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ORIGINAL ARTICLE

The Diagnostic Efficacy of Quantitative Data from Lumbar Magnetic Resonance Imaging Findings in Osteoporosis and Osteopenia Diagnosis and Differentiation in Postmenopausal Women

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Abstract

Introduction: Osteoporosis, especially the postmenopausal type, is a global health problem. Quantitative CT and advanced MRI (magnetic resonance imaging) may be used to diagnose in addition to dual-energy X-ray absorptiometry (DEXA), the gold standard. However, using these techniques in everyday practice is difficult and not applicable in all centers. The aim of our study was to evaluate the effectiveness of quantitative MRI scoring based on standard lumbar MRI examination and its correlation with DEXA data in detecting osteoporosis and osteopenia in postmenopausal women.

Methods: In our study, 190 lumbar MRI and DEXA patients were examined between 2019 and 2022. Quantitative MRI-based score (M-score) data was extracted using Bandirali et al.'s method. Measurements were averaged for L1–L4 vertebrae on T1W images. Signal-to-noise ratio (SNR) was calculated. The reference group's SNR L1-L4 and standard deviation were measured. M-score was determined as (M-score = [SNRL1-L4-SNRref]/Sdref). Comparisons were made between DEXA and MRI M-scores. $P<0.05$ was significant.

Results: The average age and BMI (body mass index) were 59.4 and 29.4, respectively. Patients were categorized as normal (n=91), osteopenia (n=79), and osteoporosis (n=20) by DEXA. Osteoporosis got the highest M-score. The M-score cut-off value for normal and osteopenia distinction was >10.3 ($p<0.03$); for normal and osteoporosis distinction was >26.26 ($p<0.001$); for osteoporosis and osteopenia differentiation was >23.8 ($p<0.001$).

Discussion and Conclusion: In our study, the M-score detected osteopenia and osteoporosis with high sensitivity and specificity. Lumbar MRI-based M-score can be used as an imaging biomarker for early diagnosis, monitoring of treatment response, and reduction of fracture risk in postmenopausal women or individuals at risk of osteoporosis.

Keywords: DEXA; lumbar vertebrae; magnetic resonance imaging; osteopenia; osteoporosis.

Global health concerns include osteoporosis, the most frequent bone disease. As the population ages and demographics change, prevalence will climb[1]. It is defined as a reduction in normal mineralized bone mass per unit volume. It is the main cause of elderly bone fractures[2,3]. Osteoporotic fragility fractures have been shown to significantly reduce health-related quality of life and lead to premature mortality[4-8]. Osteoporosis fractures are mostly vertebral[9-11]. Osteoporotic vertebral fractures are often occult and may remain asymptomatic.

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As a consequence, treatment may be substantially delayed, increasing the risk of further future fractures; hence, early and accurate detection of osteoporosis is critical[12]. Postmenopausal (estrogen deficiency osteoporosis) is the most frequent type of osteoporosis[13]. Depending on the method of diagnosis, 2-8% of males and 9–38% of women in developed nations are affected, with a female predominance[14,15]. Osteoporosis management involves primarily fracture prevention and/or treatment of related complications[9-11]. Dual-energy X-ray absorptiometry (DEXA) is considered the gold standard for the diagnosis of osteoporosis[16]. The T-score, according to World Health Organization criteria, aids in the classification of bone mineral density (BMD)[17]. However, it has been recognized that DEXA has significant limitations that may impede effective identification of osteoporosis and that the DEXA-based T-score, although having diagnostic value for osteoporosis, is not suitable as the single determinant to identify individuals at high fracture risk. In particular, it has been shown that BMD values obtained from DEXA can overlap in people with and without osteoporosis[18,19]. Therefore, instead of DEXA, different quantitative MRI methods based on quantitative computed tomography, high-resolution trabecular bone imaging and T2*mapping, magnetic resonance spectroscopy (MRS), water-fat MRI based on chemical shift encoding (CSE-MRI), ultrashort echo time (UTE) imaging of cortical bone, and quantitative susceptibility mapping (QSM) for imaging trabecular bone have been used[1,20]. However, their use in normal practice is limited, and they cannot be used in every center.

The aim of this study was to evaluate the effectiveness of quantitative scoring (M-score) derived from a standard lumbar MR protocol used in daily practice in the detection and differentiation of osteoporosis and osteopenia in postmenopausal women and its correlation with DEXA data.

Materials and Methods

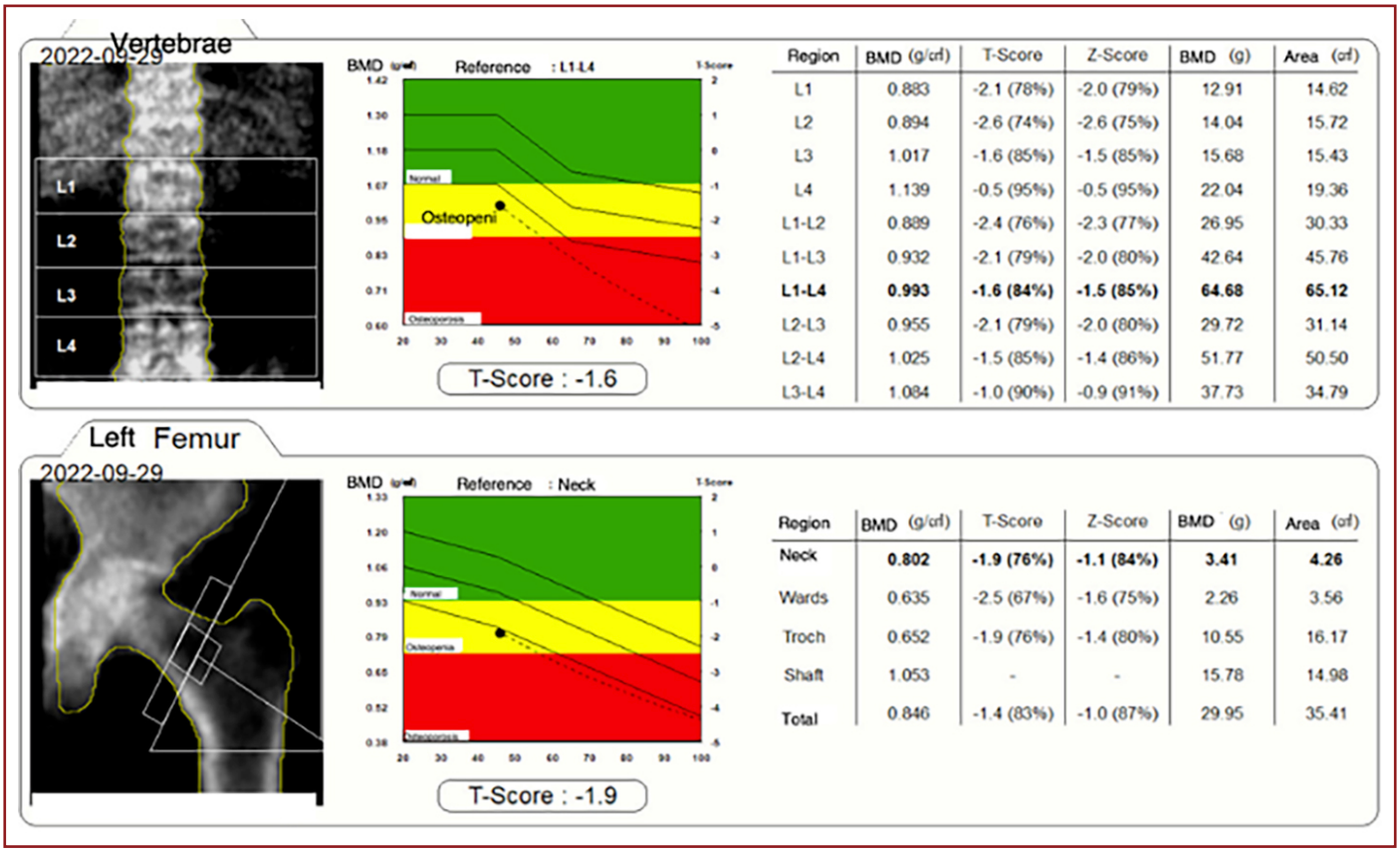
Study Design and Population

Our single-center retrospective study was performed in accordance with the principles of the Declaration of Helsinki. Approval was granted by our hospital ethics committee (2023/514/246/2). Postmenopausal women aged 45–76 years who had standard lumbar MRI and DEXA exams in our clinic between 2019 and 2022 were analyzed. MRI quantitative data extraction as M-score was performed according to the protocol in Bandirali et al.[21]. Patients with more than a 9-month interval between MRI and DEXA, those with a known history of bone disease or malignancy, those with contrast-enhanced MRI, and those with MRI contraindications (pacemaker, MRI-incompatible implant, claustrophobia, etc.) were excluded. M-score reference values were obtained from lumbar MRI scans of women who underwent DEXA examination and who did not have osteopenia or osteoporosis on DEXA examination, were between the ages of 20-35, had a BMI between 19-25, had no diagnosed health problems, and had not reached menopause.

DEXA Examination, MRI Technique, and Analysis Methods

All patients were DEXA scanned with an Osteosys Brand Primus model device. The International Society for Clinical Densitometry (ISCD) criteria were used to calculate BMD, Z-score, and T-score (Fig. 1). Since possible degenerative changes in the lumbar spine may affect the lumbar T-score in our patient population, the femoral neck and total hip T-score were also included in the diagnosis and classification of the cases. Here, the values calculated for postmenopausal women (>50 years) are compared with the reference population values of a healthy control group. T-scores are complicated statistical scores that range from >1.0 SD (normal) to -1.0 to -2.5 SD (osteopenia), -2.5 SD (osteoporosis), and -2.5 SD with one or more fragility fractures (severe osteoporosis).

Magnetic resonance imaging of all patients was performed with a 1.5 Tesla (T) MRI device (Philips Ingenia, The Netherlands). Sagittal T1W (TR: 904, TE:12) and T2W (TR: 3075, TE: 90) and axial T2W sequences were obtained in the lumbar MRI protocol. Measurements were taken on sagittal T1W images, which are the best sequence for evaluating bone marrow and anatomical structures. Two experienced radiologists blinded to clinical information and DEXA scan findings assessed all MR images by agreement. Lumbar vertebrae were evaluated individually according to the Genant classification[22]. In routine lumbar spine evaluation from L1 to L4, the region of interest (ROI) for each vertebra was manually circled within the vertebral body, excluding cortical bone, subchondral abnormalities, focal lesions (e.g., hemangioma), and the posterior venous plexus (Fig. 2). Three consecutive measurements were made on each vertebra, and their averages were used (the signal-to-noise ratio is not equivalent between vertebrae). To quantify noise in MR images, the ROI was placed in an artifact-free region 1 cm away from the patient's body at the L2–3 vertebral level as standard (Fig. 3). The signal-to-noise ratio (SNR) was calculated as the intra-vertebral intensity divided by the standard deviation of the noise. The diagnostic



Region	BMD (g/cm²)	T-Score	Z-Score	BMD (g)	Area (cm²)
L1	0.883	-2.1 (78%)	-2.0 (79%)	12.91	14.62
L2	0.894	-2.6 (74%)	-2.6 (75%)	14.04	15.72
L3	1.017	-1.6 (85%)	-1.5 (85%)	15.68	15.43
L4	1.139	-0.5 (95%)	-0.5 (95%)	22.04	19.36
L1-L2	0.889	-2.4 (76%)	-2.3 (77%)	26.95	30.33
L1-L3	0.932	-2.1 (79%)	-2.0 (80%)	42.64	45.76
L1-L4	**0.993**	**-1.6 (84%)**	**-1.5 (85%)**	**64.68**	**65.12**
L2-L3	0.955	-2.1 (79%)	-2.0 (80%)	29.72	31.14
L2-L4	1.025	-1.5 (85%)	-1.4 (86%)	51.77	50.50
L3-L4	1.084	-1.0 (90%)	-0.9 (91%)	37.73	34.79

Region	BMD (g/cm²)	T-Score	Z-Score	BMD (g)	Area (cm²)
Neck	**0.802**	**-1.9 (76%)**	**-1.1 (84%)**	**3.41**	**4.26**
Wards	0.635	-2.5 (67%)	-1.6 (75%)	2.26	3.56
Troch	0.652	-1.9 (76%)	-1.4 (80%)	10.55	16.17
Shaft	1.053	-	-	15.78	14.98
Total	0.846	-1.4 (83%)	-1.0 (87%)	29.95	35.41

Figure 1. Image of the DEXA scan: Report of BMD (g/cm^2), T-score, Z-score, BMI (g), and area (cm^2) values calculated according to ISCD criteria in lumbar vertebrae (L1-L4) and femoral head, trochanter, and shaft regions.

BMD: Bone mineral density; DEXA: Dual-energy X-ray absorptiometry; BMI: Body mass index; ISCD: International Society for Clinical Densitometry.

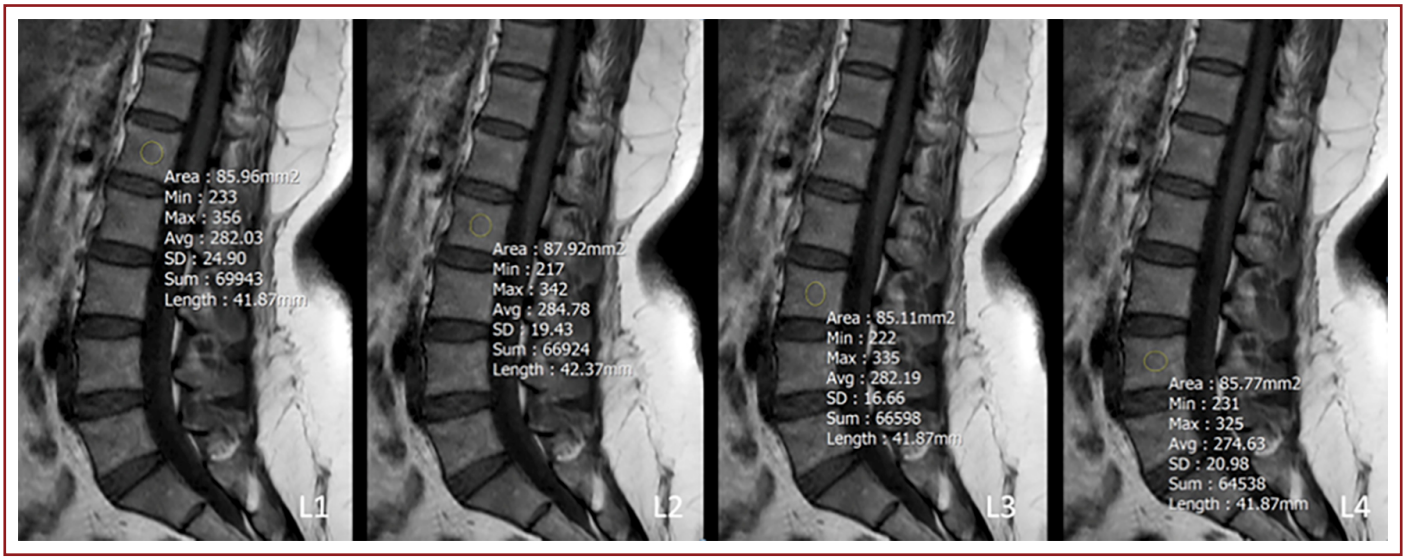


Figure 2. Signal-to-noise ratio (SNR) and M-score calculation: signal intensity, standard deviation (SD), noise measurement with ROI placed on L1-L4 vertebrae in lumbar MRI T1W images (M-score= SNR(L1-L4) -SNRref /SDref).

ROI: Region of interest; MRI: Magnetic resonance imaging.

performance of SNRL1-L4 was assessed for each patient and utilized to calculate the M-score (MRI-based score) for osteoporosis diagnosis. The SNRL1-L4 value obtained in the control group was employed in the M-score equation as the mean (SNRref) and standard deviation (SDref) (M-score: SNRL1-L4 - SNRref/SDref)[21].

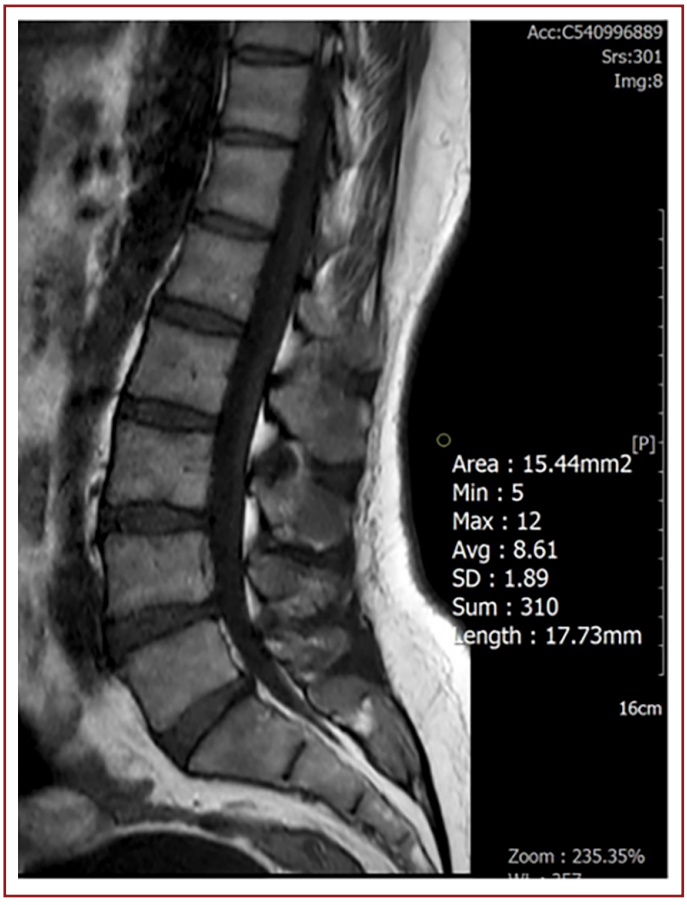


Figure 3. Measurement of noise in lumbar MRI T1W images: Noise was calculated by placing the ROI in a standard artifact-free region approximately 1 cm away from the patient's body at the L2-3 vertebral level.

MRI: Magnetic resonance imaging; ROI: Region of interest.

Statistical Method

The statistical package software IBM SPSS Statistics Standard Concurrent User V 26 (IBM Corp., Armonk, New York, USA) was used to analyze the data. Number of units (n), percentage (%), mean±standard deviation, median, and interquartile range (IQR) data were used for descriptive statistics. The numerical variables' normal distribution was assessed using the Shapiro-Wilk normality test. One-way analysis of variance was used to analyze intergroup comparisons for numerical variables with a normal distribution. In a one-way analysis of variance, the Duncan test was utilized as a multiple comparison test. Kruskal-Wallis analysis was used to compare groups of non-normally distributed numerical data. In Kruskal-Wallis analysis, the Dunn-Bonferroni test was utilized as a multiple comparison test. The Fisher's exact test was used to compare categorical data across groups. Receiver Operating Characteristic (ROC) Curve Analysis was used to assess the performance of SNRL1-4 and the M-score in differentiating the groups. The Spearman correlation coefficient was used to assess the relationship between SNRL1-4 and M-scores among themselves and with other variables. A p-value <0.05 was considered statistically significant.

Results

Bone densitometry was used to classify patients as normal, osteopenia, or osteoporosis based on WHO standards. Table 1 compares the descriptive and clinical characteristics of

Table 1. Comparison of descriptive and clinical characteristics according to bone densitometry groups

	Groups test statistics			Groups test statistics	
	Normal n=91	**Osteopenia n=79**	**Osteoporosis n=20**	**Test value**	**p**
Age (years)	57.2±10.3[a]	60.7±8.9[ab]	63.8±11.9[b]	4.998	0.008[†]
BMI (kg/m^2)	30.06±4.34	29.31±4.03	28.06±4.15	2.120	0.123[†]
Postmenopausal years (years)	7.0 (13.0)[a]	11.5 (14.2)[ab]	20.0 (20.5)[b]	11.347	0.003[‡]
MR-BMD (days)	60.0 (112.0)	60.0 (171.2)	20.0 (58.0)	3.200	0.202[‡]
Genant grade n (%)					
0	81 (89.0)	63 (80.8)	16 (76.2)		
1	10 (11.0)	13 (16.7)	5 (23.8)	5.260	0,208[&]
2	0 (0.0)	2 (2.5)	0 (0.0)		
BMD bone	1.21±0.11[a]	0.97±0.05[b]	0.84±0.05[c]	230.328	<0.001[†]
L1-4 Tscore	0.24±0.90[a]	-1.69±0.41[b]	-2.83±0.44[c]	253.216	<0.001[†]
L1-4 Zscore	1.07±0.96[a]	-0.61±0.75[b]	-1.51±0.84[c]	119.894	<0.001[†]
L1-4 BMD	69.62±8.98[a]	55.43±6.97[b]	48.22±6.23[c]	99.754	<0.001[†]
M score	15.57 (22.41)[a]	21.78 (25.91)[a]	31.98 (29.76)[b]	18.969	<0.001[‡]
SNR L1-4	134.7 (101.6)	153.9 (145.2)	212.6 (240.8)	1.509	0.470[‡]

a, b and c superscripts indicate the difference between groups in each row. There is no statistical difference between groups with the same superscript. Numerical variables are given as mean±standard deviation or median (interquartile range) values. [†]: One-way analysis of variance; [‡]: Kruskal-Wallis analysis; [&]: Fisher exact test. BMI: Body mass index; MR: Magnetic resonance; BMD: Bone mineral density; SNR: Signal-to-noise ratio.

patients based on bone densitometry groups. There were 190 patients in the study: 91 in the normal group, 79 in the osteopenia group, and 20 in the osteoporosis group. The mean age in the normal group was 57.2±10.3, 60.7±8.9 years in the osteopenia group, and 63.8±11 years in the osteoporosis group, which were significantly different. The age of the patients in the osteoporosis group was statistically higher than that of the normal group. BMI was 30.06±4.34 in the normal group, 29.31±4.03 in the osteopenia group, and 28.06±4.15 in the osteoporosis group. BMI levels were not significantly different across groups. Postmenopausal years were 7.0 (13.0) years in the normal group, 11.5 (14.2) years in the osteopenia group, and 20.0 (20.5) years in the osteoporosis group (p=0.003). Postmenopausal years were significantly higher in the osteoporosis group than in the normal group. The average number of days between MRI and BMD examination in the normal group was 60.0 (112.0), 60.0 (171.2) in the osteopenia group, and 20.0 (58.0) in the osteoporosis group. Patients with Genant grade 1 represented 11% of the normal group, 16.7% of the osteopenia group, and 23.8% of the osteoporosis group. Only two patients in the osteopenia group had Genant grade 2. The distributions of Genant grades were not significantly different across the groups.

The normal group had the greatest DEXA data, including BMD (bone mineral density) bone, T-score, Z-score, and BMD values, whereas the osteoporosis group had the lowest (p<0.001). The normal group had SNRL1-L4 of 134.7 (101.6), the osteopenia group had 153.9 (145.2), and the osteoporosis group had 212.6 (240.8). There was no statistically significant difference between groups (p=0.470). Data from DEXA and MRI M-scores were compared. M-scores in the normal group were 15.57 (22.41), 21.78 (25.91) in the osteopenia group, and 31.98 (29.76) in the osteoporosis group (p<0.001). The M-score was higher in the osteoporosis group than in the normal and osteopenia groups.

The diagnostic efficacy of SNRL1-L4 and M-scores in distinguishing osteopenia from the control group was assessed. Accordingly, the AUC (95% CI)=0.541 for SNRL1-4 is not statistically significant (p=0.361). ROC curve analysis of the M-score to identify osteopenic women from normal women indicated an AUC=0.595 with a 95% confidence interval and a diagnostic ability of 82.1% sensitivity and 36.3% specificity using a threshold of 10.3 (p=0.030). Despite the fact that the AUC value is significant, the ROC curve is quite close to the diagonal line.

The diagnostic performance of SNRL1-L4 and the M-score in differentiating osteoporosis from the normal group was assessed. Accordingly, the AUC (95% CI)=0.573 for SNRL1-4 is not statistically significant (p=0.420). ROC curve evaluation of the M-score to differentiate osteoporotic women from normal women revealed an AUC=0.799 with a 95% confidence interval and a diagnostic ability of 80.9% sensitivity and 69.3% specificity using 26.26 as the threshold (p<0.001).

The diagnostic efficacy of SNRL1-L4 and the M-score in differentiating osteoporosis and osteopenia groups was evaluated. Accordingly, the AUC (95% CI)=0.532 value for SNRL1-4 was not statistically significant (p=0.710). ROC curve evaluation of the M-score to differentiate osteoporotic women from osteopenic ones revealed an AUC=0.703 with a 95% confidence interval and a diagnostic ability of 80.9% sensitivity and 60.3% specificity using 23.8 as the threshold (p<0.001).

Table 2 shows the relationship between M-score and age, BMI, postmenopausal years, T-score, Z-score, L1-4 BMD, Genant grade, and BMD in all patients, normal, osteopenic,

Table 2. Association of M score with age, BMI, postmenopausal years, T score, Z score, L1-4 BMD', genant grade and BMD in all patients, normal, osteopenic and osteoporotic patients

	All Cases		Normal		Osteopenia		Osteoporosis	
	rho	p	rho	p	rho	p	rho	p
Age	0.027	0.704	-0.004	0.968	-0.074	0.511	0.057	0.805
BMI	**-0.182**	**0.010**	-0.114	0.264	-0.182	0.104	-0.345	0.125
Postmenopausal years	0.112	0.115	0.158	0.120	-0.059	0.600	-0.180	0.435
T Score	**-0.166**	**0.019**	-0.035	0.732	0.056	0.622	0.271	0.234
Z Score	**-0.192**	**0.006**	-0.087	0.394	-0.072	0.524	0.213	0.353
L1-4 BMD	-0.089	0.209	-0.038	0.710	0.168	0.134	0.164	0.478
Genant grade	0.046	0.518	-0.111	0.277	0.151	0.177	0.001	0.999
BMD	**-0.153**	**0.031**	-0.015	0.881	0.082	0.466	0.264	0.248

BMI: Body mass index; BMD: Bone mineral density; rho: Spearman correlation coefficient; BMC: bone mineral content.

Table 3. Association of SNR L1-4 with age, BMI, postmenopausal years, T score, Z score, L1-4 BMD, genant grade and BMD in all cases, normal, osteopenic and osteoporotic patients

	All cases		Normal		Osteopenia		Osteoporosis	
	rho	p	rho	p	rho	p	rho	p
Age	-0.022	0.755	-0.033	0.749	0.052	0.643	-0.137	0.553
BMI	**-0.241**	**0.001**	**-0.210**	**0.038**	**-0.227**	**0.042**	-0.265	0.247
Postmenopausal years	-0.050	0.484	-0.008	0.940	-0.029	0.794	-0.302	0.183
T Score	-0.010	0.889	-0.005	0.964	0.049	0.666	0.206	0.370
Z Score	-0.050	0.484	-0.030	0.766	-0.027	0.810	0.046	0.842
L1-4 BMD	-0.002	0.978	0.041	0.691	-0.018	0.874	0.086	0.712
Genant grade	-0.055	0.436	-0.104	0.310	-0.072	0.574	0.185	0.423
BMD	-0.008	0.914	0.012	0.903	0.035	0.754	0.101	0.662

BMI: Body mass index; BMD: Bone mineral density; rho: Spearman correlation coefficient.

Table 4. Relationship between SNR L1-4 and M score in all patients, normal, osteopenia and osteoporosis groups

	M score							
	All cases		Normal		Osteopenia		Osteoporosis	
	rho	p	rho	p	rho	p	rho	p
SNR L1-4	0.391	<0.001	0.345	0.001	0.395	<0.001	0.565	0.008

SNR: Signal-to-noise ratio; rho: Spearman correlation coefficient.

and osteoporotic groups. As a result, in all patients, there was a statistically significant but very weak negative connection between M-score and BMI, T-score, Z-score, and BMD. In the normal, osteopenia, and osteoporosis groups, there is no statistically significant correlation between M-score and other variables.

When the relationship of SNRL1-4 with age, BMI, postmenopausal years, T-score, Z-score, L1-4 BMD, Genant grade, and BMD was examined in all subjects, normal, osteopenia, and osteoporosis groups, there was a statistically significant weak negative correlation between SNRL1-4 and BMI (Table 3). The other variables have no statistically significant relationship.

There was a statistically significant weak positive correlation between SNRL1-4 and M-score in all cases (normal, osteopenia, and osteoporosis groups) when the relationship between SNRL1-4 and M-score was evaluated. There is a statistically significant, moderately positive correlation between SNRL1-4 and M-score in the osteoporosis group (Table 4).

Discussion

In the literature, Shen et al.[23,24] and Shah and Hanrahan[25] have shown that bone marrow signal intensity on MRI standard T1-weighted images are negatively correlated with BMD and osteoporosis and that MRI can detect osteoporosis. MRI was used by Bazzocchi et al.[26] to diagnose osteoporosis-related fragility fractures. Bandirali et al.[21] also sought to design a novel quantitative lumbar spine MRI-based approach for osteoporosis detection using conventional T1-weighted images.

Due to correlations between the MRI-based score (M-score) and radiologic indices obtained using dual-energy X-ray absorptiometry (DEXA), it has been reported that MRI can be used as a screening tool for the detection or suspicion of osteoporosis[13]. In our study, we found findings that agreed with the primary idea of the studies by Bandirali et al.[21] and Saad et al.[13] on the M-score's high sensitivity and specificity, as well as its utility as a screening tool. The M-score correlated with the DEXA test as the reference gold standard in osteoporosis and had a sensitivity of 80.9% and a specificity of 69.3% in our study. Unlike the studies in the literature, no significant correlation was found between SNRL1-L4 and BMD and other DEXA parameters. We found a statistically significant but weak negative correlation between the M-score and BMD, in accordance with the literature, and also between the M-score and BMI, T-score, and Z-score. There was a statistically significant moderately positive correlation between SNRL1-L4 and the M-score in the osteoporosis group. This suggests that the

M-score should be considered a reproducible, noninvasive, and ionizing radiation-free technique that can be used in diagnosis and follow-up. The M-score threshold in osteoporosis was determined to be 3.5 in Saad et al.'s study, 5.5 in Bandiralli et al.'s study, and 26.26 in our study. This variation in the M-score threshold might be attributed to the varied SNR values offered by each MRI scanning device, as well as the sample size and type; our sample included postmenopausal women at high risk of developing osteopenia or osteoporosis, with a heterogeneous and predominantly high BMI distribution. It has been reported that lumbar BMD may increase in patients with obesity and spinal degenerative disease and may give the false impression that these patients have a low fracture risk[27,28]. Planning more comprehensive studies by expanding the subgroups may be instructive in elucidating these differences. The diagnosis of osteoporosis by DEXA scanning is based on the T-score and not BMD[16]. Therefore, the M-score measured by MRI has been reported to be used as a predictor of osteoporosis and a parameter to be correlated with the T-score calculated by DEXA with good diagnostic performance[13]. We think that the statistically significant weak negative correlation found between M-score and T-score and Z-score and BMD when all cases were evaluated in our study will reveal more significant correlations when studied with larger case groups.

In our study, the effectiveness of lumbar MRI M-score and SNRL1-4 measurement data in identifying and differentiating osteoporosis, osteopenia, and normal groups suggests that it can be used as a quantitative tool in osteoporosis screening. The fact that MRI-based quantitative analysis does not involve ionizing radiation is also important in terms of reproducibility.

In our study, the mean time between MRI and DEXA was short, and we think that this did not affect the correlation between them. However, our study has some limitations. First, M-score thresholds may differ between centers as each MRI system provides different SNR values. Second, manual placement of ROIs may have limitations. We tried to avoid this as much as possible by placing the ROIs in a standard central position within the vertebral body, excluding cortical bone, subchondral abnormalities, focal lesions (e.g., hemangiomas), and the posterior venous plexus, and placing the out-patient ROI in a standard position 1 cm away from the vertebral body at the L2-3 level. However, the large SD values of L1-4 SNR may be due to our small sample size or technical differences. As a final limitation, our study group consisted of postmenopausal women, who form a more homogenous group due to the higher risk of osteoporosis. Multicenter studies with larger sample sizes, including both men and women, using a wider age range would be useful for reference values.

Conclusion

M-score measurement, which we found to be significantly correlated with DEXA data, can be used as a non-invasive, easy, reliable, and reproducible screening tool in the standard lumbar MRI protocol as part of routine lumbar MRI examination, particularly in postmenopausal women or individuals at risk of osteoporosis. Early diagnosis may help reduce the risk of fracture. Technological advances and large cohort studies that ensure inter-center agreement will be useful in assessing the efficacy of the MRI-based scoring method in this context.

Ethics Committee Approval: The study was approved by the Dr. Lütfi Kırdar City Hospital Clinical Research Ethics Committee (no: 2023/514/246/2, date: 29/03/2023).

Peer-review: Externally peer-reviewed.

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Authorship Contributions: Concept: H.G.D.; Design: H.D.G., Ö.A.K.; Data Collection or Processing: N.F.; Analysis or Interpretation: H.G.D., Ö.A.K., N.F.; Literature Search: H.G.D.; Writing: H.G.D.; Critical Review: H.G.D., Ö.A.K., N.F.

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