ORIGINAL ARTICLE

Comparison of Performance of Risk Assessment Tools for Low BMD and Fracture Risk Identification in Pakistani Women

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ABSTRACT:

Objective: To evaluate the efficacy of four risk assessment tools for identifying low Bone Mineral Density (BMD) in a sample of Pakistani females.

Methodology: It was a cross sectional study including 200 females above 40 years. DXA scans were performed. Subjects were categorized into low risk and high risk categories for low BMD on the basis of T scores. Questionnaires were filled and risk indices were calculated for all subjects. Sensitivity, specificity, positive and negative predictive values were calculated, Receiver Operating characteristic (ROC) curves were plotted and Area Under Curve (AUC) were obtained.

Results: A total of 200 females including 174(87%) postmenopausal, and 26(13%) premenopausal were included. Average age was 60.76±10.52 years with average age of menopause being 47.64±6.63 years. In terms of sensitivity, specificity and AUC, the WHO risk assessment tool FRAX showed the best performance with a sensitivity of 79%, specificity 94% and AUC of 0.869 for detecting low BMD.

Conclusion: It is not cost effective to use DXA for screening purposes. We propose that risk assessment tools such as FRAX may be utilized to identify individuals with low BMD. This may prove beneficial in minimizing the medical and social burden that fragility fractures pose to developing health care systems.

Keywords: Bone Mineral Density, Pakistan, Prediction, Risk Assessment tools, Screening

INTRODUCTION:

Osteoporosis is a silent disease commonly associated with aging. It is characterized by a decrease in bone strength or the bone mineral density.[1,2] A fragility fracture is usually the first sign bringing this condition to clinical attention. Such events may lead to consequent disabilities causing considerable morbidity and mortality.[3,4] Osteoporotic fractures are the cause of immense medical, economic and social burden in most Asian countries.[5] In Pakistan 9.91 million people are affected by osteoporosis, and these numbers are estimated to rise to 11.3 million by 2020.[6] There is no data available for hip fracture incidence in Pakistan. Osteoporosis remains largely underdiagnosed in this part of the world.[7] The International Osteoporosis Foundation has emphasized the need for development of fragility fracture prevention policies in Pakistan.[8]

DXA (Dual Energy X-ray Absorptiometry) is the WHO recommended gold standard technique used for diagnosing osteoporosis. Unfortunately this technique remains expensive and is not readily available in developing countries.[6] Amarnath et al reported overuse of DXA in low risk females and its underutilization among high risk females in a study published in 2015.[9] Furthermore, use of DXA for mass screening is not cost effective without the selection of a high risk population. A number of risk indices have been developed for this purpose.[10-12] These indices are based on the various risk factors that contribute to the development of low BMD and osteoporosis.

Therefore the objective of this study was to assess the utility of four of these risk indices namely OSTA, ORAI, OPERA and FRAX without BMD when applied to a sample of Pakistani women. The Osteoporosis Self-Assessment Tool for Asians (OSTA) was developed by a multicenter large population based study which was carried out in eight Asian countries by Koh et al. In this study risk factors pertinent to osteoporosis in postmenopausal women were assessed. A formula containing only two variables; age and weight was then derived.[10] It is a simple formula based index and has shown good sensitivities in different Asian populations.[13,14]

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Osteoporosis Risk Assessment Index (ORAI) utilizes three variables including age, weight and current estrogen use. The Osteoporosis Prescreening Risk Assessment Tool (OPERA) predicts low BMD on the basis of five variables, including previous fracture history and early menopause in addition to weight, age and steroid use. A person is considered at risk of low BMD if positive for two of these variables (Table-1). This index showed good validity in Italian postmenopausal women.[11] The WHO developed FRAX risk indicator is part of osteoporosis management guidelines in different countries. This is a web based calculator which computes fracture risk probabilities on the basis of a person's history.[15]

METHODOLOGY:

This cross sectional study was conducted from March to August 2016 at the Nuclear Medicine Department, Ziauddin Hospital, Clifton Campus, Karachi, after obtaining approval from the Ethics Review Committee of Ziauddin University. A total of 200 females above forty years of age were recruited by consecutive sampling technique, from the Gynecology OPD of Ziauddin Hospital. We excluded patients with any prior diagnosis or treatment for osteoporosis, malignancies with metastasis to bone or females having history of oophorectomy with or without hysterectomy and pregnant females.

After taking informed consent from all participants, their height, weight and BMI were recorded. Participants were interviewed and a questionnaire including information on demographic profile and risk factors of low BMD was filled for all subjects. DXA scanning was performed and BMD was estimated using Hologic Discovery Wi (S/N 88577) DXA Scanner. BMD was calculated from three sites including hip, spine (L1 to L4) and 33% of distal forearm (one third radius). Diagnosis of low BMD was based on the basis of the lowest T score observed for any of the three measured sites according to WHO recommendations. Participants were classified as either normal, osteopenic or osteoporotic according to the International Society for Clinical Densitometry (ISCD) guidelines. Categorization of postmenopausal women was based on T scores which represent the standard deviations by which the measured BMD differs from the mean BMD of a similar gender young adult. Z scores were used for premenopausal females which is the SD by which the measured BMD differs from the mean BMD of a healthy population of same gender and age. Postmenopausal women were categorized into three categories; normal females having T score $\geq$ -1 SD , osteopenic females having T score between -1 and -2.5 and osteoporotic females having T score $\leq$ 2.5 SD. Premenopausal females were divided into two categories on basis of Z score; normal BMD i.e. Z score upto $\pm$1.9 SD and low BMD i.e. Z score $\leq$ -2 SD. Four risk assessment tools (OSTA, OPERA, ORAI and FRAX without BMD) were calculated for each participant on the basis of information from the anthropometric data and questionnaires. Developer recommended cutoffs were used for each risk index. On the basis of these cutoffs participants were categorized into high and low risk groups for having low BMD. (Table 1)

Data was analyzed using SPSS version 20. Descriptive statistics (means, standard deviations, frequencies and percentages) were used to define the characteristics of sample. Sensitivity, specificity, positive and negative predictive values (PPV and NPV) were calculated on 95% confidence level. Sensitivity refers to the ability of a risk index to correctly classify persons at risk of low BMD (true positive fraction). Specificity was defined as the percentage of persons correctly classified as having normal BMD as low risk (true negative fraction). The PPV and NPV represent the proportion of females who were tested as having high risk or low risk on the basis of risk indices and who actually had low or normal BMD values respectively on DXA results. These values were calculated at T-score thresholds of -1 and -2.5 to determine their performance for predicting low BMD and osteoporosis respectively. The sensitivity, specificity, NPV and PPV were calculated separately for different anatomical sites (hip, spine and forearm). ROC curves were plotted for each index to graphically represent the overall accuracy of a test. Diagnostic accuracy of different tools was measured by the AUC.

RESULTS:

The average age of females in our sample was 60.7$\pm$10.52 years, ranging from 40 to 93 years. The average age at menopause was 47.6 years. 13% of the women were premenopausal and 87% of the sample comprised of postmenopausal women. The prevalence of low BMD was found to be greater among postmenopausal group. According to WHO criteria 55 women (27.5%) had normal BMD (T score>–1 for postmenopausal and Z score upto 1.9 SD for premenopausal women). 74 women (37%) were osteopenic (T score between –1 and –2.5 for postmenopausal and Z score = -2 SD for premenopausal women. 71(35.5%) were classified as osteoporotic (T score<-2.5). Table 2 represents the demographic data.

Table: 1
Risk Indices Description

RISK INDEX	RISK FACTORS	CALCULATION	CUT OFF VALUE
OSTA	Body weight, age	0.2x (body weight in kg – age in years): round off to the closest integer	< 2
ORAI	Weight, age and current estrogen use	Age ≥ 75 +15 Age 65–74 years +9 Age 55–64 years +5 Age 45-54 years 0 Weight <60 +9 Weight 60–69 kg +3 Weight > 70 0 Current estrogen use 0 No current estrogen use 2	Total score≥9
OPERA	Age, weight, low trauma fracture history, early menopause, steroid use	Age ≥ 65 years Weight < 57 kg History of low trauma fracture after age 45 Early menopause before 45yrs Steroid use> 6 months > 5mg/day Each factor carries 1 point	Total score ≥2
FRAX	Age, sex, ethnicity, weight, height, history of prior fractures, parental history of hip fracture, current smoking, glucocorticoid use, rheumatoid arthritis secondary osteoporosis, alcohol use	Computer based Algorithm Major Osteoporotic and Hip fracture risks were computed.	Age-specific fracture intervention thresholds were used.[16]

Table: 2
Study sample characteristics

Variables	Mean ± SD
Age of Patients	60.76±10.52
Age at Menopause	47.64±6.63
Height	155.02±6.33
Weight	69.25±15.32
BMI	28.74±5.79
BMD Hip	0.8194±0.15
BMD Spine	0.924±0.18
BMD Forearm	0.591±0.099
T-score Hip	-1.00±1.26
T-score Spine	-1.08±1.610
T-score Forearm	-1.58±1.616

Sensitivity, specificity, NPV and PPV for all tools was calculated at T scores of < -1 (low BMD) and at T score < -2.5 respectively. FRAX showed best sensitivities 79% and 83% for T score <-1 and <-2.5 at any one of the three measured sites. The sensitivities of the simpler tools; OSTA, ORAI and OPERA were 66%, 77% and 63% respectively for T score<-1. All four risk indices showed better sensitivities in detecting osteoporosis, T score<-2.5, but lower specificities were observed at this T score cutoff. All indices showed good PPVs at T score<-1 ranging from 89% to 97%. (Table 3)

Table: 3
Performance of Risk Indices by T score cut offs for any site

Tools	Any Site <-1				Any Site <-2.5			
	Se	Sp	PPV	NPV	Se	Sp	PPV	NPV
OSTA	66	78	89	47	80	60	49	86
ORAI	77	80	91	56	85	51	46	78
OPERA	63	96	97	50	68	63	48	80
FRAX	79	94	97	63	83	53	47	86

Se: sensitivity, Sp; specificity, PPV: positive predictive value, NPV: negative predictive value

BMD was calculated at three sites including hip, spine and the non-dominant forearm at T score <-1. These are presented in Table 4. All tools showed good sensitivities for detecting low BMD at hip, ranging from 70% for OPERA to 88% for FRAX. Overall, FRAX performed efficiently for low BMD detection at all sites with sensitivity ranging from 80% at the spine to 88% at the hip.

Table: 4
Performance of risk indices by BMD sites for low BMD

Tools	Total Hip				Spine				Forearm			
	Se	Sp	PPV	NPV	Se	Sp	PPV	NPV	Se	Sp	PPV	NPV
OSTA	77	65	65	77	69	62	67	64	69	70	79	58
ORAI	84	58	62	81	75	55	65	67	79	67	80	66
OPERA	70	72	68	75	65	73	72	65	63	79	83	57
FRAX	88	65	68	86	80	64	71	74	80	75	84	70

Se: sensitivity, Sp; specificity, PPV: positive predictive value, NPV: negative predictive value

Table: 5
AUC for the risk indices at T<-1 and T<-2.5 for any site

Tools	Area Under Curve (AUC)	
	Any Site <-1	Any Site<-2.5
OSTA	0.670	0.713
ORAI	0.781	0.676
OPERA	0.799	0.657
FRAX	0.869	0.680

Figure: 1
Receiver Operating Characteristics based on T score<-1 (low BMD)

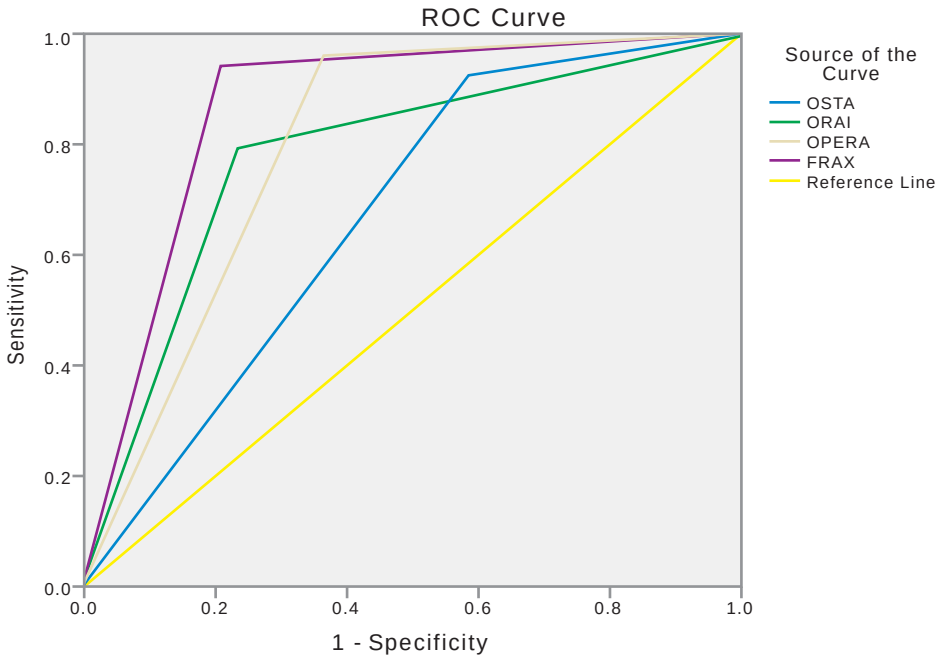

Figure: 2
Receiver Operating Characteristics based on T score<-2.5

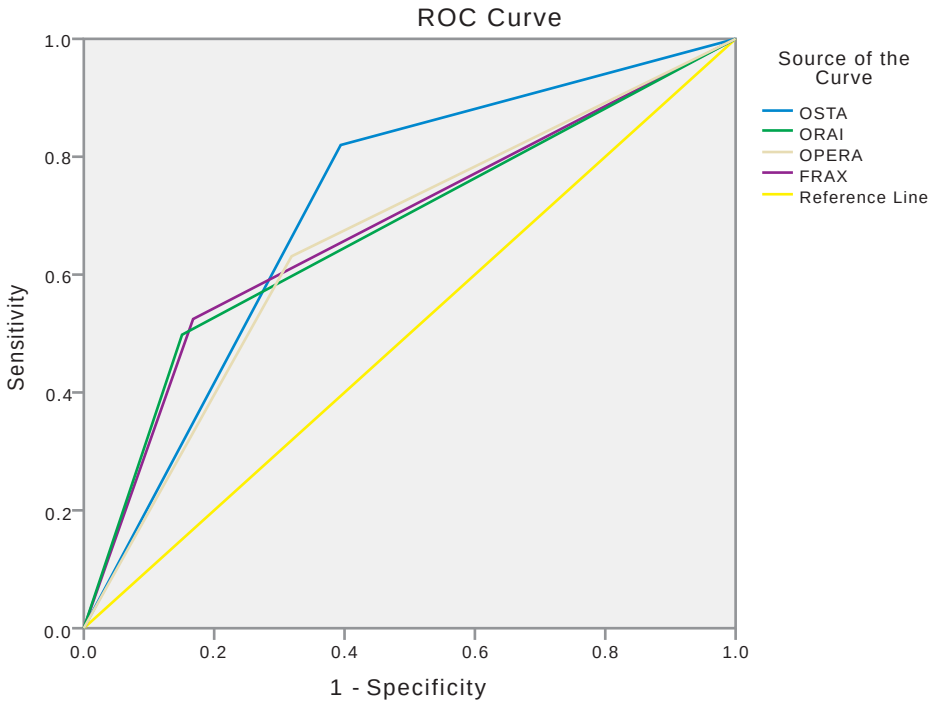

Table-5 represents area under ROC curves (AUC) values for the four risk indices by T score cut-offs. The AUC represents the diagnostic accuracy of a tool. It ranges from 0.5 for a non-informative tool to 1.0 for perfect concurrence. FRAX showed very good accuracy for detecting low BMD with AUC of 0.869. However, OSTA performed better than FRAX at T score<-2.5 (for osteoporosis) and an AUC of 0.713.

DISCUSSION:

Osteoporosis has been defined as a disease with high risk of fragility fractures accompanied by low BMD (T score< -2.5 SD) by the National Institute of Heath Consensus Conference. Low BMD values have been

found to be strongly correlated to hip fractures, the most devastating outcome of this disease.[18] It has long been debated that risk factors be included in osteoporosis diagnosis. This concept has led to the development of risk indices for identifying high risk individuals. WHO developed fracture assessment model FRAX has found its place in many national guidelines.[19]

In our study, FRAX showed high sensitivity for low BMD detection at all measured sites with 80% sensitivity at lumbar spine to 88% for hip. Among the simpler risk indices, ORAI also showed good sensitivities ranging from 75% at lumbar spine to 84% for total hip. The AUC was greatest for FRAX at T<-1, which is an indicator of its efficiency in detecting low BMD. However, for osteoporosis detection (T<-2.5), OSTA performed better than all other tools represented by AUC of 0.713.

These differences in risk indices performance may be explained by the fact that these indices have been developed in different population samples. The OSTA index was derived from a multicenter cohort comprising mainly Chinese population. This tool includes body weight as part of risk calculation.[10] Since weight is an anthropometric measure that differs substantially among populations, this tool might work more efficiently in one ethnic sample than another.[14, 20] Secondly OSTA was developed for identification of low BMD at the T<-2.5 in its development study,[10] this could be a reason for OSTA's relatively better performance at T<-2.5 in our study group. FRAX on the contrary is a country specific model with country specific intervention thresholds. The WHO Collaborating Centre at Sheffield recommends using country specific intervention thresholds which have been developed according to its hip fracture incidence and demographics.[14] Due to these factors and inclusion of multiple risk factors for generation of fracture risks FRAX showed better performance. FRAX had an AUC of 0.869 in our study which is comparable to the AUC of 0.79 for FRAX without BMD in American females[21] and AUC of 0.857 in Thai females.[22]

For a tool to be used for screening purposes, it should have an AUC of 0.7 or greater. The AUC for ORAI and OPERA were 0.781 and 0.799 respectively showing fairly good diagnostic accuracy for low BMD detection. These results are comparable to results from other studies assessing simple tools and comparing simple and complex ones.[13]

Dabbagmanesh et al reported a sensitivity range of 70% at spine to 80% at femoral neck for OSTA and a range of 73% at spine to 84% at femoral neck for ORAI which is comparable to our study.[23] Patel et al conducted a study including seventy two perimenopausal females in 2014. He reported 70% sensitivity and 85% specificity of OSTA for identifying T<-1 which is higher than our values of 66% and 78% respectively.[24] These slightly higher values may be due to the fact that Quantitative Ultrasound(QUS) was employed for BMD measures in his study while we used DXA in our study. Secondly, sensitivity and specificity values were calculated in a subgroup of 50 to 55 years in his study, while we calculated these values for the whole sample. Generalizability and practicability are essential characteristics of a good screening tool.[25] In our study we identified the best tool that may be applied to the whole high risk population which may prove as a more practical approach for screening purposes rather than advising different indices in different age groups.

Many studies have compared the power of complex models to simpler ones. Majority of them have concluded that simpler models like OSTA and ORAI provide similar or in some instances even better performance compared to the more complex ones like FRAX.[12,22,26] Our results reflect a greater AUC for FRAX, value >0.8 in predicting low BMD (T<-1). This value is slightly higher but comparable to that observed for ORAI and OPERA. Both of these models have values above 0.7 for T<-1 which reflects their considerable diagnostic accuracy. The OSTA tool showed not so good performance (AUC= .670) for T<-1. But it was the only tool to have an AUC above 0.7 for detecting osteoporotic females (T<-2.5). This may be explained by the fact that OSTA has been shown to have considerably good performance among older females who are more prone to exhibit osteoporotic T scores. Most of the studies reporting high diagnostic accuracies for OSTA have calculated the predictive power for T<-2.5, [27,28] while we have calculated these values for detecting low BMD i.e. individuals with osteopenia and osteoporosis(T<-1) and for BMD values of osteoporosis alone(T<-2.5). Secondly most of these studies were conducted on cohorts comprising of only postmenopausal older females while we included both pre and post-menopausal females above 40 yrs.[13,28,29] Mean age of Singaporean females in the study conducted by Chan et al was 68.4 ± 5.5years[13] which was considerably higher compared to mean age of our sample which was 60.7 years.

As with most studies, our study also had certain limitations. For instance, our study sample was recruited from females visiting outpatient department of a tertiary care. The subjects may differ from the general population in some ways. Another limitation was the small sample size due to budget constraints.

CONCLUSION:

Measuring BMD is undoubtedly the best method for low BMD detection. However, DXA screening of large population is not cost effective. The FRAX tool may be used for this purpose. The high specificity observed for FRAX and simpler indices may prove beneficial in identifying true negatives and thus lowering the overutilization of DXA by avoiding unnecessary exams.

In a country where the health care system is still developing, diagnostic and therapeutic facilities are not readily accessible to all people, such measures may prove to be advantageous. Further studies on a greater sample size are required for further assessment of the clinical utility of these risk indices

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