ORIGINAL RESEARCH



Associations between trabecular bone score and bone mineral density in Taiwanese older adult men

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Abstract

Osteoporosis is a common bone disease in older adults, and it is a predictor of bone fracture. This study determined the mean trabecular bone score (TBS) of older Taiwanese men in different age groups and analyzed the effectiveness of TBS in predicting osteoporosis risk. A total of 1568 men aged 50 and older were enrolled. The demographic characteristics; bone mineral density (BMD) T-scores of the spine, total hip, and femoral neck; and TBS of the spine were recorded to statistically determine osteoporosis-related factors. The average age (range) of the included patients was 59.5 \pm 7.5 (50.0–92.7) years. The mean (range) TBS was 1.386 \pm 0.073 (0.999–1.605). The TBS was moderately and positively correlated with the BMD T-scores of the spine, total hip, and femoral neck (r = 0.516, 0.499, and 0.480, respectively). The lowest of the BMD T-scores measured at multiple sites revealed a higher rate of osteoporosis (5.5%) than did BMD T-scores measured at individual sites. Moreover, bone microarchitecture degradation was noted in 2.2% of the patients. Compared with the use of BMD alone, a combination of BMD and TBS predicted more patients (1.4%) to be at a high risk of osteoporosis. Combining the lowest BMD and TBS revealed that 20.3% of patients aged \geq 70 years had a high risk of osteoporosis. TBS can be used to clinically assess the risk of osteoporosis in older adults without osteoporosis. We recommend combining the lowest BMD T-score and TBS for predicting the risk of osteoporosis.

Keywords

Trabecular bone score; Bone mineral density; Osteoporosis; DXA; Older men

1. Introduction

With the rapid aging of the world population [1, 2], agingrelated diseases have become a major public health concern worldwide. Osteoporosis is a systemic disease characterized by low bone mass and bone tissue microarchitecture degradation; it is common in older adults and is a predictor of bone fracture [3]. Osteoporotic fractures have become an increasing burden among countries in the Asia-Pacific region [4]. Taiwan has been classified as being at a "very high" risk of osteoporotic fractures, and it is the only country to be classified as such [5]. Records from Taiwan's National Health Insurance Research Database for the period 1999-2001 indicated an increase in the estimated prevalence of osteoporosis, but osteoporosis diagnoses were made in only 1.63% and 11.35% of male and female adults aged older than 50 years, respectively; these underestimations are consistent with the global trend [6]. A study based on the Nutrition and Health Survey in Taiwan from 2005 to 2008 reported that the prevalence rates of osteoporosis in male and female adults aged older than 50 years were 23.9% and 38.3%, respectively [7]. Therefore, from the perspective of public health, the problem of osteoporosis is expected to become increasingly urgent.

Currently, bone mineral density (BMD), measured through dual-energy x-ray absorptiometry (DXA), is the gold standard for diagnosing osteoporosis and is used to assess fracture risk [3, 8, 9]. The World Health Organization (WHO) recommends the use of the T-score at the femoral neck (FN) for diagnosing osteoporosis [10], whereas the International Society for Clinical Densitometry (ISCD) recommends using the lowest of the T-scores measured at the lumbar spine (L1-L4), FN, or total hip [11]. However, approximately half of patients with bone fractures exhibit normal bone density or low bone mass measured according to BMD T-scores [12]. The risk of bone fracture depends on the strength of the bone, including its mass and quality (e.g., microarchitecture). In addition, the risk of osteoporosis in patients with bone fractures has been underestimated because BMD can be used to assess only bone mass and not bone quality [13-15].

The trabecular bone score (TBS) is a noninvasive and novel measure of bone microarchitecture. It can be derived through the analysis of texture changes in previously obtained standard grayscale lumbar spine BMD images [16]. As a measure of bone microarchitecture, the TBS contributes to the evaluation of bone strength and facilitates the estimation of fracture risk without fully relying on BMD [17–19]. Furthermore, the

TBS is useful for evaluating the effectiveness of pharmacological treatments for osteoporosis [20, 21] and for assessing fracture risk in healthy older adults and patients with chronic diseases [22, 23]. Studies have demonstrated the effectiveness of the TBS in predicting osteoporosis and have indicated that a combination of BMD and the TBS can predict the risk of osteoporosis and fracture more effectively than can BMD alone [13, 24–26]. However, these studies have focused mainly on white women. A similar study involving a patient sample of Asian men has yet to be conducted.

To fill the aforementioned research gap, the present study was conducted to determine the mean TBS of older Taiwanese men in different age groups; to analyze the association between the TBS, demographic characteristics, and BMD; and to assess the value of the TBSs in predicting fracture risk.

2. Materials and methods

2.1 Research design and participants

This retrospective study was conducted at a single medical center. We identified and reviewed the DXA and TBS data of 4770 male patients for the period from June 2018 to June 2020. The inclusion criteria were as follows: (1) being a male patient aged 50 years or older, (2) having a DXA record of qualified BMD in at least two body parts (lumbar spine and hip), and (3) having a body mass index (BMI) between 15 and 37 kg/m². The exclusion criteria were as follows: (1) not having TBS or BMD data or (2) having records indicating a compression fracture at the lumbar spine. On the basis of these criteria, 3202 patients were excluded; thus, a total of 1568 patients were included in this study. All patients were divided into three age groups at 10-year intervals (50–59, 60–69, and \geq 70 years).

2.2 BMD measurement

BMD measurements at the lumbar spine (L1-L4) and hip region were obtained using a central DXA scanner (Discovery Wi, Hologic, Bedford, MA, USA) operated using software supplied by the manufacturer (version 13.3.5.2). The scanning parameters were as follows: dual-energy voltage, 140/100 kVp; average current, 2.5 mA; and scan mode, 41 s fast array at 60 Hz. Before the measurements, a Hologic phantom was used for daily calibration (calibration standard), and the maximum precision error of the scanner was 0.27% (percentage of the coefficient of variation). The scans were performed by an experienced technician certified by the ISCD, and the least significant change was 1.94% for the spine, 2.13% for the total hip, and 3.41% for the FN. According to the WHO criteria, a Tscore of ≤ -2.5 indicates osteoporosis, a T-score between -2.5and -1 indicates low bone mass, and a T-score of ≥ -1 indicates normal bone density. For the BMD T-score calculations, we used the manufacturer-provided NHANES III corrected reference range for a population of young white women.

2.3 TBS assessment

The TBS at the spine was analyzed using the DXA data for the lumbar spine (L1–L4) and TBS iNsight software (version 3.0; Med-Imaps SASU, Merignac, France), and the precision error

was 1.33%. The derived TBS was divided into three categories for Asian populations [27]: a TBS of \geq 1.310 indicates a normal bone microarchitecture, a TBS between 1.230 and 1.310 indicates a partially degraded bone microarchitecture, and a TBS of \leq 1.230 indicates a degraded bone microarchitecture.

2.4 Association between TBS and BMD

To analyze the associations between the BMD of the spine, total hip, and femoral neck with spine TBS and demographic variables, Pearson correlation coefficients were used. A subgroup analysis was performed on three age groups, namely, 50 to 59 years, 60 to 69 years, and 70 years or older.

2.5 Diagnosis of osteoporosis according to BMD T-Score and TBS

According to WHO criteria, a T-score less than or equal to -2.5 indicates osteoporosis. The prevalence of osteoporosis according to T-score values from the BMD data for the spine, FN, and total hip and the lowest T-score of the spine, FN, and total hip was assessed. The prevalence of osteoporosis was determined using a combined BMD and TBS assessment; for analysis, patients with a lowest T-score of the spine, FN, and total hip of less than or equal to -2.5 or a degraded TBS (TBS of ≤ 1.230) were included. A subgroup analysis was performed on three age groups (50 to 59 years, 60 to 69 years, and 70 years or older).

2.6 Inconsistent selection conditions between TBS and BMD

To analyze the discrepancies between the assessments performed using BMD and those using TBS, all patients were divided into nine groups according to the lowest BMD T-score (normal bone density, low bone density, and osteoporosis) and TBS categories (normal TBS, partially degraded TBS, and degraded TBS). A subgroup analysis was also performed on three age groups (50 to 59 years, 60 to 69 years, and 70 years or older).

2.7 Statistical analysis

We used descriptive statistics to describe the patients' age, height, weight, BMI, TBS, and BMD. Each patient's BMI was calculated by dividing their weight by the square of their height (kg/m²). The demographic variables and the BMD and TBS of three age groups were compared using one-way analysis of variance with Tukey's post hoc test, and p < 0.017 (0.05/3) was considered statistically significant. The correlations among the variables were determined using a Pearson's two-tailed test for every age group distribution; a p value of < 0.05 was considered statistically significant. The chi-square test was performed to determine consistency between BMD and the TBS in predicting osteoporosis. Regression standardization was used for Pearson's one-tailed test to predict the TBS, with significance set at p < 0.05.

TABLE 1. Baseline characteristics of patients.							
	Total	50–59 yr	60–69 yr	≥70 yr	50–59 yr <i>vs.</i> 60–69 yr	50–59 yr <i>vs.</i> ≥70 yr	60–69 yr <i>vs.</i> \geq 70 yr
	(n = 1568)	(n = 952)	(n = 458)	(n = 158)			
Age, yr	59.5 ± 7.5	54.6 ± 2.8	64.2 ± 2.9	75.5 ± 4.9			
	(50.0–92.7)	(50.0–60.0)	(60.0–70.0)	(70.0–92.7)			
Height, m	1.69 ± 6.1	1.70 ± 5.9	1.67 ± 5.51	1.65 ± 6.1	< 0.0001	< 0.0001	< 0.0001
	(1.40–1.90)	(1.40–1.90)	(1.51–1.83)	(1.49–1.80)			
Weight, kg	71.1 ± 10.2	72.8 ± 10.1	59.5 ± 9.8	65.4 ± 9.2	< 0.0001	< 0.0001	< 0.0001
	(40.5–107.3)	(41.3–103.7)	(40.5–107.3)	(46.3–90.5)			
BMI, kg/m ²	24.8 ± 3.0	25.0 ± 3.0	24.8 ± 3.0	24.3 ± 3.2	0.6017	0.0191	0.1326
	(15.2–36.8)	(16.4–36.8)	(15.2–36.1)	(17.2–32.0)			
Spine BMD, g/cm ²	0.988 ± 0.149	0.986 ± 0.140	0.993 ± 0.158	0.983 ± 0.175	0.6380	0.9785	0.7385
	(0.563–1.591)	(0.592–1.591)	(0.584–1.529)	(0.563 - 1.485)			
Femoral neck BMD, g/cm ²	0.751 ± 0.121	0.772 ± 0.111	0.735 ± 0.123	0.672 ± 0.123	< 0.0001	< 0.0001	< 0.0001
	(0.377–1.172)	(0.452–1.172)	(0.432–1.150)	(0.377–1.052)			
Total Hip BMD, g/cm ²	0.921 ± 0.131	0.941 ± 0.120	0.909 ± 0.135	0.840 ± 0.144	< 0.0001	< 0.0001	< 0.0001
	(0.496–1.363)	(0.496–1.363)	(0.539–1.293)	(0.504–1.240)			
Spine TBS	1.386 ± 0.073	1.400 ± 0.068	1.373 ± 0.072	1.345 ± 0.082	< 0.0001	< 0.0001	< 0.0001
	(0.999–1.605)	(1.107–1.605)	(1.057–1.569)	(0.999–1.545)			

TABLE 1. Baseline characteristics of patients.

BMI, body mass index; BMD, bone mineral density; TBS, trabecular bone score.

3. Results

3.1 Basic characteristics

This study included 1568 older Taiwanese older men with a mean age of 59.5 ± 7.5 years (Table 1). The mean TBS, mean total hip BMD, and mean FN BMD exhibited a gradual decreasing trend with increasing age in all age groups; nevertheless, the mean spine BMD did not exhibit such a trend.

3.2 Correlation between TBS and BMD

Significant correlations were observed between spine TBS and spine BMD and between total hip BMD and FN BMD (0.516, 0.499, and 0.480; Fig. 1). Spine TBS was weakly and negatively correlated with age (r = -0.283) and weakly and positively correlated with height (r = 0.196). This study also evaluated Pearson correlation coefficients (r values) between every pair of variables in each age group, as presented in **Supplementary material**. We also established subgroups according to age (50–59, 60–69, and \geq 70 years) and observed that spine TBS exhibited a significant negative correlation with age (r = -0.116, -0.124, and -0.218) and significant positive correlations with spine BMD (r = 0.590, 0.470, and 0.468), total hip BMD (r = 0.487, 0.441, and 0.467), and FN BMD (r = 0.459, 0.432, and 0.415) in these groups (**Supplementary Table 1**).

3.3 Diagnosis of osteoporosis according to BMD T-Score and TBS

According to the WHO criteria, a T-score of ≤ -2.5 indicates osteoporosis. Using the BMD data derived for the spine, FN, and total hip, we diagnosed osteoporosis in 51 (3.3%), 50 (3.2%), and 6 (0.4%) older men in our study, respectively. Using the lowest T-score derived for the spine, FN, and total hip, we diagnosed osteoporosis in 87 (5.5%) older men in our study (Table 2). The distribution of patients with osteoporosis in the three age groups (50–59, 60–69, and \geq 70 years) is presented in Table 3. Similar to the results observed in the complete sample, the prevalence of osteoporosis identified using the lowest T-score for the spine, FN, and total hip in the age subgroups was higher than that identified using the scores at an individual site. In our subgroups established according to age (50–59 years, 60–69 years, and \geq 70 years), the prevalence of osteoporosis increased with age.

According to the TBS assessment, 35 patients had a degraded bone microarchitecture and 170 had a partially degraded bone microarchitecture. The ratios of patients with a degraded bone microarchitecture also increased with age. The prevalence of bone microarchitecture degradation in the patients was lower than that of osteoporosis (Table 3). Subsequently, the TBS and BMD were combined to predict the risk of osteoporosis; this combination predicted an increased proportion of patients (from 5.5% to 6.9%) to be at a high risk of osteoporosis. In the age subgroups, up to 20.3% of patients in the \geq 70-year-old subgroup had a high risk of osteoporosis (Table 2).

3.4 Inconsistent selection conditions between TBS and BMD

Table 3 presents the distribution of BMD and TBS assessments in the various age groups. When the TBS and BMD were combined for assessment, only 14 patients were determined to have both osteoporosis and a degraded bone microarchitecture. Among the patients without osteoporosis, 0.8% (7/907) of those with a normal bone density had a degraded bone microarchitecture and 2.4% (14/574) of those with low bone mass had a degraded bone microarchitecture.

4. Discussion

We retrospectively reviewed the demographic records and DXA-derived BMD and TBS data of older Taiwanese men, and we analyzed the correlations between these variables. The lowest of the BMD T-scores measured at multiple designated sites were associated with a higher rate of osteoporosis (5.5%) than did those measured at individual sites. Moreover, 2.2% (35/1568) of the patients had bone microarchitecture degradation. We observed that in our patients, the osteoporosis prevalence that was predicted using a combination of the TBS with the lowest of BMD T-scores at multiple sites increased by 1.4% compared with the prevalence that was predicted using only BMD T-scores at individual sites. The osteoporosis prevalence predicted by combining the lowest BMD and the TBS was as high as 20.3% in our subgroup of patients aged ≥ 70 years.

The prevalence of osteoporosis in older men is lower than that in older women, and one in five older men is expected to experience an osteoporotic fracture [28, 29]. Previous Taiwanese studies have estimated men to have higher BMD and TBS values compared with women [30, 31]. The mean TBS in our study was 1.386 \pm 0.073, which is similar to those reported by studies on men in southern Taiwan (mean TBS: 1.392 \pm 0.089, age range 30–90 years) and men in Korea (mean TBS: 1.383 ± 0.097 , age range 40–69 years) [31, 32]. Furthermore, the mean TBS in our study is higher than those reported in studies on 894 Australian men (mean TBS: 1.226 ± 0.153 , age range 24–98 years) and 811 Canadian men (mean TBS: 1.297 \pm 0.107, age range \geq 40 years) [33– 35]. According to the findings of our study and those of other studies on men, East Asian participants had higher TBS values than Western participants. However, these findings require further investigation.

Our results indicate that the TBS had a significant negative correlation with age. Among the three age groups, the \geq 70-year group had the lowest mean TBS, and this finding is similar to that of a previous Taiwanese study [31]. We also noted decreased TBS with age in patients, a finding that is consistent with those of previous studies on healthy men and women in Mexico, Australia, Thailand, Korea, and Iran [32, 33, 36–38]. These findings suggest that older adults have lower bone quality and strength regardless of ethnicity.

We also studied the correlation between BMD and age; we observed that the FN BMD and total hip BMD exhibited a significant negative correlation with age. However, spine BMD was not significantly correlated with age; this result is similar

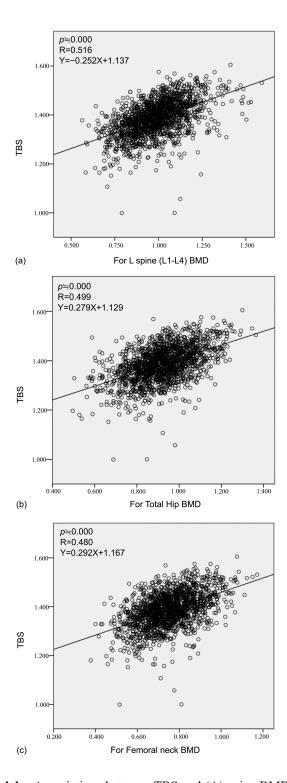


FIGURE 1. TBS regression models. Associations between TBS and (A) spine BMD, (B) total hip BMD, and (C) femoral neck BMD. TBS, trabecular bone score; BMD, bone mineral density; FN, femoral neck.

to that reported in another study [30]. The inconsistency in the trend of BMD with age between the spine and hip regions could be attributed to degenerative spondylopathy, which may lead to more osteophytes and subchondral sclerosis in older adults. Degenerative spondylopathy engenders abnormally high densities and may even lead to a false-negative BMD assessment. Numerous studies have reported similar results, and it has been argued that TBS could be a superior predictor of osteoporosis than BMD, especially in older patients with significant osteophytes, osteoarthritis, and spondyloarthritis in the lumbar spine [39–42]. Our study also indicated that the spine TBS exhibited a significant negative correlation with age in all groups. According to our results and those of previous studies, the spine TBS is more suitable than spine BMD for the evaluation of spinal bone health in older adults.

According to WHO recommendations, we applied FN BMD to assess the risk of osteoporosis. We observed that only 3.2% of all patients in our study could be classified as having osteoporosis. However, the ISCD officially recommends using the lowest BMD T-score at the spine, FN, and total hip to

TABLE 2. Numbers of patients at high risk of fracture in different age groups, as determined by combining BMD T-scores (T-score ≤-2.5) and TBS values (TBS ≤1.230).

	T-score of BMD ≤ -2.5				TBS ≤1.230	Combined lowest BMD and TBS [#]
	Spine	FN	Total hip	Lowest*		
All (n = 1568)	51 (3.3%)	50 (3.2%)	6 (0.4%)	87 (5.5%)	35 (2.2%)	108 (6.9%)
50–59 yr (n = 952)	26 (2.7%)	11 (1.2%)	1 (0.1%)	30 (3.2%)	8 (0.8%)	34 (3.6%)
60–69 yr (n = 458)	17 (3.7%)	20 (4.4%)	2 (0.4%)	31 (6.8%)	16 (3.5%)	42 (9.2%)
\geq 70 yr (n = 158)	8 (5.1%)	19 (12.0 %)	3 (1.9%)	26 (16.5%)	11 (7.0%)	32 (20.3%)

*Lowest: participants for whom the lowest T-score for the spine, FN, or total hip was ≤ -2.5 .

#Combination of the lowest values (BMD and TBS): participants for whom the lowest T-score was ≤ -2.5 or TBS was ≤ 1.230 . TBS, trabecular bone score; BMD, bone mineral density; FN, femoral neck.

TABLE 5. Relationships between TBS and DND across unterent age groups.							
TBS assessments	Normal TBS	Partially degraded TBS	Degraded TBS				
Total $(n = 1568)$	1363 (86.9%)	170 (10.8%)	35 (2.2%)				
50–59 yr (n = 952)	863 (90.7%)	81 (8.5%)	8 (0.8%)				
Normal bone density $(n = 609)$	588 (96.6%)	21 (3.4%)	0 (0.0%)				
Low bone mass $(n = 313)$	260 (83.1%)	49 (15.7%)	4 (1.3%)				
Osteoporosis (n = 30)	15 (50.0%)	11 (36.7%)	4 (13.3%)				
60-69 yr (n = 458)	385 (84.1%)	57 (12.4%)	16 (3.5%)				
Normal bone density $(n = 245)$	223 (91.0%)	16 (6.5%)	6 (2.4%)				
Low bone mass $(n = 182)$	148 (81.3%)	29 (15.9%)	5 (2.7%)				
Osteoporosis $(n = 31)$	14 (45.2%)	12 (38.7%)	5 (16.1%)				
\geq 70 yr (n = 158)	115 (72.8%)	32 (20.3%)	11 (7.9%)				
Normal bone density $(n = 53)$	48 (90.6%)	4 (7.5%)	1 (1.9%)				
Low bone mass $(n = 79)$	53 (67.1%)	21 (26.6%)	5 (6.3%)				
Osteoporosis ($n = 26$)	14 (53.8%)	7 (26.9%)	5 (19.2%)				

TABLE 3. Relationships between TBS and BMD across different age groups.

TBS, trabecular bone score.

predict the risk of osteoporosis. When we applied the ISCD recommendation, we determined that 5.5% of the patients had osteoporosis. Our results are similar to those of a previous study that used the lowest T-score across multiple sites to assess osteoporosis risk in women aged over 45 years and to diagnose osteoporosis in older Chinese adults [30].

Studies have suggested that the TBS could serve as a complementary measure to DXA, especially in patients with normal bone density or low bone mass, as determined on the basis of BMD [21, 26, 43-45]. Moreover, data regarding the association between the TBS and BMD in men are lacking; therefore, these measures are not commonly used among older men. Our results reveal that among the patients with normal bone density or low bone mass-as determined on the basis of BMD-1.4% (21/1481) had a degraded bone microarchitecture and 9.5% (140/1481) had a partially degraded bone microarchitecture. Furthermore, our results indicate that combining the lowest BMD T-score across multiple sites with the spinal TBS predicted an increased prevalence of osteoporosis from 5.5% to 6.9% in the older age group. These results are consistent with those of previous studies and suggest that spinal TBS is useful for predicting osteoporosis risk in both older men and women.

Several studies have reported a negative correlation between BMI and the TBS and a positive correlation between BMI and lumbar spine BMD [19, 46]. Similarly, our study revealed that BMI was positively correlated with spine BMD, FN BMD, and total hip BMD in all age groups. Nevertheless, we also observed no significant correlation between the TBS and BMI in patients aged >70 years. Osteoporosis rates increase with age, but in our sample, we excluded patients with compression fractures at the lumbar spine; this possibly caused a sampling error because the entire population of older men was not adequately represented. Future research should collect more data to investigate the association between the TBS and BMI in older men aged >70 years.

This study has some limitations. First, our study had a retrospective design and included a sample of patients selected from a single hospital of clinical population; therefore, the study population may not adequately represent the entire population of older adults in Taiwan and may not be representative of the broader general population. Second, we did not review the spinal x-ray data of all patients; therefore, we may have included patients with improper vertebrae. Finally, several clinical risk factors for osteoporosis were not considered, such as lifestyle, family history, and medical history.

A future BMD and TBS can be used in combination to predict osteoporosis in a greater number of older adult Taiwanese men. Because the incidence of osteoporosis is the highest among older adult men, clinicians should pay careful attention to TBS degradation among older patients without low BMD.

5. Conclusions

By combining the lowest BMD and TBS for prediction, we observed that the prevalence of osteoporosis increased with age in older Taiwanese men and that up to one-fifth of older Taiwanese men aged \geq 70 years exhibited a high risk of osteoporosis. Furthermore, we noted that several patients with normal bone density and low bone mass exhibited a degraded bone microarchitecture. To avoid underestimating the risk of osteoporosis, we recommend combining the lowest BMD and TBS to predict osteoporosis risk.

ABBREVIATIONS

TBS, trabecular bone score; BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry; WHO, World Health Organization; ISCD, International Society for Clinical Densitometry; BMI, body mass index; FN, femoral neck.

AVAILABILITY OF DATA AND MATERIALS

The data are contained within this article and supplementary material. The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

MLH, TJH, and SSL—Conceptualization; MLH, TJH, WCH, and SSL—methodology; MLH and TJH—software; MLH, TJH, WCH, and SSL—validation; MLH, TJH, and WCH—formal analysis; MLH, TJH, and SSL—investigation; MLH, TJH, and SSL—resources; MLH and TJH—data curation; MLH—writing—original draft preparation; TJH and SSL—writing—review and editing; TJH—visualization; TJH and SSL—supervision; MLH—project administration; MLH—funding acquisition. All authors have read and agreed to the published version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This retrospective cohort study was approved by our local institutional review board (IRB Serial No.:11005-011). Because the patients remained anonymous and the images and clinical data were deidentified, the requirement for informed consent was waived.

ACKNOWLEDGMENT

We would like to express our respect and gratitude to the patients who accepted to participate in this study. The authors also wish to thank the BMD technologists team for their help and contribution making this study possible.

FUNDING

This study was supported by Chi Mei Medical Center (grant number: CMFHR 11193).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.jomh.org/ files/article/1619939713184874496/attachment/ Supplementary%20material.docx.

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How to cite this article: Mei-Lan Huang, Tsyh-Jyi Hsieh, Song-Shei Lin, Wen-Chuan Huang. Associations between trabecular bone score and bone mineral density in Taiwanese older adult men. Journal of Men's Health. 2023; 19(1): 15–22. doi: 10.22514/jomh.2023.005.