

Original Article

Evaluation of Heel-Based Quantitative Ultrasound Bone Densitometry as a Screening Tool for Post-Menopausal Osteoporosis

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Abstract: Osteoporosis is the major cause of fragility fractures in postmenopausal women. It has been aptly termed as the 'silent disease', as most women are asymptomatic, and a fragility fracture is often the first presentation. Fragility fractures have significant implications in terms of decreased quality of life, and increased morbidity, mortality, and healthcare cost. This study has showed that a multivariable logistic regression model based on clinic-demographic parameters and speed of sound that can be used to predict osteoporosis using quantitative ultrasonography. The Cross-sectional study done for a period of one year in Departments of Orthopaedics and Radiodiagnosis, PGIMER, Chandigarh with a Sample Size of N=100 subjects. By itself, estimation of osteoporosis using speed of sound, may not be very reliable or accurate, however, a multivariable model taking into account age, body mass index along with speed of sound, can improve the diagnostic accuracy of such estimates. However, these results need to be validated in a larger cohort of patients. The speed of sound measured at the heel by quantitative ultrasonography was found to be significantly lower (mean difference of approximately 20 m/s) in subjects who had a DEXA proven osteoporosis verses who did not have osteoporosis. Using the normative data of speed of sound of the Japanese population as the reference (Strategy 1), QUS was found to have a poor accuracy for diagnosis of osteoporosis. A cut-off value of speed of sound of less than 1536 m/s at the heel was found to have sensitivity of 91.7% for diagnosis of DEXA proven osteoporosis. On the other hand, a cut-off value of speed of sound of less than 1467 m/s at the heel was found to have specificity of 91.5%. For determining the optimal cut-off for diagnosing osteoporosis based on speed of sound, cut-offs obtained from receiver operating curve analysis (strategy 2b) were found to have a lower percentage of misclassification, as compared to cut-offs obtained from normative data of young Indian females (strategy 2b). In the univariate analysis age, body mass index, hip circumference and time since menopause were significantly associated with DEXA proven osteoporosis.

Keywords: quantitative, ultrasound, bone densitometry, post-menopausal osteoporosis

1. INTRODUCTION

Osteoporosis is the major cause of fragility fractures in postmenopausal women. It has been aptly termed as the 'silent disease', as most women are asymptomatic, and a fragility fracture is often the first presentation [1]. Fragility fractures have significant implications in terms of decreased quality of life, and increased morbidity, mortality, and healthcare cost [2]. Dual Energy X-Ray Absorptiometry

(DXA) is the gold-standard modality to diagnose osteoporosis [3]. However, its use in developing countries has been limited owing to high cost of the equipment, limited portability, and the need for experienced operators to perform the scan. Quantitative ultrasonography (QUS) has emerged as a low cost, portable, operator-independent technique, that holds promise for use in developing countries, especially in primary and secondary healthcare setups. Osteoporosis has been defined by the World Health Organization on the basis of bone mineral density (BMD), measured on the dual energy X-Ray absorptiometry (DEXA) scan. In this context, it is important to understand the concept of T and Z scores. Whereas the T score compares an individual's BMD to premenopausal women, the Z score compares it to age and gender-matched controls. A DEXA T-Score of less than -2.5 standard deviations below the mean is considered as osteoporosis. Scores between -1 to -2.5 are considered as osteopenia. A T-Score of greater than -1 is considered as normal [5]. According to the International Society of Clinical Densitometry (ISCD), BMD is classified on the basis of age, as well as gender, as follows [4].

- In post-menopausal women: the WHO classification applicable
- In men aged 65 years and above: the WHO classification is applicable
- In men 50-64: the T-score is used. if both T-score below 2.5 and risk factors are present
- In men less than 50 years of age: densitometric criteria along is not sufficient to diagnose osteoporosis and presence of one or more risk factors with low BMD requires further workup
- In women 20 years of age to menopause: Z score rather than T score should be used; densitometric criteria along is not sufficient to diagnose osteoporosis and presence of one or more risk factors with low BMD requires further workup
- In individuals below 20 years of age (both male and female): Z-score should be used; densitometric criteria along is not sufficient to diagnose osteoporosis and presence of one or more risk factors with low BMD requires further workup

It is estimated that currently over 200 million people worldwide are suffering from osteoporosis and that 1 in 3 women over the age of 50 will experience an osteoporotic fracture in their remaining lifetime. In the year 2000, there were an estimated 9 million new osteoporotic fractures, of which 1.6 million were at hip, 1.7 million at forearm and 1.4 million were clinically vertebral fractures [6]. There are estimated 1.5 million fragility fractures each year. In North American women under the age of 50 have normal BMD, 27% are osteopenic and 70 % are osteoporotic at the hip, lumbar spine or forearm by the age of 80 years\ . Furthermore, the remaining lifetime risk for common fragility fractures is estimated to be 17.5% for hip fractures, 15.6% for clinically diagnosed vertebral fractures, and 16% for distal forearm fractures, among white women aged more than 50 [7]. A study conducted in Delhi by Khadilkar and co-authors, has estimated the prevalence of osteoporosis in women above age 50 years of age to be 42.5%, whereas the prevalence in the same age group has been reported by several studies conducted on small populations through the country, to be ranging from 8-62% [8]. Studies in the UK have shown a lifetime risk for any fracture, in women at age of 50 years, to be 53.2%; thus 1 in 2 women of 50 will potentially get an osteoporotic fracture in their remaining lifetime[9]. In USA, 7% survivors of all types of fragility fracture, have a degree of permanent disability; 8% end up requiring long term nursing home care due to complications such as pressure sores, bronchopneumonia and urinary tract infections [10]. Premorbid status is a strong predictor of outcome following osteoporotic fractures. Hip fractures have been studied in relation to ability to walk, with 40% unable to walk independently 1 year after fracture, and 60% requiring assistance with at least one essential activity of daily life (e.g., dressing, bathing) and 80% unable to perform at least one instrumental activity of daily living such as driving or shopping [11]. After getting a vertebral fracture, significant problems may develop; while the impact of

single vertebra fracture is often low, multiple fractures can lead to progressive loss of height and kyphosis, and severe back pain in acute and chronic stages. The psychological impact of functional loss can lead to depression and social isolation. BMD can be measured by various methods ranging from x-rays (single energy /dual energy absorptiometry, radio grammetry), ultrasound (calcaneal ultrasonography, distal radius ultrasonography), CT, MRI to gamma rays. Dual energy x-ray absorptiometry (DXA) is a method of measuring bone mineral density (BMD) using spectral imaging. Two x-ray beams with different energy levels are used, aimed at the bones of the patient, with soft tissue absorption subtracted out; the BMD is measured using absorption of each beam by bone. Soft tissue and bone have different attenuation coefficient to x-rays. Single x-ray beam passing through the body will be attenuated by both soft tissue and bone, but it is not possible to determine how much attenuation is attributable to bone. However, attenuation coefficients vary with energy of x-rays. DXA uses two energies of x-ray; the difference in total absorption between the two can be used to subtract out absorption by soft tissue, leaving just absorption by bone, which is related to bone density. It is currently gold standard for modality for diagnosis of osteoporosis. Although it has few shortcomings, e.g., the machine is not portable, equipment is costly, requires a trained operator, the advantage is a minimal risk of radiation exposure to the patient [12]. Modern radiology imaging software programs allow BMD to be calculated from the region of interest (ROI) on CT scans without any additional cost or radiation exposure. Normative data for HU for any ROI are compared with subjects HU values. Also, studies have shown that HU values decrease linearly by decade of life. So, this data is also taken into consideration while interpretation of results [13]. The velocity of transmission and the amplitude of ultrasound signal are influenced by bone tissue reflecting its density, architecture, and elasticity. Using modalities such as speed of sound (SOS) and broadband ultrasound attenuation (BUA), quantitative ultrasound (QUS) is a relatively new method to determine bone mineral density. It has the advantage of being a portable, cost-effective modality which is less time consuming, easy to use, and does not require skilled personnel. It is a non-invasive modality with no risk of radiation exposure. However, there is lack of sufficient studies and/or data to prove the accuracy of this modality, and also there is lack of standardized population-based data for comparison of results. Variable results based on site of measurement (e.g., distal radius, calcaneus) have been reported and there is also insufficient data on variable affecting results (e.g., temperature of measured part, shape/structure of body part) [14]. Thus, there is a need for low-cost, accurate and portable tools that can be useful for screening of osteoporosis in developing countries, especially in the rural and semi-urban setups. One such tool is Quantitative ultrasound (QUS), which utilizes sound waves to estimate bone mineral density [15]. Heel-based QUS technology, which involves estimation of BMD from the calcaneus, has seen major improvements in terms of accuracy, and is the most commonly available QUS tool. This method is low-cost, does not require specialized training, does not possess radiation hazard and is truly portable, with most machines weighing between 10-12 kg. However, the major limitation of QUS is its accuracy. A few studies have shown that QUS has high sensitivity but low specificity for diagnosing postmenopausal osteoporosis [16-21]. One of the major reasons cited for suboptimal accuracy is the lack of population specific normative data on QUS densitometric parameters [22,24]. Moreover, data on QUS for diagnosis of osteoporosis from the Indian subcontinent is limited [22]. Hence, this study determined if QUS can be used as a reliable screening tool for the diagnosis of postmenopausal osteoporosis. In a preliminary study, the QUS based bone densitometry parameters of more than 500 young, healthy, North Indian females aged 20-30 years have been evaluated (data on file, PGIMER). Therefore, this study also aims to determine whether using normative bone densitometric data from our own population can help improve the accuracy of QUS in the diagnosis of osteoporosis. This study compared the diagnostic accuracy (sensitivity, specificity, and predictive values) of heel based QUS for post-menopausal osteoporosis by using: normative data provided by manufacturer of the QUS machine (data from adult Japanese population) and normative data from our own population (data from young healthy North

Indian women aged 18-30 years, unpublished).it determine the optimal cut-off values for heel based QUS speed of sound (SOS) measurements for prediction of osteoporosis.

2. MATERIALS & METHOD

This is a Cross-sectional study done for a period of one year in Departments of Orthopaedics and Radiodiagnosis, PGIMER, Chandigarh with a Sample Size of 100 subjects

- Women > 45 years of age, who have been advised DXA assessment for any indication, by any clinical department, were included in the study as per the inclusion and exclusion criteria (described in section 3.4). Recruitment of these patients was done from the DXA facility at the Outpatient Department, PGIMER, Chandigarh.
- DXA was performed as per existing protocols.
- Heel-based QUS assessment was performed in the same sitting.
- Certain clinical parameters were obtained at the same sitting.

A portable ultrasound-based bone densitometer machine (CM 200, Furuno Electric Co. Ltd, Japan) [23] was used to calculate BMD using SOS (Speed of Sound) as the measurement parameter. All measurements were made from the left heel, as per manufacturer's instructions. The set standard of calibration as mentioned by the manufacturer was performed daily before taking the measurements. DXA Scan was done on the Hologic Discovery machine using standard protocols. For calibration of the machine and acquisition, the manufacturer's instructions were followed. The measurement sites were the pelvis and lumbo-sacral spine. The following clinical parameters were determined from each subject:

- Age
- Weight
- Height
- Body Mass Index
- Past history of fracture
- History of maternal fracture
- Rheumatoid arthritis
- Time since menopause
- Smoking and alcohol intake
- Corticosteroid use
- Hip circumference: measured around the widest portion of the buttocks, with the tape parallel to the floor

DXA Variables: T-Score, Z Score, Bone Mineral Content, Bone Mineral Density

QUS: Speed of Sound and T Score

For assessment of diagnostic accuracy of QUS, DXA was considered as the gold standard. Osteoporosis was defined as per the WHO definition of a DXA T score of less than -2.5, at either the hip or spine [24-26].

For labelling a case as 'osteoporosis' on QUS, two strategies were used:

- Strategy 1 (Manufacturer's T Score): Using the manufacturer provided values of T-score, a T-score value of less than -2.5 was considered as 'osteoporosis'. This is based on data from the Japanese population.

- Strategy 2 (Indian-population specific T-score): This has been determined by a previous study (Sharma et al, data on file, PGIMER) looking at QUS values in young, healthy North Indian women (aged 18-30 years). The optimal cut-off was determined by calculating mean plus or minus one standard deviation.

2 x 2 tables were constructed to evaluate the accuracy of QUS in diagnosis DEXA proven osteoporosis. Sensitivity, specificity, positive predictive value and negative predictive values for both strategies were calculated with 95% confidence intervals. A receiver operating characteristic (ROC) analysis was conducted to determine the optimal cut-off point for diagnosis of osteoporosis by QUS (DXA T-Score being the 'gold standard'). The sensitivity, specificity, predictive values for each cut-off point of interest, as well as the Area Under Curve (AUC) were reported. Normality of the study data was determined by the Shapiro-Wilk test. The baseline study demographic data was described using appropriate methods of central tendency and distribution. Bone mineral density (at hip and spine) and speed of sound were compared between women who had osteoporosis and those who did not, using the *t*-test. Correlation between hip and spine DEXA based bone mineral density and speed of sound as determined by the Pearson's correlation coefficient. 2 x 2 tables were constructed for determining the accuracy of QUS for diagnosing osteoporosis; sensitivity, specificity and predictive values were determined. Receiver operating curve analysis was performed to determine the optimal cut-off values of speed of sound for diagnosing osteoporosis. Univariate analysis was performed to identify significant predictors of osteoporosis. Using significant predictors derived from the univariate analysis, a multivariable logistic regression model was constructed.

3. RESULTS & DISCUSSION

A total of 201 subjects who fulfilled the inclusion criteria were included in the study. The evaluation of data collected for the study has been presented below. The mean age of the study population was 59.7 $\pm$ 7.2 years. The details of other variables such as BMI, Hip Circumference and Time since menopause have been presented in Table 1. Of the 201 study subjects, previous history of fracture was noted in 0.49% (n=1), 5.5% (n=11) participants gave history of smoking (past or present), 1.5% (n=3) participants gave history of alcohol consumption and 1.5% (n=3) were diagnosed cases of Rheumatoid Arthritis (Table 02).

Table 01: Baseline demographics of the study population – continuous variables

Sr. No.	Variable	Mean	SD	Range
1	Age (years)	59.70	7.19	46-84
2	BMI (kg/m ²)	27.91	4.63	16.43-42.16
3	Hip Circumference (cm)	73.86	10.48	58-106
4	Time since menopause (years)	11.53	6.76	1-36

Table 02: Baseline demographics of the study population – nominal variables

Sr. No.	Variable	Number	Percentage
1	Previous history of fracture	1	0.49
2	History of Smoking (present or past)	11	5.5
3	Alcohol Consumption	3	1.5
4	Rheumatoid arthritis	3	1.5

A total of 84 women (41.8%) were found to have osteoporosis (T Score < -2.5 as determined by DEXA scan). Of these, 38 had a T score of less than -2.5 at hip, 69 at spine and 18, at both regions. Women with osteoporosis were noted to have a significantly lower mean bone mineral density at hip ($P < 0.001$) and spine ($P < 0.001$) as compared to those who did not have osteoporosis (Table 3).

Table 03: Osteoporosis in the study cohort

Sr. No.	Variable	Osteoporosis (Mean $\pm$ SD)	No Osteoporosis	P Value
1	Bone mineral density of hip	0.69 (± 0.10)	0.87 (± 0.11)	<0.001
2	Bone mineral density of spine	0.70 (± 0.10)	0.90 (± 0.10)	<0.001
3	Total Number (percentage)	84(41.79)	117(58.21)	

The speed of sound, as determined by QUS, was noted to be significantly lower ($P < 0.001$) in women with osteoporosis (1489 ± 33.29) as compared to those without osteoporosis (1511.04 ± 38.39) (Table 4).

Table 04: Comparison of speed of sound in women with DEXA proven osteoporosis

Sr. No.	Anatomical Location	Osteoporosis (Mean $\pm$ SD)	No Osteoporosis	Mean Difference	P Value
1	Either Hip and/or Spine*	1489.93 (± 33.29)	1511.04 (± 38.39)	21.11	<0.001
2	Hip	1484.85 (± 34.71)	1505.63 (± 37.45)	20.78	0.005
3	Spine	1489.99 (± 34.07)	1508.61 (± 38.09)	18.62	0.002

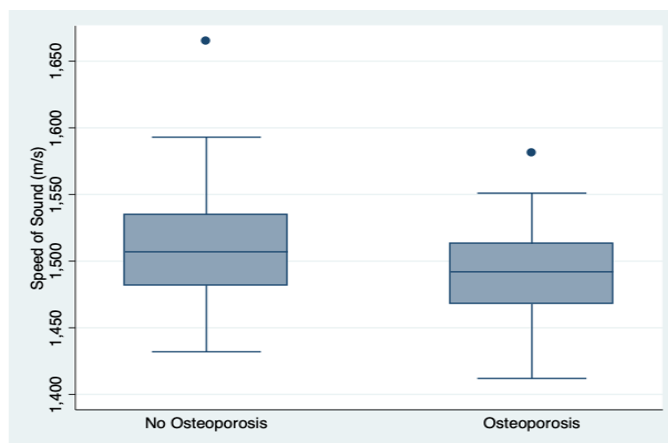


Figure 01: Comparison of Speed of Sound between women who had osteoporosis versus no osteoporosis on the basis of bone mineral density calculated at either hip or spine by the DEXA scan.

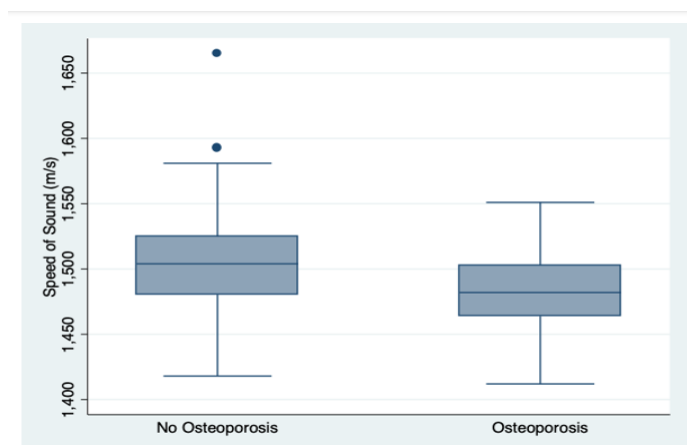


Figure 02: Comparison of Speed of Sound between women who had osteoporosis versus no osteoporosis on the basis of bone mineral density calculated at hip by the DEXA scan.

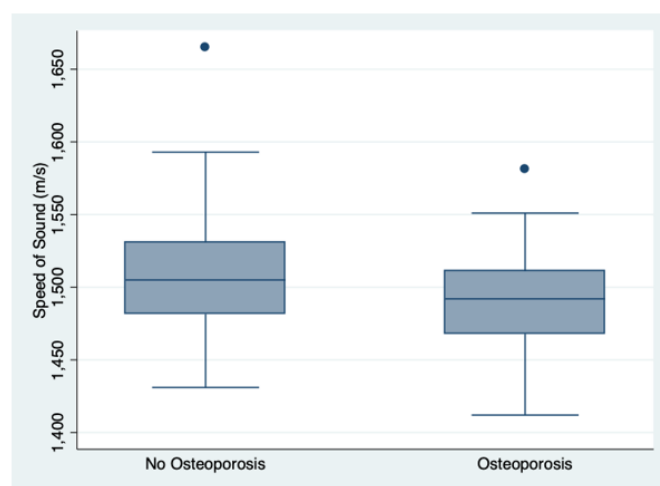


Figure 03: Comparison of Speed of Sound between women who had osteoporosis versus no osteoporosis on the basis of bone mineral density calculated at spine by the DEXA scan.

A strong correlation was noted between DEXA bone mineral density at both the hip and spine ($P < 0.001$) (Table 5).

Table 05: Correlation between SOS & DEXA BMD

Sr. No.	Variable	Correlation Coefficient	P Value
1	BMD at Hip	0.4	<0.001
2	BMD Spine	0.4	<0.001

Using the default definitions of osteoporosis (speed of sound T Score of < -2.5) provided by the QUS machine, concordance with DEXA results was determined (Strategy 1). The default definitions are based on normative data of speed of sound of the Japanese population. QUS was noted to have poor sensitivity, specificity and predictive values if the default (machine embedded) definitions of osteoporosis were used (Table 6 and 7).

Table 06: Concordance between DEXA and QUS for the diagnosis of osteoporosis

Osteoporosis by QUS (SOS T Score < -2.5)	Osteoporosis by DEXA (DEXA BMD T Score at Hip or Spine < -2.5)		
	Yes	No	Total
Yes	13	7	20
NO	71	110	181
Total	84	117	201

Table 07: Accuracy of QUS for diagnosing OP – default definitions*

Parameter	Value (95% CI)
Sensitivity	61.9% (51-72)
Specificity	63.2% (54-72)
Positive Predictive Value	54.7% (44-65)
Negative Predictive Value	69.8% (60-78)
Diagnostic Accuracy	62.7% (56-69)

*Default definition of osteoporosis, based on speed of sound and T Score determined from the Japanese population

In order to determine the optimal cut-off values for rendering an accurate diagnosis of osteoporosis, receiver operating curve (ROC) analysis was performed. It was found that a cut-off value of SOS < 1536.5 m/s would yield a sensitivity of 91.7% and a specificity of 24.8%. On the other hand, a SOS value of <1467.5 m/s would yield a sensitivity of 23.8% and specificity of 91.5% (Table 8).

Table 08: Optimal cut-off of QUS for the diagnosis of osteoporosis

Cut-off	Sensitivity	Specificity	PPV	NPV	Diagnostic Accuracy
Inf	100.0%	0.00%	41.800%		41.80%
1,629.0	100.0%	0.90%	42.000%	100.000%	42.30%
1,546.5	97.6%	18.80%	46.300%	91.700%	51.70%
1,538.5	92.9%	23.90%	46.700%	82.400%	52.70%
1,536.5	91.7%	24.80%	46.700%	80.600%	52.70%
1,535.5	89.3%	24.80%	46.000%	76.300%	51.70%
1,533.5	89.3%	25.60%	46.300%	76.900%	52.20%
1,531.0	89.3%	26.50%	46.600%	77.500%	52.70%
1,468.5	28.6%	89.70%	66.700%	63.600%	64.20%
1,467.5	23.8%	91.50%	66.700%	62.600%	63.20%
1,466.0	23.8%	92.30%	69.000%	62.800%	63.70%
1,462.0	17.9%	92.30%	62.500%	61.000%	61.20%
-Inf	0.0%	100.00%		58.200%	58.20%

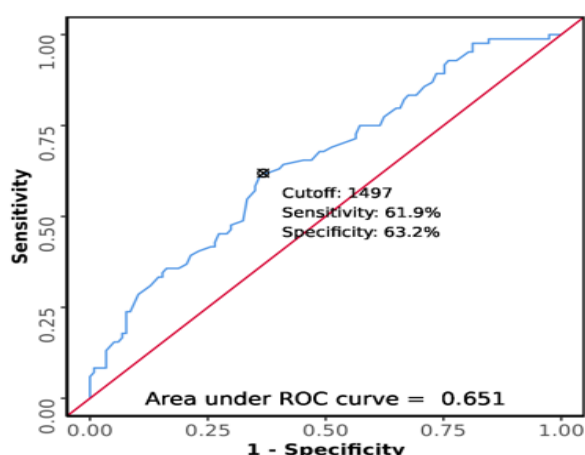


Figure 04: Receiver operating curve showing diagnostic performance of speed of sound in predicting osteoporosis based on manufacturer provide data

From normative data of 580 Indian women in the 20-30 years age group, the mean speed of sound was noted to be 1530 ± 75.9 . Mean $\pm$ one standard error was used to determine the upper and lower cutoffs for normal. The upper cut-off for speed of sound in young Indian females was noted to be 1568 m/s, whereas the lower cutoff was noted to be 1453 m/s. Using these estimates, the accuracy of prediction of osteoporosis by QUS was noted to be marginally better, but this yielded a higher percentage of misclassification (Table 9).

Table 09: Comparison with normative data-based predictions

Sr. No.	Speed of Sound Cutoff	Cutoff Obtained From	Sensitivity	Specificity	PPV	NPV	Misclassification
1	1479m/s	Japanese Population	36.9%	79.50%	56.40%	63.70%	38.81%
2	1536.5 m/s	ROC Analysis (Strategy 2a)	91.7%	24.80%	46.70%	80.60%	48.76%
3	1467.5 m/s	ROC Analysis (Strategy 2a)	23.8%	91.50%	66.70%	62.60%	36.82%
4	1568 m/s	Normative Data (Strategy 2b)	98.8%	7.70%	43.50 %	90.00%	53.23%
5	1453 m/s	Normative Data (Strategy 2b)	10.7%	96.60%	69.20%	60.10%	40.30%

To determine the statistically significant predictors of osteoporosis in the study cohort, univariate analysis was performed on 8 variables. Age, BMI, hip circumference and time since menopause were noted to be significantly different in women who had osteoporosis versus those who did not (Tables 10 and 11). The other variables were not found to be significantly different.

Table 10: Univariate analysis for prediction of Osteoporosis – continuous variables

Sr. No.	Variable	Osteoporosis (Mean $\pm$ SD)	No osteoporosis (Mean $\pm$ SD)	P Value
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1	Age (years)	61.33 (± 6.96)	58.52 (± 7.16)	0.06
2	BMI (kg/m^2)	25.04 (± 4.43)	27.79 (± 4.94)	<0.001
3	Hip Circumference (cm)	71.60 (9.12)	75.49 (11.10)	0.005
4	Time since menopause (years)	12.86(± 7.19)	10.58 (± 6.30)	0.044

Table 11: Univariate analysis for prediction of osteoporosis – nominal variables

Sr. No.	Variable	Osteoporosis (percentage)	No osteoporosis (percentage)	P Value
1	Previous history of fracture	0 (0.0%)	1 (0.9%)	1.00
2	Smoking	7 (8.3%)	4 (3.4%)	0.207
3	Drinking	3 (3.6%)	0 (0.0%)	0.071
4	Rheumatoid arthritis	1 (1.2%)	2 (1.7%)	1.00

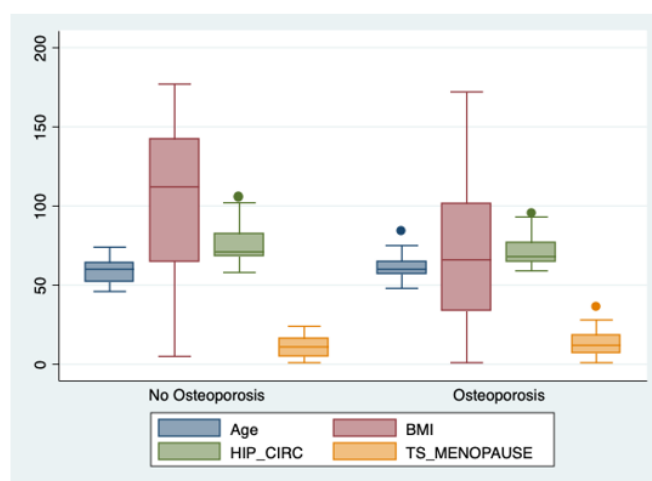


Figure 05: Error bar showing comparison of continuous variables among the participants with osteoporosis vs those without. BMI= body mass index; HIP_CIRC= hip circumference; TS_MENOPAUSE= time since menopause.

Based on the results of the univariate analysis, predictors with a P-Value <0.1 were included in the multivariable logistic regression model (Table 12). A stepwise backward elimination technique was used to develop the final model. In the final model, age and BMI were noted to be significant predictors of osteoporosis. This model had an AUC value of 0.72, indicating good discrimination. The goodness of fit test p value was 0.433, and the Brier Score was 0.20.

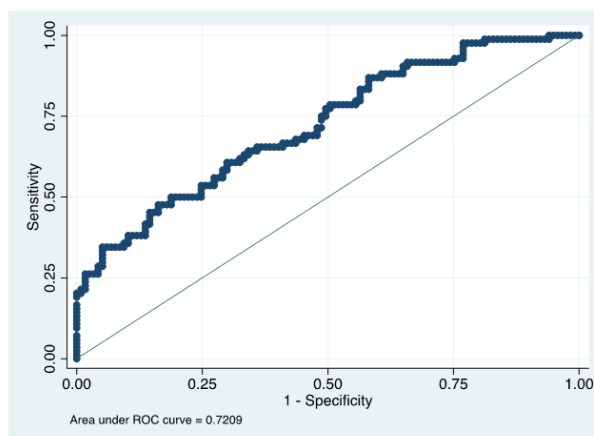


Figure 06: Receiver operating curve showing diagnostic performance of the multivariable logistic regression model

Table 12: Logistic regression model for prediction of osteoporosis

Parameters	Coefficient	Standard error	Z	P > z	95% CI
Age	0.049	0.0225	2.19	0.029	0.005 to 0.093
Body mass index	-0.012	0.0032	-3.63	0.00	-0.018 to -0.005
Speed of sound	-0.015	0.0047	-3.06	0.002	-0.024 to -0.005

The probability of having DEXA proven osteoporosis can be calculated from the formula:

$$P = \frac{e^{(\beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3)}}{1 + e^{(\beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3)}}$$

Where:

P = Predicted probability of DEXA proven osteoporosis

β_0 = model constant

β_1 = regression coefficient – age

β_2 = regression coefficient – BMI

β_3 = regression coefficient – speed of sound

x1 = Age (years)

x2 = BMI

x3 = Speed of sound (m/s)

For example: in a 75year old female with BMI of 28 kg/m² and speed of sound reading of 1500m/s from her left calcaneum, the probability of having osteoporosis is 75.22%. On the other hand, in a 50-year-old female with BMI of 23 kg/m² and speed of sound reading of 1550 m/s from her left calcaneum, the probability of having osteoporosis is 31.08 %.

DISCUSSION

Osteoporosis is a disabling disease characterized by compromised bone strength, which predisposes a patient to increased risk of fracture. Osteoporosis is the major cause of fragility fractures in postmenopausal women. It has been aptly termed as the 'silent disease', as most women are asymptomatic, and a fragility fracture is often the first presentation [1]. It is estimated that currently over 200 million people worldwide are suffering from osteoporosis and that 1 in 3 women over the age of 50 will experience an osteoporotic fracture in their remaining lifetime [11]. The Indian Society of Bone Mineral Research [28] states that as of 2015, nearly 20% of the 230 million Indian women over age 50 have osteoporosis with prevalence of osteoporosis ranging from 8 to 62% in Indian women of different age groups. The burden of osteoporosis is even more in country like India, given the fact that:

- There is an increasing number of elderly populations given the increasing life expectancy than before
- As it is a silent disease, it has no warning signs and hence people tend to take no measures towards its prevention
- The nutritional status of the Indian population is not up to the mark as compared to the western population
- There are no set screening programs and/or guidelines for early osteoporosis detection in India

Hence, more often than not, the first presentation of osteoporosis is a fragility fracture. As compared to Western countries, osteoporotic fractures in the Indian population occur 10-12 years earlier in age [29]. More than 4.5 million women above the age of 60 years in India have a fractured spine. More than 250,000 people in India sustain a hip fracture every year, of which most are in the elderly age group. Fragility fractures being more difficult to manage lead to more morbidity and significantly increase the cost of treatment on the individual and the nation as a whole. Thus, osteoporosis should be diagnosed well before it can progress to lead to fracture. So far, the gold standard to diagnose osteoporosis has been the DEXA scan [9]. However, it is not without its limitations: it is not a cost-effective modality which requires appropriate set up, equipment, highly trained manpower, and it is not portable. Additionally, it is of limited use in individuals with spine deformity or previous fractures, and has problems related to calibration; DEXA performed at two different centres cannot be compared. Given the aforementioned problems, the application of DEXA in resource limited set ups, becomes next to impossible, making it inaccessible to the at-risk populations for the diagnosis of osteoporosis. Hence, there is a need for other modalities and screening tools that can be implemented at the grass root level and can be made assessable to the vulnerable population. Quantitative ultrasound for the measurement of bone mineral density has been around for more than three decades [30], but its use has been limited due to its lack of accuracy of diagnosis. The technology works on the data and estimates based on the regional population. In the present study, the estimates were available from a Japanese population group. So, on analysis of our data we found that the mean bone mineral density of young Indian women was higher than the mean bone mineral density of this Japanese population group; this may partly explain the poor accuracy. We also noted that the sensitivity, specificity, and predictive values were very poor using the definitions provided by the quantitative ultrasound machine. Hence, if one was to use the parameters provided by the machine, it would result in very poor diagnostic accuracy. Therefore, to improve the diagnostic accuracy, we looked at cut-off derived for current study by means of receiver operating characteristic curve analysis and we also looked at the cut-off derived from the study based on young Indian women. The cut-off derived from current study was 1536 m/s which was slightly lower than the cut-off derived from the study based on young Indian women, which

was 1568m/s. However, by using the cut-off derived from the young Indian women, we were getting higher percentage of misclassification. Hence, we believe that the results from the receiver operating characteristic curve analysis study should be used for predicting osteoporosis. Even after using cut-offs from our own population, the diagnostic accuracy of the quantitative ultrasonography machine remained sub-par. This may be because of several factors:

- The machine may be affected by variations in temperature. It has been found that Ultrasound velocity decreased linearly with increasing temperature, temperature trends in velocity are likely to be due to the influence of fat, present in the bone marrow and in the soft tissues, which has a negative thermal coefficient for acoustic velocity [31]. We also noted that in winter months, multiple attempts were required to obtain the data.
- Size of the foot and width of the heel have also has been shown to affect the measurements [32]. Although the newer machine designs have tried to correct for this, it may remain a significant factor.

Changes of bone mineral density at heel may not replicate the changes of bone mineral density at the hip or at the spine. It has been shown that the spine is the first site to be affected by osteoporosis, followed by the spine, whereas the peripheral skeleton may be affected relatively late. So, this explains why several people who had osteoporosis at the lumbar spine did not show significantly low measurements by quantitative ultrasonography at heel. Moreover, Indians also tend to walk bare foot, and this may also be a reason for relatively higher bone mineral density at the heel thereby leading to a confounding result. Our results parallel those of several other investigators who have found that the speed of sound by itself may not be very accurate for diagnosis of osteoporosis. So, in order to cover up for this deficiency we looked at creating a logistic regression model which took into account, other parameters. In the univariate analysis, we found that the following parameters: age, body mass index, hip circumference, and time since menopause, were significantly associated with osteoporosis. Previous studies have also noted a similar correlation. With age, it is known that rate of bone loss is 3% per decade for cortical bone and 7-11% per decade for trabecular bone; however, in women, a 10-year period of more rapid bone loss of both cortical and trabecular bone is superimposed on the slow loss, beginning at the time of menopause ⁶⁹. Thus, in any predictive model age should be considered as one of the predictive variables. Similarly, body mass index is also a well-known predictor because studies have shown that a higher BMI actually has a protective factor and is associated with better bone mineral density, although a ceiling effect has been noted [33,34]. Thirdly, hip circumference is a measure of obesity. Studies have shown that obesity is associated with increased BMD, better bone microarchitecture and strength, and generally lower or unchanged circulating bone resorption, formation and osteocyte markers. Hence, hip circumference can be used as good predictor [35]. Lastly, time since menopause is also an important factor affecting osteoporosis. Early menopause deprives the females of protective and anabolic effects of hormone and hence leads to early osteoporosis. Studies have shown that women lose about 50% of their trabecular bone and 30% of their cortical bone during the course of their lifetime, about half of which is lost during the first 10 years after the menopause [36]. In constructing the multivariable logistic regression model, fully adjusted models were obtained with three predictors: age, body mass index and speed of sound. We used several performance parameters to study the performance of the model. The area under the curve is a measure of the discrimination of the model. It helps the model to differentiate between those who have the condition versus those who did not. For this model the area under the curve estimate was 0.72, which indicated a good discrimination. We also performed a goodness of fit test and the Brier test which determines the model calibration. Overall, our model was found to have a good discrimination as well as calibration. Moreover, it consists of only three parameters, which are easily and readily measurable at even a

primary health care centre. Thus, we feel that this model can be used even by primary care physicians and those with extremely resource challenged setups, to predict osteoporosis with a high degree of certainty. Hence, such probability-based estimates can help decide whether more investigation is required to come to a diagnosis or treatment is to be started straight away. In resource limited setups, in the presence of high probability of osteoporosis, treatment can be initiated, and patient can be referred for DEXA scan. There are several strengths of our study; it a prospective study, we have a fairly large sample size, we have correlation with DEXA and clinical demographics of all outpatients and we were able to adjust for the confounding factors by the univariate and multivariate analysis. Moreover, the logistic regression model has shown good discrimination and good calibration.

4. CONCLUSIONS

The first study from the Indian subcontinent to demonstrate that a multivariable logistic regression model incorporating clinical–demographic parameters and speed of sound (SOS) can effectively predict osteoporosis using quantitative ultrasonography (QUS). While SOS measurement alone showed limited diagnostic reliability, its integration with key variables such as age and body mass index (BMI) substantially enhanced the predictive accuracy for osteoporosis diagnosis. Importantly, SOS values measured at the heel were found to be significantly lower (mean difference ≈ 20 m/s) among individuals with DEXA-confirmed osteoporosis compared to those with normal bone mineral status, and SOS exhibited a strong, positive correlation with DEXA-derived bone mineral density (BMD). The findings further indicate that applying normative SOS cut-offs derived from the Japanese population (Strategy 1) results in suboptimal diagnostic accuracy in the Indian context. Conversely, data-driven cut-offs obtained through receiver operating characteristic (ROC) analysis provided better discrimination, reducing the rate of misclassification. An SOS threshold below 1536 m/s yielded a sensitivity of 91.7%, whereas a threshold below 1467 m/s achieved a specificity of 91.5% for DEXA-confirmed osteoporosis. Additionally, univariate analysis revealed that age, BMI, hip circumference, and time since menopause were significantly associated with osteoporosis risk. A multivariable logistic regression model comprising age, BMI, and SOS demonstrated robust performance in predicting osteoporosis, underscoring the utility of combining clinical parameters with QUS-based metrics. These findings highlight the potential of using a simple, non-invasive, and cost-effective diagnostic strategy at primary and secondary healthcare levels, particularly in resource-limited settings. Nonetheless, given the study's scope and sample size, further validation in larger, multicentric cohorts is warranted before widespread clinical implementation.

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