waves and provide easy accessibility [11].

The use of calcaneal QUS as a diagnostic method for osteoporosis compared to the current gold standard (DXA) has been evaluated in several studies. Many approaches have been evaluated including bone health, prediction of fracture risk, and correlation with T-scores [12]. For every SD decrease in the QUS-measured variable, fracture risk for the hip and spine increase by two-fold, which is comparable to DXA [13,14]. However, there is little consensus for using QUS as a diagnostic tool for osteoporosis compared to DXA. However, there is little consensus for using QUS as a diagnostic tool for osteoporosis compared to DXA. The interpretation of QUS result in assessment of bone quality and related medical treatment remains to be elucidated. A meta-analysis concluded that there is no definite threshold for QUS when identifying osteoporosis compared to DXA T-scores [15,16].

As a prescreening tool for osteoporosis, the goal is to classify low-risk and high-risk patients and to ensure DXA examination for the high-risk patients. This should increase the accessibility of DXA and improve the diagnosis rate for osteoporosis. For that purpose, a high-sensitivity examination is required as well as a triage approach that can identify two cutoffs at device-specific sensitivity and specificity levels of 90% or 95%[12]. This approach could determine the correlation between the QUS and DXA value, allowing the assessment of the benefit of calcaneal QUS and making it possible to establish a cutoff where follow-up DXA (spine and hip) is required.

It is also important to establish cutoff levels that can rule in or rule out osteoporosis. Although several studies have compared values between calcaneal QUS and DXA, few studies have been conducted on Asian populations. We performed a large population-based study in Taiwan to explore the relationship between cutoff and accuracy of calcaneal QUS to identify elderly (age > 60 y/o) with low QUS levels (T <= -2.0) and to investigate the ability of QUS to reduce the number of patients who require referral for DXA at cutoffs corresponding to 90–95% certainty levels.

2. Materials And Methods

This study was conducted from January 2020 to March 2020 during the annual municipal elderly health examination in Kaohsiung Municipal Min-Sheng Hospital. Calcaneal QUS was performed on every elderly subject who participated in the health examination. For subjects that met two criteria (age ≥ 65 years old and calcaneal QUS ≤ -2.0), DXA examination was arranged for further evaluation of osteoporosis. Both spine and hip DXA were recorded as T-score of BMD. Demographic data including age, sex, height, body weight, medical history, fracture history, and potential secondary causes of osteoporosis were recorded. A total of 772 patients were enrolled and subjects who were diagnosed with osteoporosis and were under treatment or those with old fractures of the calcaneus were excluded. The study was approved by the local and regional ethics committees and was conducted in accordance with the Code of Ethics (Declaration of Helsinki). Informed consent was waived. According to World Health Organization (WHO) criteria for the classification of osteoporosis, a T-score of −1.0 and greater was considered normal bone density, a T-score between −1.0 and −2.5 was considered low bone density(osteopenia), and a T-score of −2.5 and less was defined as osteoporosis.

The QUS was measured using a Pegasus device (BeamMed Ltd., Tel Aviv, Israel), which is designed to measure the speed of sound (SOS) (m/s) of ultrasonic waves that travel longitudinally along the bones at a center frequency of 1.25 MHz. The machine uses gel as a coupling agent between the probe and skin. QUS can be measured at either the left or right calcaneus. The device was calibrated before each data collection using a verification phantom provided by the manufacturer. The QUS T-score was calculated according to the normative data derived from a sex- and age-matched Asian population, provided by the manufacturer. The QUS scans were performed by two independent physicians. Patients with calcaneal QUS values under -2.0 SDs are referred for a DXA scan. BMD, which is expressed in grams per centimeter squared (g/cm2), was measured using the DXA technique. The DXA machine was calibrated daily using a spine phantom supplied by the manufacturer prior to measurements. Then the subjects were positioned and instructed to stay motionless throughout the scan. Each complete scan took approximately 15 min. BMD T-scores were calculated based on an Asian age- and sex-matched population provided by the DXA manufacturer. Measurements were made to ensure coverage of the lumbar and hip regions. The average, as well as individual, vertebral, and hip BMD were recorded.

2.1. Statistical analyses

Data are presented as means ± SDs for numerical variables and frequency or percentage for categorical variables. Correlation analyses were performed using a two-tailed Pearson correlation coefficient with a significance level of $p < 0.05$. A receiver operating characteristic (ROC) curve and the area under the curve (AUC) were calculated to assess the discrimination power of QUS with regard to the gold standard of DXA. The optimal cut-off value for calcaneal QUS for classification of bone status was based on Youden's J statistics as equation 1 [17]:

$$J = \text{sensitivity} + \text{specificity} - 1 \quad (1)$$

All statistical analyses were conducted using Statistical Package for Social Sciences (SPSS) version 26.0 for Windows (SPSS Inc., Chicago, IL).

3. Results

This study consisted of 772 patients including 352 men (45.6%) and 420 women (54.4%). Mean age was 72.9 ± 6.3 years (range, 48–99 years). QUS and DXA values are shown in Table 1. Histogram data for QUS, SOS, and BUA are shown in Figure 1; histogram data for DXA-hip and DXA-spine are given in Figure 2; and scatter plots with regression lines are shown in Figure 3. The correlation coefficient between QUS and DXA-hip was 0.171 ($p < 0.001$); that between QUS and DXA-spine was 0.135 ($p < 0.001$). These values were 0.298 and 0.237, respectively, in females and 0.216 and 0.255 in males. All results were significant.

Table 1. Descriptive statistics of QUS and DXA variable.

	N	Minimum	Maximum	Mean	Std. Deviation
QUS_T	772	-6.70	1.11	-2.6596	.78859
DXA_Hip	772	-4.90	1.20	-2.2846	.89920
DXA_Spine	772	-5.20	1.90	-2.1874	1.25186
Valid N (listwise)	772				

Abbreviation: QUS_T = quantitative ultrasonography T-score, DXA-Hip = dual-energy X-ray absorptiometry of Hip, DXA-Spine = dual-energy X-ray absorptiometry of Spine, Valid N (listwise) = the number of cases that don't have any missing values on any of the variables shown in the table.

To evaluate the discriminating power based on a single QUS variable to predict osteoporosis, ROC analyses were performed with the ground truth set as DXA-spine T-score < -2.5. Results of the ROC analyses are shown in Figure 4. To increase the discriminating power, multivariate logistic regression was performed with more independent variables. Age, sex, body weight, height, BMI, SOS, BUA, and QUS-T were defined as explanatory variables to predict the osteoporosis status defined by DXA-spine. Logistic regression coefficients are shown in Table 2. The logistic regression model had 66.2% accuracy, 67.2% sensitivity, and 64.9% specificity. Using the predicted probability obtained from the logistic regression model, the ROC curve was recalculated and is shown in Figure 5. This more sophisticated logistic regression model had an AUC of 0.731.

Table 2. Descriptive statistics of QUS and DXA variable.

Unweighted Cases[a]		N	Percent
Selected Cases	Included in Analysis	772	100.0
	Missing Cases	0	.0
	Total	772	100.0
Unselected Cases		0	.0
Total		772	100.0

a. If weight is in effect, see classification table for the total number of cases.

Model Summary

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	941.230a	772	100.0

a. Estimation terminated at iteration number 5 because parameter estimates changed by less than .001.

Classification Table[a]

Observed			Predicted True_state		Percentage Correct
			0	1	
Step 1	True_state	0	287	140	67.2
		1	121	224	64.9
	Overall Percentage				66.2

a. The cut value is .500.

To identify the optimal cutoff value of QUS for the diagnosis of osteoporosis, the Youden's Index was adopted, using absolute values. The sensitivity and specificity are shown in Table 3. Youden's Index is the sum of sensitivity and specificity minus one and 2.725 was established as the optimal cutoff value, as shown in Figure 6.

Table 3. Corresponding sensitivity and specificity level with different cutoff values of QUS.

Cutoff value	sensitivity	1-specificity	Youden's J
2.6050	0.545	0.478	0.067
2.6150	0.542	0.471	0.071
2.6250	0.536	0.457	0.080
2.6350	0.533	0.450	0.084
2.6450	0.530	0.445	0.085
2.6550	0.525	0.438	0.087
2.6650	0.525	0.429	0.096
2.6750	0.516	0.424	0.092
2.6850	0.510	0.419	0.091
2.6950	0.504	0.415	0.090
2.7050	0.501	0.410	0.092
2.7150	0.493	0.400	0.092
2.7250	0.490	0.391	0.099
2.7350	0.478	0.384	0.094
2.7450	0.472	0.382	0.091
2.7550	0.467	0.375	0.092
2.7650	0.461	0.375	0.086
2.7750	0.455	0.372	0.083
2.7850	0.443	0.368	0.076
2.7950	0.429	0.368	0.061
2.8050	0.426	0.363	0.063

Abbreviation: Cutoff value = optimal decision threshold, sensitivity = measures the proportion of actual positives that are correctly identified, 1-specificity = missed diagnosis rate, Youden's J = single statistic that captures the performance of a dichotomous diagnostic test.

4. Discussion

We assessed the validity of QUS as a screening method for osteoporosis in a Taiwanese population. We found a significant correlation between QUS and DXA T-scores in both the hip and spine ($p < 0.05$). The correlation coefficient between QUS and DXA-hip was 0.174, higher than that between QUS and DXA-

spine (0.133). This may originate from the fact that the calcaneus and femoral neck belong to the lower limbs, sharing similar bony architectures. However, the DXA-spine remains the first-choice diagnostic method for osteoporosis in clinical practice. Therefore, once osteoporosis is suspected based on calcaneus QUS, further DXA examination is required to confirm the diagnosis of osteoporosis.

The correlations between QUS and DXA also differed within each sex. For example, in females, it was 0.298 for DXA-hip but 0.237 for DXA-spine; in males, the values were 0.216 and 0.255, respectively. This difference arises from several reasons, one of them is skin contact surface with the ultrasound transducer over the calcaneus region. The subcutaneous fat component is more abundant in females, providing a more consistent medium for conducting the ultrasound wave. In contrast, subcutaneous fat levels are lower in males, and more ultrasound energy is dissipated at various tissue junctions, resulting in inconsistent QUS measurements. In this study, about 31 outlier cases were identified, all with abnormally high SOS values. Males made up 23 of these outliers (about 67.5%). This phenomenon also can be explained by skin contact surface heterogeneity of the calcaneus region between both sexes.

The physical basis of QUS is measured by two ultrasound parameters on the calcaneus region, i.e., the SOS and BUA. The SOS and BUA are combined to calculate the T-score of QUS, as predefined by the manufacturer. The histogram data for QUS, SOS, and BUA are shown in Figure 1. The data are similar. However, the histogram data for DXA-hip and DXA-spine show a right-skewed (log-normal) distribution (Fig. 2)[18]. This may have caused the discrepancies between QUS and DXA.

Many biological variables obey the law of normal distribution. On mathematical basis, a normal distribution is the limit resulting from a large binomial process. However, not all clinically relevant data are described by the normal distribution. For example, blood pressure data are reported as lognormal distribution. The right-skewed distribution is often transformed by natural logarithm function for subsequent processing. In this study, the lognormal distribution nature of bone mineral density is interesting and worth further studies.

Figure 3 shows the results of regression analyses, including scatter plots of QUS and DXA-Hip and DXA-spine data. The plots are concentrated around the -2.5 region, with fewer cases at QUS > -1.0. The reason for this is due to the inclusion criteria during the annual health examination; only subjects with QUS -2.0 were chosen for further DXA examination. This results in a highly concentrated data distribution; therefore, we adopted some cases with higher QUS values to study the regression line.

Figure 4 shows the sensitivity and specificity of using only QUS as a predictive variable for osteoporosis, according to ROC analyses. The area under curve (AUC) was 0.55 not far from the reference line which is AUC of 0.5. To increase discriminative power, we ran a multivariate logistic regression. The predictive variables included age, sex, body weight, height, BMI, BUS, and SOS. The logistic regression model had a sensitivity of 67.2% and a specificity of 64.9%, with an overall accuracy of 66.2%. Female had a 4.4-fold higher odds ratio than males with osteoporosis. Another significant predictive variable was QUS (where a lower value = osteoporosis more likely). Due to the improved performance of this more sophisticated logistic regression, the probability predicted by this model can be used as a new test variable for ROC

analyses. These results suggest that using a more sophisticated model will increase the discrimination power for osteoporosis. The weighting of individual factors can also be examined based on the results of the logistic model described in Table 2. However, the use of a multivariate model requires a scoring system such as the Glasgow Coma Scale, and will take more time to perform.

The WHO defined the status of osteoporosis as a DXA T-score < -2.5. In this study, the ground truth of the examined osteoporotic subjects was established using the DXA T-score of either the spine or hip. The lumbar vertebrae T-score was recorded as the average value for the L1–L5 lumbar segments. This process automatically omits segments that are abnormal, such as those with a compression fracture. On the other hand, the DXA-hip value adopts only the femoral neck area as the sampling region. This is compatible with criteria used in clinical situations.

To determine the optimal cutoff value for QUS data, Youden's J statistic was adopted. The Youden Index seeks the maximum value in an ROC curve (specificity + sensitivity – 1). As shown in Figure 6, the maximum value corresponded to a QUS of 2.725. Therefore, when the QUS is used alone as a predictive variable of osteoporosis, -2.725 is automatically the optimal threshold for defining disease status. This value is similar to the criteria established by the WHO when judging DXA results

There were two main limitations of this study. First, during the annual health examination for elderly patients, we did not collect data on subjects younger than 65 years old. Second, for cases that did not meet the inclusion criteria (age ≥ 65 years old and calcaneal QUS ≤ -2.0), the DXA scan was performed only for a small portion of patients. Therefore, we lack data on patients with higher QUS values.

5. Conclusions

In conclusion, QUS is a feasible and noninvasive method for measuring bone status in elderly populations in Taiwan. Due to the significant correlation between QUS and DXA, the potential for QUS as a pre-screening tool has been well explored. Although QUS is not the gold standard for diagnosis of osteoporosis, because of convenience and low cost, it is an attractive alternative to conventional DXA in some situations. Multivariate logistic regression models have more discriminative power than single variable model using the QUS. Furthermore, the optimal Younden's Index cutoff value for QUS to confirm osteoporosis is -2.725.

Declarations

Author Contributions: Conceptualization, Tzu-Hao Wang, Guan-Fan Chen, Da-Ying Chou, Dian-Min Lin, Shu-Yuan Lin, Min-Ho Chan, Yu-Jie Huang and Tsair-Fwu Lee; Data curation, Chia-Chi Yen and Wei-Chun Lin; Formal analysis, Da-Ying Chou, Dian-Min Lin and Min-Ho Chan; Investigation, Wei-Chun Lin; Methodology, Chia-Chi Yen, Wei-Chun Lin, Tzu-Hao Wang, Guan-Fan Chen, Shu-Yuan Lin, Min-Ho Chan and Yu-Jie Huang; Project administration, Chia-Chi Yen and Tsair-Fwu Lee; Resources, Chia-Chi Yen and Dian-Min Lin; Supervision, Chia-Chi Yen, Wei-Chun Lin and Tsair-Fwu Lee; Validation, Tzu-Hao Wang and

Da-Ying Chou; Writing – original draft, Chia-Chi Yen, Wei-Chun Lin, Tzu-Hao Wang, Guan-Fan Chen, Da-Ying Chou, Dian-Min Lin, Shu-Yuan Lin, Jia-Ming Wu and Min-Ho Chan; Writing – review & editing, Chia-Chi Yen, Wei-Chun Lin, Yu-Jie Huang, Chin-Dar Tseng and Tsair-Fwu Lee.

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Conflicts of Interest: The authors declare that there are no conflicts of interest. Part result of this study has been submitted in an abstract form at Phenma 2020.

Data availability: The data supporting the results of this article are included within this manuscript and supplementary.

Ethical Statement: The requirement for informed consent was waived by Kaohsiung veterans gerneral hospital institutional review board (KSVGH20-CT7-13) given the retrospective nature of the study.

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Figures

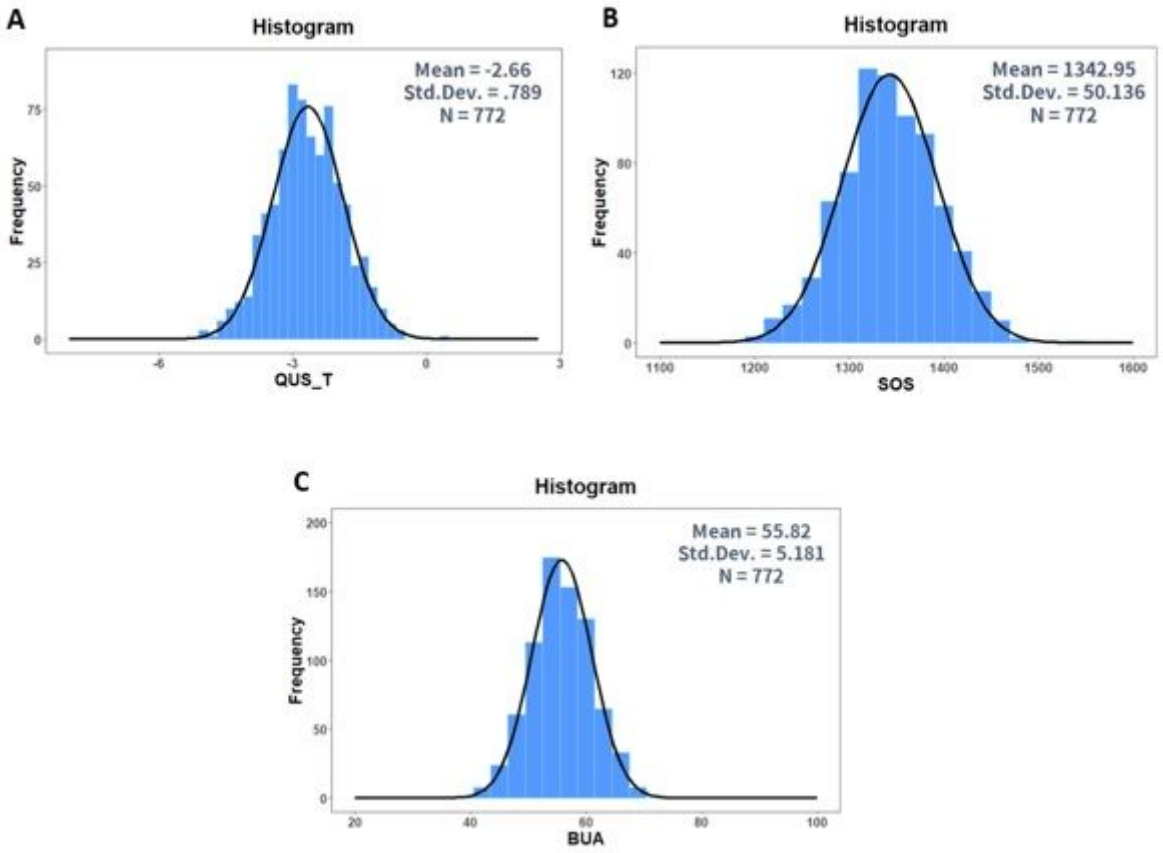

Figure 1

(A) Histogram of calcaneus QUS T-score data. (B) Histogram of the SOS data by QUS machine. (C) Histogram of the BUA data by QUS machine. Abbreviation: QUS_T = quantitative ultrasonography T-score, SOS = speed of sound, BUA = broadband ultrasound attenuation, BUA = broadband ultrasound attenuation

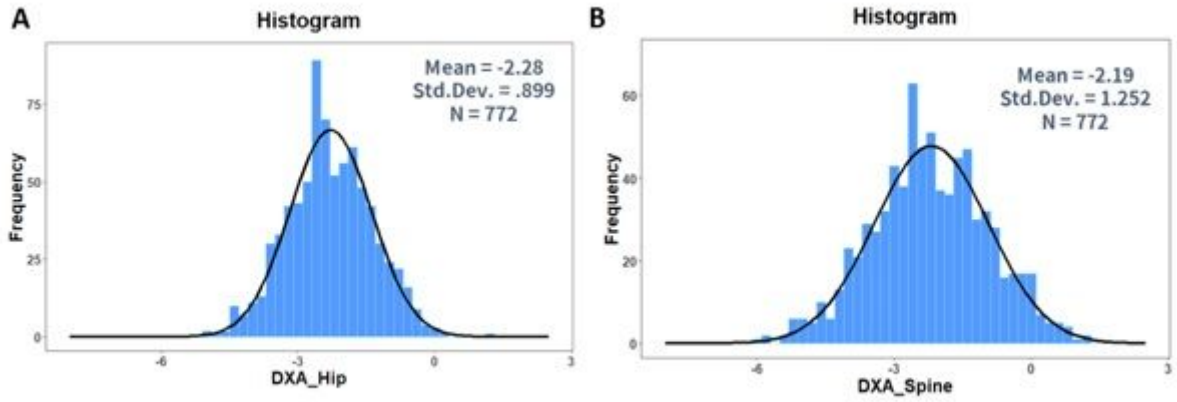

Figure 2

(A) Histogram of DXA-Hip data. (B) Histogram of DXA-Spine data. Abbreviation: DXA-Hip = dual-energy X-ray absorptiometry of Hip, DXA-Spine = dual-energy X-ray absorptiometry of Spine.

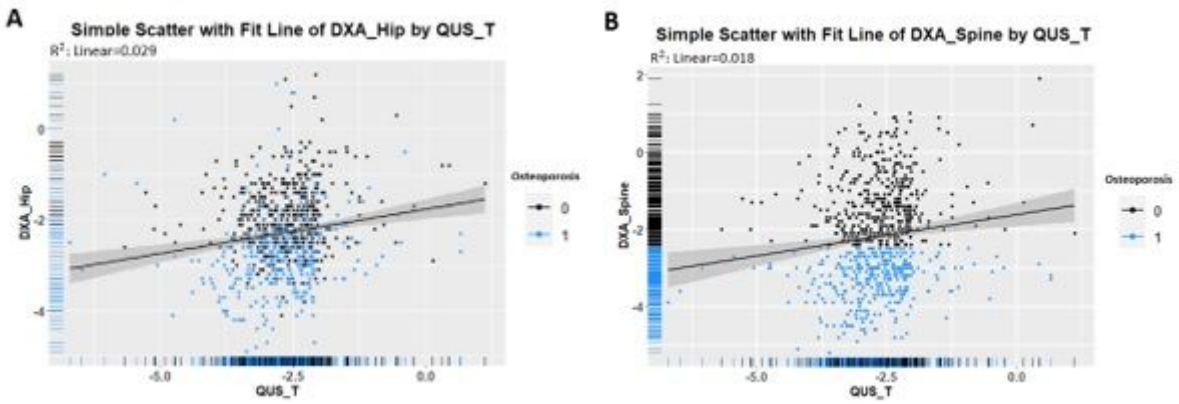

Figure 3

(A) Scatter plot and regression line of calcaneus QUS and DXA-Hip. (B) Scatter plot and regression line of calcaneus QUS and DXA-spine. Abbreviation: QUS_T = quantitative ultrasonography T-score, DXA-Hip = dual-energy X-ray absorptiometry of Hip, = DXA-Spine: dual-energy X-ray absorptiometry of Spine.

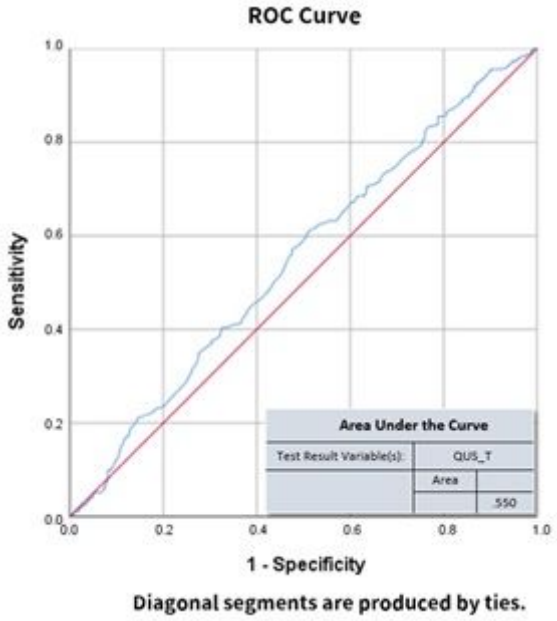

Figure 4

ROC curve analysis using QUS as predictive variable. The test result variable(s) = QUS_T has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased. Abbreviation: ROC Curve = receiver operating characteristic curve, sensitivity = measures the proportion of actual positives that are correctly identified, 1-specificity = missed diagnosis rate.

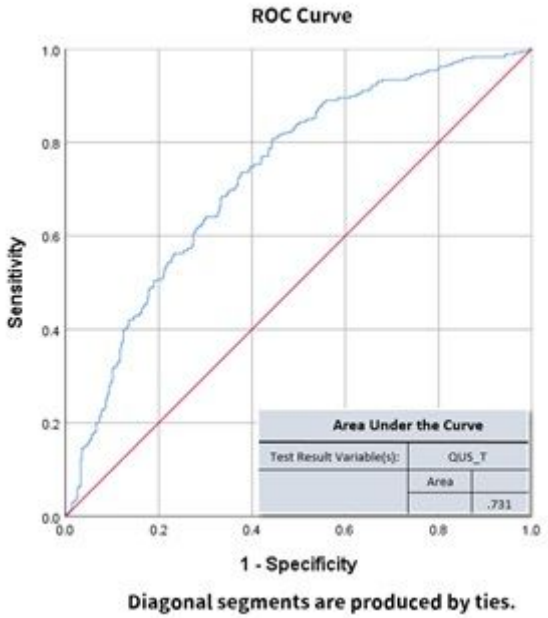

Figure 5

ROC curve analysis using logistic regression model as predictive variable. Abbreviation: ROC Curve = receiver operating characteristic curve, sensitivity = measures the proportion of actual positives that are correctly identified, 1-specificity = missed diagnosis rate.

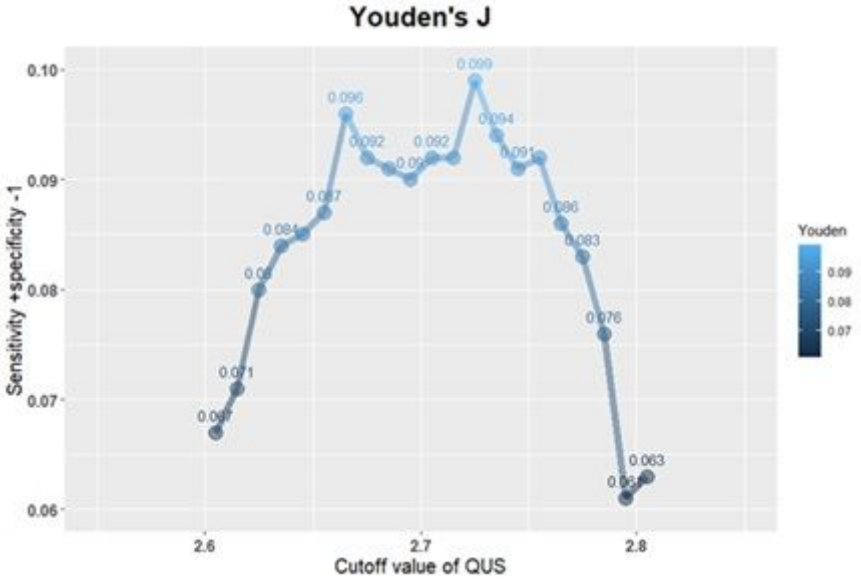

Figure 6

ROC curve analysis with coordinates for calculating the Youden's index. Abbreviation: Youden's J = single statistic that captures the performance of a dichotomous diagnostic test.