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ORIGINAL ARTICLE

# TBS as a complementary tool for assessing vertebral fractures and spinal deformity in children and adolescents with osteogenesis imperfecta

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## Abstract

**Summary** This study evaluated trabecular bone score (TBS) for assessing vertebral fractures and spinal deformity in children and adolescents with osteogenesis imperfecta (OI). TBS showed superior performance in identifying vertebral fractures compared to areal bone mineral density (aBMD), especially in patients without densitometric osteoporosis, suggesting its potential for monitoring vertebral fractures and spinal deformity risk.

**Background** TBS, derived from a textural greyscale analysis of lumbar spine dual-energy X-ray absorptiometry (DXA) images, offers a non-invasive and indirect evaluation of bone microarchitecture. This method potentially enhances the assessment of skeletal phenotypes beyond the scope of aBMD. We aim to explore the utility of TBS in assessing vertebral fractures and spinal deformity in children and adolescents with OI.

**Methods** In this cross-sectional study, 153 children and adolescents with OI were enrolled. DXA was used to measure TBS and aBMD, and their Z-scores were calculated based on reference values for BMD and TBS in normal children and adolescents with the same age and sex. Lateral thoracolumbar films were used to evaluate vertebral fractures and calculate the spine deformity index (SDI). The accuracy of TBS and aBMD for identifying vertebral compression fractures (VCFs) was assessed using area under the curve (AUC).

**Results** TBS Z-score was negatively correlated with the age of children with OI ($r = -0.435$, $P < 0.001$) and was positively correlated to aBMD Z-score at the lumbar spine and femoral neck (both $P < 0.01$), even after adjusting for confounding factors. TBS Z-score was as effective as lumbar spine aBMD Z-score in discriminating VCFs (AUC, 0.667 vs 0.666, $P > 0.05$). Notably, in patients without densitometric osteoporosis, TBS Z-score demonstrated superior discriminative power for VCFs compared to lumbar spine aBMD Z-score (AUC, 0.719 vs 0.545, $P < 0.05$). In this population, only the TBS Z-score ($r = -0.358$, $P < 0.05$), rather than the lumbar spine aBMD Z-score, was negatively correlated with the SDI.

**Conclusion** TBS has a close correlation with bone mineral density in children and adolescents with OI. In patients without densitometric osteoporosis, the Z-score of TBS is more effective than that of bone mineral density in assessing VCFs and spinal deformity, highlighting the potential of TBS in evaluating the risk of VCFs and monitoring the progression of spinal deformity.

**Keywords** Osteogenesis imperfecta · Spinal deformity · Trabecular bone score · Vertebral compression fracture

## Introduction

Osteogenesis imperfecta (OI), also known as "brittle bone disease," is a group of clinically and genetically heterogeneous skeletal disorders, with an estimated incidence of 1 in 15,000 to 20,000 live births [1, 2]. OI is characterized by impaired bone material properties, which lead to a susceptibility to bone fractures, progressive bone deformity, and short stature [3]. According to the Sillence classification, OI is primarily divided into four clinical types: type I (mild OI), type II (perinatal lethal OI), type III (progressively deforming OI), and type IV (moderate OI between type I and type III) [4]. The majority of OI cases are caused by pathogenic variants in *COL1A1* or *COL1A2* genes, which encode chains of type I collagen [5]. Recently, new pathogenic genes have been identified in patients with OI that affect the folding,

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posttranslational modification, and processing of type I collagen, bone mineralization, or osteoblast differentiation [1, 6].

Accurate assessment of bone status is essential for judging the severity, formulating treatment strategies, and predicting the prognosis of OI. Dual-energy X-ray absorptiometry (DXA) is widely used to measure areal bone mineral density (aBMD), which is a major determinant of fracture risk in children and adolescents [7, 8]. However, aBMD only accounts for approximately 60–70% of the variation in bone strength, with bone microarchitecture also playing an important role [9, 10]. Furthermore, some patients with OI may not exhibit a relevant decline in lumbar spine aBMD due to their existing vertebral fractures [11]. Recent advancements in imaging have revealed significant defects in the bone microarchitecture of patients with OI [12, 13], highlighting the need for accessible qualitative indexes of bone. The trabecular bone score (TBS) is a grey-level textural index extracted from DXA images of the lumbar spine, which can reflect the deterioration of trabecular microstructure and is minimally influenced by vertebral fractures. In adults with primary osteoporosis and glucocorticoid-induced osteoporosis, lower TBS values are associated with increased risk of major osteoporotic fractures, with this result being independent of BMD values and other clinical risk factors [14–16]. Preliminary studies with small samples suggest that moderate or severe adult patients with OI have TBS values below the threshold for fractures [12, 17], and TBS Z-scores are negatively correlated with fracture rate of pediatric patients with OI [18]. These findings indicate the potential of TBS as a valuable tool for aiding clinical diagnosis and treatment decisions in patients with OI, but large-scale research is still needed to confirm its utility in evaluating skeletal phenotype, fracture risk, and vertebral bone deterioration in patients with OI.

This study aims to investigate the correlations between TBS and its Z-score with age, Sillence classification, aBMD and its Z-score, bone turnover markers, fracture frequency and the spinal deformity index (SDI), and analyze the discriminatory ability of TBS Z-score in identifying vertebral compression fractures (VCFs) in a relatively large sample of children and adolescents with OI.

## Methods

### Study design

In this cross-sectional, single-center study, a large cohort of children and adolescents with OI was recruited from Endocrinology Department of Peking Union Medical College Hospital (PUMCH) between April 2014 and April 2023. The study was approved by the Research Ethics Committee of PUMCH (JS-2081).

### Study population

Children and adolescents under 18 years of age were eligible if they met one of the following inclusion criteria: (1) had a history of fracture under minor trauma, along with the presence of extraskeletal manifestations of OI such as blue sclerae, dentinogenesis imperfecta, or ligamentous laxity [19]; (2) had a variant in pathogenic genes of OI identified by targeted next generation sequencing and confirmed by Sanger sequencing [20]. Patients were excluded if they had any of the following situations: had unmeasurable aBMD at the lumbar spine, femoral neck, or total hip; with a history of bone disorders other than OI; with previous treatment that affects bone metabolism, such as oral or intravenous BPs, subcutaneous injection of denosumab or teriparatide; body mass index (BMI) below 15 kg/m$^2$ or above 37 kg/m$^2$, as TBS analysis is not recommended in these patients [21].

### Genetic diagnosis

Genomic DNA was extracted from peripheral leukocytes of patients with OI using a genomic DNA Extraction Kit (Qiagen). The next generation sequencing (NGS, Illumina HiSeq2000 platform, Illumina Inc., San Diego, CA, USA) was completed using a panel covering 20 known candidate genes of OI and more than 700 genes related to bone disorders [20]. The polymerase chain reaction was applied to amplify the targeted fragment with the variant identified by NGS, which was confirmed by a 3730xl DNA sequencer (Applied Biosystems Inc., Foster City, CA, USA) [20]. The pathogenicity of detected variants was determined according to 2015 American College of Medical Genetics and Genomics (ACMG) guidelines [22] and we have disclosed all genetic data in Supplementary Table 1 [29].

According to the inherited pattern, we categorized patients with OI into autosomal dominant (AD) and non-AD groups. The AD group consisted of patients carrying variants in *COL1A1*, *COL1A2*, or *IFITM5* genes. Patients with variants in other genes were classified as non-AD. For variants in *COL1A1* and *COL1A2* genes, variants resulting in amino acid substitutions in chains of type I collagen were considered collagen structural defects. Nonsense or frameshift variants were categorized as collagen quantitative reductions. Splicing variants were not analyzed in this study due to the difficulty of predicting their effect on collagen metabolism.

### Measurements of serum biochemical markers

Serum levels of calcium (Ca), phosphate (P), and alkaline phosphatase (ALP, a bone formation marker) were measured by an automatic biochemical analyzer (ADVIA 1800, Siemens, Germany). Serum concentrations of 25-hydroxyvitamin D (25OHD), intact parathyroid hormone (PTH), and β-isomerized carboxy-telopeptide of type I collagen (β-CTX, a bone resorption marker) were evaluated by electrochemiluminescence (E170, Roche Diagnostics, Switzerland). All the measurements were completed in the clinical central laboratory of PUMCH.

### Measurement of BMD and TBS

aBMD of the lumbar spine (L1–L4), femoral neck, and total hip were measured by DXA (Prodigy Advance, GE Lunar Corporation, Madison, WI, USA) using software suitable for children. Age- and sex-adjusted Z-scores of aBMD at the lumbar spine and femoral neck were calculated based on the reference data from normal children in China [23]. According to the guidelines of the International Society for Clinical Densitometry (ISCD) for the pediatric population, aBMD Z-score less than or equal to − 2.0 indicated densitometric osteoporosis, and aBMD Z-score higher than − 2.0 indicated no densitometric osteoporosis [24]. The height-for-age Z-score (HAZ)-adjusted spine areal BMD-for-age Z-score ($BMD_{HAZ}$) was evaluated using the reference data from a previous study [25].

TBS was obtained using TBS iNsight v2.1 software (Med-Imaps, Merignac, France) through analyzing the raw data of L1-L4 DXA images. Lumbar TBS was calculated as the mean value of individual measurements for vertebrae L1-L4. Age- and sex-adjusted Z-scores of TBS were calculated using the reference data of healthy children and adolescents obtained from the same DXA devices [26]. Patients with OI were defined as "degraded microarchitecture" if the TBS Z-score was less than or equal to − 2.0 [27].

### Assessment of vertebral compression fractures and spinal morphometry

Lateral thoracolumbar films were completed and VCFs were assessed by a radiologist. According to the Genant semiquantitative approach, the severity of VCFs was categorized into four grades: Grade 0 (normal), Grade 1 (20–25% decrease in anterior, middle, or posterior height of vertebrae), Grade 2 (25–40% decrease in any height of vertebrae), and Grade 3 (40% decrease in any height of vertebrae) (Fig. S1) [28, 29]. The SDI value was calculated by summing the grade of each fractured vertebra from T4 to L4. The SDI value ranged from 0 (no fracture) and 39 (all assessed vertebrae were fractured and the severity was grade 3) [30].

The body height of the patients was measured using a Harpenden stadiometer (Seritex Inc., East Rutherford, NJ, USA). For patients who were unable to stand, body length in the supine position was measured. The body height and weight Z-scores were calculated based on the reference data of Chinese children [31]. To calculate the annual fracture rate, we divided the number of fractures up to the DXA measurement by the age at the DXA scan.

### Statistical analyses

Kolmogorov–Smirnov and Shapiro–Wilk tests were used to determine the normality of the data. Continuous data with a normal distribution, including age, height, weight, BMI, serum levels of biochemical markers, BMD and its Z-score, and TBS Z-score, were presented as mean ± standard deviation (SD) and were compared using one-way ANOVA between OI I, III and IV groups. Continuous data with a non-normal distribution, including age of onset, previous fracture times, annual fracture rate, TBS, and SDI, were presented as median (interquartile range, IQR) and were compared using the Kruskal–Wallis test between three groups. These data were compared using Student's *t*-test or Mann–Whitney test between patients with and without vertebral fractures. Categorical data were expressed as numbers and percentages (%) and were compared using Pearson's chi-square test. Associations were assessed using the $\chi^2$ test for qualitative variables and using the *t*-test and Pearson's correlation coefficient for quantitative variables. Pearson's partial correlation analysis was employed to assess correlations between continuous variables when adjusting for multiple covariates, including sex, height, weight, and clinical classification. The discriminative ability of different measurements for the presence of VCFs was evaluated using receiving operator characteristic (ROC) analysis, and the discriminative values were quantitatively assessed by the area under the ROC curve (AUC). The differences between AUCs were evaluated using the Delong test.

All statistical analyses were performed using SPSS statistics software for Windows (version 25.0; IBM Corp., Armonk, NY, USA). Graphs were created by GraphPad Prism software version 8.4.2 (GraphPad Software, La Jolla, CA, USA). Statistical significance was defined as *P*-values less than 0.05.

## Results

### Phenotypic characteristics

A total of 153 patients with OI (102 boys and 51 girls), with a mean age of 10.18 ± 3.53 years (range, 1.33 to 18.00

years), were enrolled in this study. The median age at initial fracture was 2.7 years (IQR, 1.5, 6), and the median number of previous fractures was 4 (IQR, 3, 6). Of these patients, 40.5% (62/153) had a family history of fractures. The mean Z-scores for height and weight of patients with OI were − 1.079 ± 2.825 and 0.018 ± 1.878, respectively. The distribution of Sillence classification was as follows: type I ($n = 70$), type III ($n = 33$), type IV ($n = 43$), and type V ($n = 7$). The characteristics of patients with different clinical severity are shown in Table 1.

All patients with OI underwent genetic testing, and the identified gene variants were as follows: *COL1A1* ($n = 68$), *COL1A2* ($n = 29$), *IFITM5* ($n = 7$), *WNT1* ($n = 3$), *FKBP10* ($n = 3$), *P3H1* ($n = 3$), *BMP* ($n = 2$), *PLS3* ($n = 2$), *SEC24D* ($n = 2$), *CRTAP* ($n = 1$), *PLOD2* ($n = 1$), *P4HB* ($n = 1$), *TMEM38B* ($n = 1$), *SERPINF1* ($n = 1$), *SERPINH1* ($n = 1$),

**Table 1** Phenotypic characteristics of OI patients

| Characteristic | OI type I ($n = 70$) | OI type III ($n = 33$) | OI type IV ($n = 43$) | Total ($n = 153$) | *P*-value | Reference |
|---|---|---|---|---|---|---|
| Age (years) (mean ± SD) | 10.05 ± 3.47 | 10.86 ± 4.05 | 9.83 ± 3.22 | 10.18 ± 3.53 | 0.434 | |
| Sex (male/female) | 44/26 | 22/11 | 34/9 | 102/51 | 0.191 | |
| Age of onset (years) (median (IQR)) | 3 (2, 6) | 1.4 (0.3, 2.0) | 3.0 (2.0, 6.0) | 2.7 (1.5, 6) | < 0.001 | |
| Previous fracture times (median (IQR)) | 3 (2, 4) | 6 (4, 15) | 4 (3, 6) | 4 (3, 6) | < 0.001 | |
| Annual fracture rate (median (IQR)) | 0.32 (0.24, 0.46) | 0.60 (0.31, 1.21) | 0.45 (0.30, 0.66) | 0.38 (0.27, 0.65) | < 0.001 | |
| Patients with vertebral fractures (*n* (%)) | 28 (40.0) | 20 (60.6) | 19 (44.2) | 69 (45.1) | 0.142 | |
| Height (cm) [a] (mean ± SD) | 136.3 ± 21.9 | 126.4 ± 20.5 | 132.3 ± 18.5 | 134.5 ± 19.5 | 0.099 | |
| Height Z-score (mean ± SD) | − 0.206 ± 1.612 | − 3.836 ± 4.463 | − 1.283 ± 1.745 | − 1.079 ± 2.825 | < 0.001 | |
| Weight (kg) [a] (mean ± SD) | 36.4 ± 15.6 | 31.7 ± 12.6 | 34.2 ± 14.3 | 35.6 ± 14.17 | 0.341 | |
| Weight Z-score (mean ± SD) | 0.737 ± 1.931 | − 1.256 ± 1.967 | − 0.006 ± 1.233 | 0.018 ± 1.878 | 0.001 | |
| BMI (kg/m$^2$) (mean ± SD) | 18.9 ± 3.5 | 19.3 ± 5.1 | 19.0 ± 3.9 | 19.0 ± 4.0 | 0.883 | |
| Ca (mmol/L) (mean ± SD) | 2.44 ± 0.10 | 2.44 ± 0.10 | 2.44 ± 0.11 | 2.44 ± 0.12 | 0.987 | 2.13 ~ 2.70 |
| P (mmol/L) (mean ± SD) | 1.68 ± 0.19 | 1.65 ± 0.17 | 1.65 ± 0.22 | 1.64 ± 0.25 | 0.665 | 1.29 ~ 1.94 |
| ALP (U/L) (mean ± SD) | 296 ± 90 | 272 ± 88 | 302 ± 85 | 281 ± 94 | 0.332 | 58 ~ 400 |
| β-CTX (ng/ml) (mean ± SD) | 1.038 ± 0.432 | 0.875 ± 0.437 | 0.958 ± 0.409 | 0.942 ± 0.441 | 0.094 | 0.40 ~ 3.30 |
| Lumbar spine aBMD (g/cm$^2$)[b] (mean ± SD) | 0.607 ± 0.182 | 0.481 ± 0.201 | 0.493 ± 0.168 | 0.566 ± 0.201 | < 0.001 | |
| Z-score of lumbar spine aBMD (mean ± SD) | − 0.865 ± 2.064 | − 2.653 ± 1.965 | − 1.613 ± 2.009 | − 1.498 ± 2.131 | < 0.001 | > − 2.0 |
| Z-score of lumbar spine aBMD$_{HAZ}$ (mean ± SD) | − 0.629 ± 1.855 | − 1.128 ± 2.091 | − 1.098 ± 1.981 | − 0.839 ± 1.913 | 0.406 | |
| Femoral neck aBMD (g/cm$^2$)[b] (mean ± SD) | 0.547 ± 0.142 | 0.406 ± 0.214 | 0.448 ± 0.165 | 0.504 ± 0.179 | < 0.001 | |
| Z-score of femoral neck aBMD (mean ± SD) | − 2.379 ± 1.489 | − 4.562 ± 2.654 | − 3.740 ± 2.004 | − 2.795 ± 2.018 | < 0.001 | > − 2.0 |
| Total hip aBMD (g/cm$^2$) (mean ± SD) | 0.543 ± 0.143 | 0.462 ± 0.227 | 0.491 ± 0.166 | 0.528 ± 0.179 | 0.068 | |
| TBS (median (IQR)) [c] | 1.336 (1.234, 1.390) | 1.266 (1.092,1.376) | 1.294 (1.156, 1.380) | 1.321 (1.206, 1.390) | 0.159 | |
| TBS Z-score (mean ± SD) | − 1.127 ± 1.377 | − 1.758 ± 1.551 | − 1.479 ± 1.802 | − 1.249 ± 1.653 | 0.158 | > − 2.0 |
| SDI (median (IQR)) | 0 (0, 7) | 6 (0, 15) | 1 (0, 9) | 1 (0, 10) | 0.041 | |

*OI* osteogenesis imperfecta, *BMI* body mass index, *Ca* calcium, *P* phosphate, *ALP* alkaline phosphatase, *β-CTX* β-isomerized carboxy-telopeptide of type I, *aBMD* areal bone mineral density, *HAZ* height-for-age Z-score, *TBS* trabecular bone score, *IQR* interquartile range, *SD* standard deviation

*P*-value was obtained using one-way ANOVA for data with a normal distribution or using Kruskal–Wallis test for data with a non-normal distribution. Values were given as number (proportion), mean ± SD or median (IQR)

[a]The reference ranges for height and weight of different ages were based on standardized growth charts for Chinese children and adolescents (31)

[b]The reference range of aBMD was based on a cross-sectional study in healthy Chinese children and adolescents (23)

[c]The reference range of TBS was based on a cross-sectional study in healthy children and adolescents (26)

and no genetic variants were detected in the remaining 28 patients (Fig. S2 and Tables S1 and S2) [29].

## TBS and its correlations with phenotypes of OI

Among the 153 patients, the mean TBS Z-score was − 1.249 ± 1.653, with 28.8% (44/153) showing degraded vertebral microarchitecture (Table 1). TBS Z-scores of type I/III/IV patients with OI were all significantly less than zero, indicating that TBS values in patients with OI were lower than those in normal children and adolescents. However, the differences in TBS and its Z-score among patients with OI type I, III, and IV were not significant ($P = 0.159$ and $P = 0.158$, respectively) (Fig. 1 and Table 1), which may be attributed to the relatively small sample size.

TBS showed a weak negative correlation with age ($r = -0.187$, $P < 0.05$) (Fig. 2A). In addition, TBS Z-score was negatively correlated with age ($r = -0.435$, $P < 0.001$) (Fig. 2B), and this correlation remained significant after adjusting for sex, height, weight, and clinical classification ($r = -0.308$, $P < 0.001$). No correlations were found between TBS with sex, height, or weight of the patients.

The Z-scores of aBMD at the lumbar spine and femoral neck were − 1.498 ± 2.131 and − 2.795 ± 2.018, respectively, and the Z-score of $aBMD_{HAZ}$ was − 0.839 ± 1.913 (Table 1). The differences in lumbar spine aBMD and its Z-score among patients with OI type I, III, and IV were significant (both $P < 0.001$) (Fig. 1). TBS Z-score was positively correlated with the Z-score of lumbar spine aBMD ($r = 0.447$, $P < 0.001$) and femoral neck aBMD ($r = 0.295$, $P < 0.01$) (Fig. S3), and this correlation remained significant after adjusting for age, sex, height, and weight (lumbar spine, $r = 0.576$; femoral neck, $r = 0.377$; both $P < 0.001$). The correlation between the TBS Z-score and the $aBMD_{HAZ}$ Z-score was also significant ($r = 0.392$, $P < 0.001$). Meanwhile, there were no significant correlations between TBS or its Z-score and serum β-CTX or ALP levels.

The annual fracture rate was considered to be an important parameter of bone fragility. However, there were no significant correlations between the annual fracture rate with Z-scores of TBS ($r = -0.036$, $P = 0.489$) and lumbar spine aBMD ($r = -0.063$, $P = 0.476$).

## TBS and VCFs discrimination

VCFs were found in 45.1% (71/153) of patients with OI (Table 2), with Grade 1 of VCFs in 24 patients, Grade 2 in 17 patients, and Grade 3 in 30 patients. Thirty-five percent

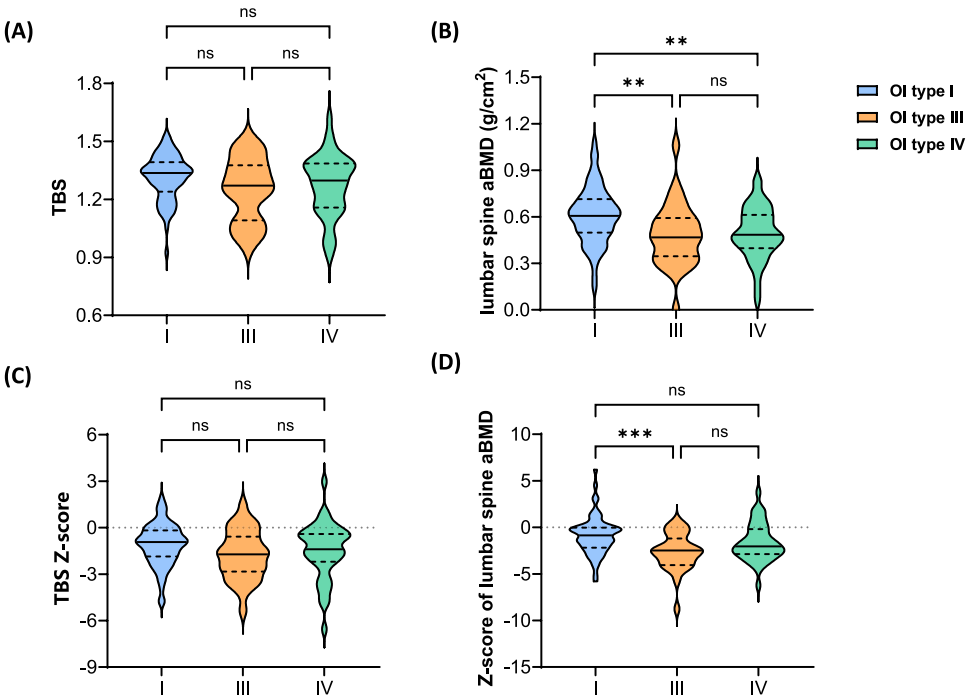


**Fig. 1** Comparison of TBS, TBS Z-score, lumbar spine aBMD, and its Z-score in OI patients with different clinical classifications. **A** Comparison of TBS among patients classified by OI clinical type. **B** Comparison of lumbar spine aBMD among patients classified by OI clinical type. **C** Comparison of TBS Z-score among patients classified by OI clinical type. **D** Comparison of lumbar spine aBMD Z-score among patients classified by OI clinical type. Statistical analysis was performed using one-way ANOVA for normally distributed data and Kruskal–Wallis test for non-normally distributed data. Data were presented as violin plots with median (solid line) and interquartile range (IQR, dotted line). TBS, trabecular bone score; aBMD, areal bone mineral density; OI, osteogenesis imperfecta. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

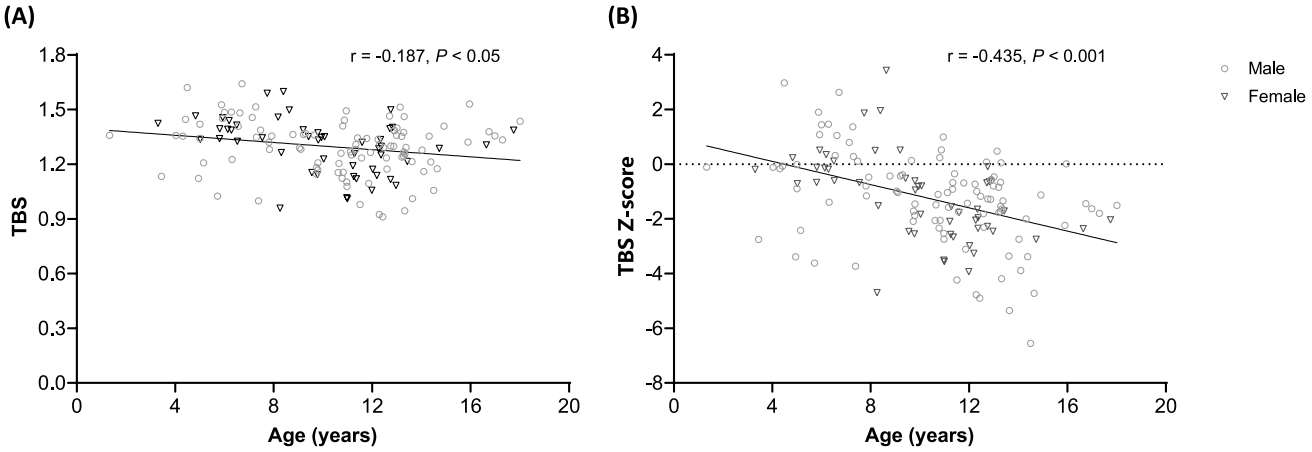


**Fig. 2** Relationships between TBS, TBS Z-score and age in patients with OI. **A** The correlation between TBS and age in patients with OI. **B** The correlation between TBS Z-score and age in patients with OI. Linear regression analyses were conducted to evaluate the relationships between TBS, TBS Z-score, and age. Correlations were significant for both TBS ($r = -0.187$, $P < 0.05$) and TBS Z-score ($r = -0.435$, $P < 0.001$). Simple linear regression lines are shown in each panel. TBS, trabecular bone score; OI, osteogenesis imperfecta

(25/71) of patients with VCFs did not show densitometric osteoporosis. Patients with VCFs had a significantly lower TBS Z-score than those without VCFs ($-1.778 \pm 1.613$ vs $-0.748 \pm 1.539$, $P < 0.001$).

In the entire study population, the AUCs in ROC plots for discriminating VCFs were 0.667 and 0.666 for Z-score of TBS and lumbar spine aBMD, respectively, with no significant difference between them (Fig. 3A). Interestingly, among the patients without densitometric osteoporosis according to their aBMD ($n = 37$), TBS Z-score showed a greater AUC for identifying VCFs than Z-score of lumbar spine aBMD (0.719 vs 0.545, $P < 0.05$) (Fig. 3B), indicating the higher discriminative power of TBS Z-score for VCFs.

## Correlation of TBS and spinal deformity

Patients with OI had a median SDI of 1 (IQR, 0, 10), of which the SDI value of patients with OI type III was

**Table 2** Comparison of patients with OI with and without vertebral fractures

| | Vertebral fractures | No vertebral fractures |
|---|---|---|
| Patient (*n*) | 71 | 82 |
| Age (years) (mean ± SD) | 10.6 ± 2.8 | 9.8 ± 4.0 |
| Gender (male/female) | 49/20 | 53/31 |
| Height Z-score (mean ± SD) | − 1.241 ± 1.778 | − 0.694 ± 2.199* |
| Weight Z-score (mean ± SD) | 0.219 ± 1.325 | 0.151 ± 1.560 |
| Ca (mmol/L) (mean ± SD) | 2.44 ± 0.13 | 2.44 ± 0.08 |
| P (mmol/L) (mean ± SD) | 1.64 ± 0.25 | 1.64 ± 0.19 |
| ALP (U/L) (mean ± SD) | 282 ± 99 | 281 ± 91 |
| β-CTX (ng/ml) (mean ± SD) | 0.943 ± 0.408 | 0.919 ± 0.457 |
| Z-score of lumbar spine aBMD (mean ± SD) | − 2.145 ± 2.049 | − 0.831 ± 2.017*** |
| Z-score of femoral neck aBMD (mean ± SD) | − 3.280 ± 2.240 | − 2.345 ± 1.964** |
| TBS [a] (mean ± SD) | 1.234 ± 0.146 | 1.355 ± 0.126*** |
| Z-score of TBS (mean ± SD) | − 1.830 ± 1.537 | − 0.775 ± 1.363*** |
| SDI (median (IQR)) | 10 (3, 5) | 0 (0, 0)*** |

*OI* osteogenesis imperfecta, *Ca* calcium, *P* phosphate, *ALP* alkaline phosphatase, *β-CTX* β-isomerized carboxy-telopeptide of type I, *aBMD* areal bone mineral density, *TBS* trabecular bone score, *IQR* interquartile range, *SD* standard deviation

Values were given as number (proportion), mean ± SD or median (IQR)

[a]The reference range of TBS was based on a cross-sectional study in healthy children and adolescents (26)

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ in comparison with OI patients with vertebral fractures

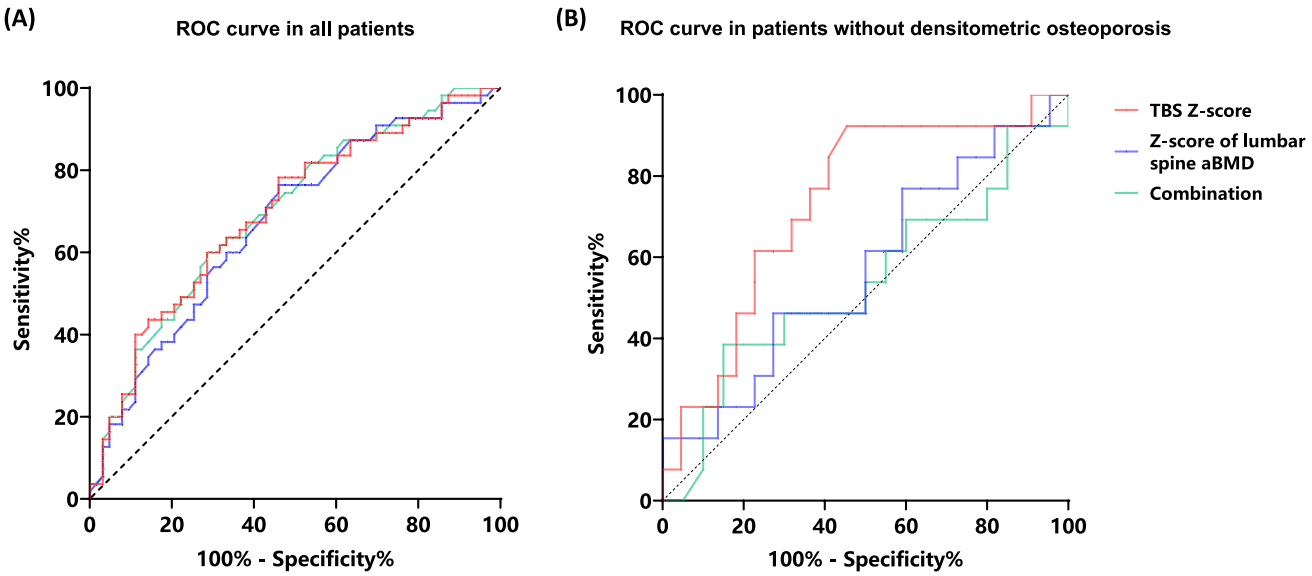


**Fig. 3** ROC curve analysis for the discriminative value of TBS Z-score, Z-score of lumbar spine aBMD and the combinations of the two measurements in identifying VCFs. **A** ROC curve analysis for the accuracy of TBS Z-score, Z-score of lumbar spine aBMD, and their combination in discriminating VCFs in all patients. **B** ROC curve analysis for the accuracy of TBS Z-score, Z-score of lumbar spine aBMD, and their combination in discriminating VCFs in patients without densitometric osteoporosis. ROC, receiving operator characteristic; TBS, trabecular bone score; aBMD, areal bone mineral density; VCF, vertebral compression fracture

significantly higher than that of patients with OI type I ($P<0.05$) (Table 1). Patients with VCFs ($n=71$) had a median SDI value of 10 (IQR, 3, 15), which was significantly higher than those without VCFs ($P<0.001$).

Negative correlations were found between SDI with the Z-score of TBS ($r=-0.446$) (Fig. 4A), lumbar spine aBMD ($r=-0.479$) (Fig. 4B), and $aBMD_{HAZ}$ ($r=-0.423$) (all $P<0.001$). However, in patients without densitometric osteoporosis, only TBS Z-score exhibited a negative correlation with SDI ($r=-0.358$, $P=0.035$) (Fig. 4C), while the Z-score of lumbar spine aBMD ($r=-0.250$, $P=0.148$) (Fig. 4D) or $aBMD_{HAZ}$ ($r=-0.242$, $P=0.162$) was not significantly correlated with SDI.

## Association of TBS and genotype of OI

In this study, 104 patients with OI were categorized into the AD OI and 21 were non-AD OI (Table S3). Among the 97 patients with OI with pathogenic variants in *COL1A1* or *COL1A2*, 34 patients carried the nonsense or frameshift variants, while 46 had glycine substitution variants in either *COL1A1* or *COL1A2*. The remaining 17 patients with OI were identified with splicing variants of *COL1A1* or *COL1A2*. No differences in TBS or its Z-score were found between the AD and non-AD OI (Table S3) [29]. Also, no significant difference was found in TBS or its Z-score between patients with the quantitative reduction and with structural defects of type I collagen (Table S3) [29].

## Sub-group analysis of OI patients with identified pathogenic variants

A total of 93 patients with OI (60 boys and 33 girls), with a mean age of $10.27\pm3.60$ years, were found to carry pathogenic variants, including variants in *COL1A1* (52.6%), *COL1A2* (25.8%), *ITIFM5* (7.5%), *WNT1* (3.2%), *PLS3* (2.1%), *P3H1* (2.1%), and *FKBP10*, *CRTAP, PLOD2*, *TMEM38B*, *SERPINF1*, *SERPINH1* (each 1.0%) (Supplementary Table 1). In this genetically homogeneous sub-group, the mean TBS Z-score was $-1.254\pm1.676$, and 30.1% (28/93) of patients displayed degraded vertebral microarchitecture. A negative correlation was found between age and TBS Z-score ($r=-0.421$, $P<0.001$), which remained significant after adjusting for sex, height, weight, and clinical classification ($r=-0.300$, $P<0.01$). Additionally, TBS Z-score was positively correlated with the aBMD Z-score of the lumbar spine ($r=0.364$, $P<0.01$).

Patients with VCFs had a significantly lower TBS Z-score than those without VCFs ($-1.705\pm1.445$ vs $-0.793\pm1.784$, $P<0.01$). In this cohort with identified pathogenic variants, the AUC for discriminating VCFs using TBS Z-score was 0.669, and the AUC value was 0.651 using lumbar spine aBMD Z-score. Among patients without densitometric osteoporosis according to their aBMD ($n=24$), TBS Z-score exhibited a higher but non-significant AUC for identifying VCFs than lumbar spine aBMD Z-score (0.774 vs 0.590, $P=0.117$). According to the deformation of the spine, the median SDI of these patients with VCFs ($n=46$)

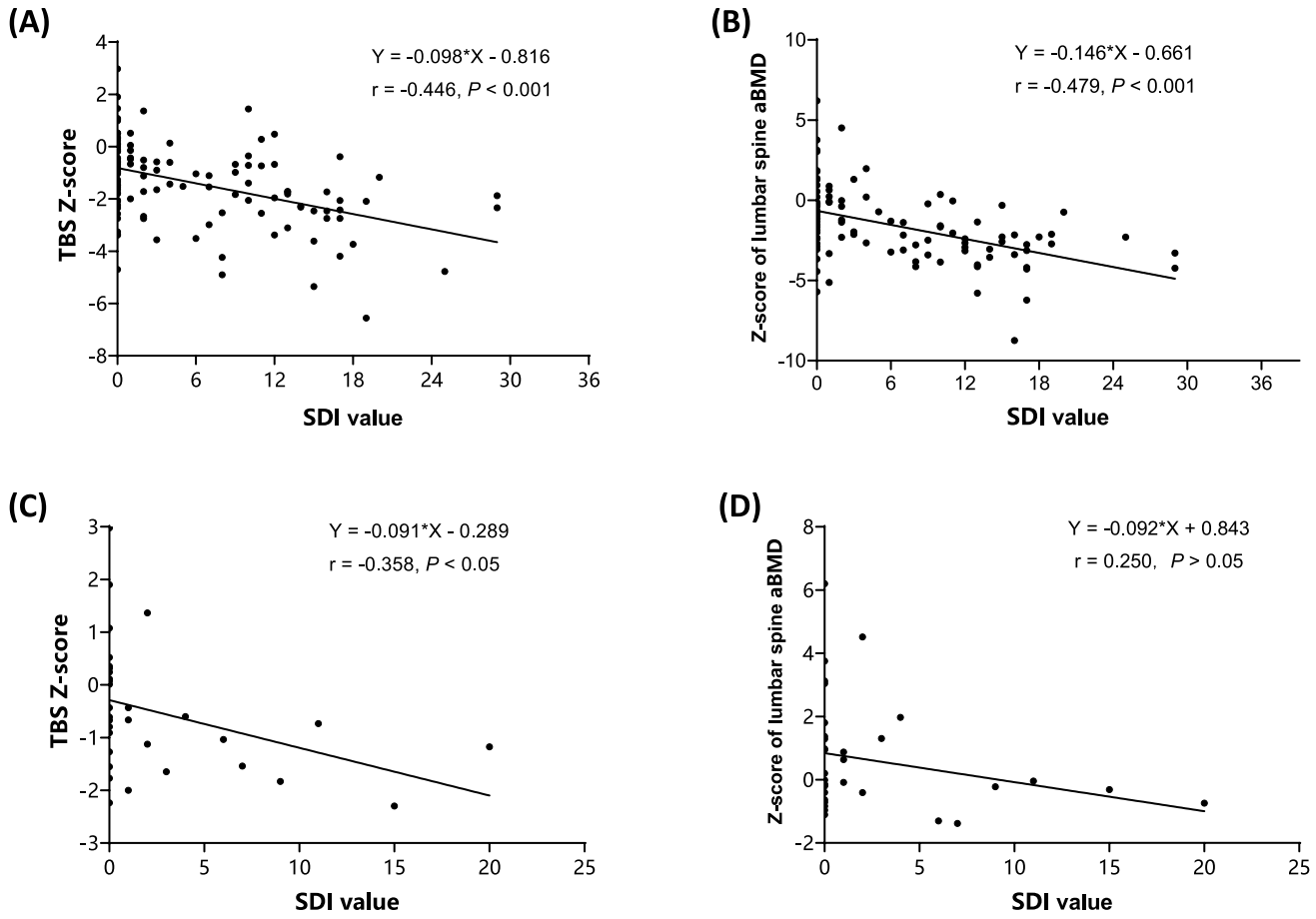


**Fig. 4** Correlations between Z-scores of TBS or lumbar spine aBMD and SDI. **A** The correlation between TBS Z-score and SDI in all OI patients. **B** The correlation between Z-score of lumbar spine aBMD and SDI in all OI patients. **C** The correlation between TBS Z-score and SDI in OI patients without densitometric osteoporosis. **D** The correlation between Z-score of lumbar spine aBMD and SDI in OI patients without densitometric osteoporosis. Linear regression analyses were performed to evaluate the correlations between TBS Z-score, lumbar spine aBMD Z-score, and SDI. Simple linear regression lines and corresponding equations were shown in each panel. TBS, trabecular bone score; aBMD, areal bone mineral density; SDI, spinal deformity index

was 11 (IQR, 5, 14), which was significantly higher than that of patients without VCFs ($P < 0.001$). Negative correlations were found between SDI with TBS Z-score ($r = -0.359$, $P < 0.01$) and lumbar spine aBMD Z-score ($r = -0.448$, $P < 0.001$).

## Discussion

This cross-sectional study, conducted in a relatively large sample of children and adolescents with OI, evaluated their bone quality using lumbar TBS and analyzed its relationship with age, Sillence classification, aBMD, bone turnover markers, fracture rate, and SDI. To the best of our knowledge, this is the first study to investigate the value of TBS as an assessment tool for VCFs and spinal deformities in patients with OI. Our study found that the TBS Z-score was positively correlated with aBMD Z-score in patients with OI. Notably, in those without densitometric osteoporosis, TBS Z-score exhibited superior discriminative power for VCFs compared to aBMD Z-score and had an inverse relationship with the severity of spinal deformity. These findings demonstrated the potential of TBS as a valuable complementary tool for evaluating bone quality in children and adolescents with OI.

BMD measurement by DXA is the most commonly used tool for predicting fragility fractures in various skeletal disorders. According to WHO classification, BMD is important for the diagnosis of primary osteoporosis, which is defined when a BMD T-score is less or equal to − 2.5 [32]. However, numerous studies have shown that patients without very low BMD can develop fragility fractures, and BMD cannot fully reflect the risk of fractures. The National Osteoporosis Risk Assessment study found that 82% of 2,259 postmenopausal women with a fracture had a BMD T-score above − 2.5 as measured with peripheral densitometry [33]. Similarly, a

population-based prospective study revealed that up to 56% of non-vertebral fractures occurred in elderly women with BMD in the normal or osteopenia range, and the percentage was even higher in elderly men (79%) [34]. As we know, vertebral fractures will significantly interfere with lumbar spine BMD measurement of DXA and may result in a false increase in BMD values and their corresponding Z-scores [11]. Therefore, it is crucial for patients with OI to complete a quantitative evaluation of bone microstructure and other determinants of bone strength. TBS is a grey-level textural index extracted from lumbar spine DXA images, which evaluates pixel gray-level variation and serves as an indirect index of trabecular architecture. It is believed to estimate fracture risk based on its correlations with connectivity density, trabecular number, and trabecular separation [35]. Currently, TBS is utilized in the evaluation of osteoporosis, in which a lower TBS suggests less well-textured bone with more fracture-prone microarchitecture [36]. While DXA is useful for detecting vertebral fractures, TBS can provide additional information about bone microarchitecture, especially in patients of whom vertebral fractures have already occurred. Because TBS is less affected by vertebral fractures, it can reliably reflect bone fragility in patients with OI [11].

In the current study, we observed a negative correlation between the TBS Z-score and the age of patients with OI, which remained significant after adjusting for confounding factors. This result implied that pediatric patients with OI experienced a gradual degradation of bone microarchitecture assessed by TBS, resulting in a widening gap between them and their peers. It is worth noting that TBS has a notable increase during puberty in healthy children and adolescents [37, 38]. However, we did not observe an increasing trend of TBS in children with OI, suggesting that the impaired bone quality might impede the improvement of trabecular microstructure.

Due to increased bone fragility, VCFs are a common complication in patients with OI, and they may even occur in those with mild OI [39]. VCFs can cause back pain, height loss, kyphosis, scoliosis, and even compromised cardio/respiratory function [40]. Identification and prediction of VCFs are very important for prompt management to prevent the above complications. However, a considerable number of VCFs could be asymptomatic in the early stages and often be missed in diagnosis. In our study, 35% of patients with OI and VCFs did not show osteoporosis according to their aBMD measured by DXA. We found that among patients without densitometric osteoporosis, the TBS Z-score had higher accuracy than the Z-score of lumbar spine aBMD in discriminating VCFs. A previous study reported that TBS Z-scores were negatively associated with the annual fracture rate in non-severe types of children and adolescents with OI [18]. However, this study had a relatively small sample size and did not exclude patients with OI who had received anti-resorptive treatment. It also did not explore the potential of TBS as an indicator of VCFs and spinal deformity. Our study investigates the value of TBS in evaluating VCFs and spinal deformity in a relatively large sample of treatment-naive children and adolescents with OI. The results indicate that TBS may be a more accurate index to reflect the risk of VCFs and monitor the progression of spinal deformity, especially in patients without densitometric osteoporosis. Although studies on the identification or prediction of VCFs with TBS in OI are very limited, our results align with studies in patients with osteoporosis. In a cohort of 528 men and women over 50 years old who had sustained a low-trauma non-vertebral fracture, TBS improved the discrimination of VCFs as compared to lumbar spine BMD in patients without densitometric osteoporosis [41]. Furthermore, in patients with chronic inflammatory rheumatic diseases receiving long-term glucocorticoid treatment, TBS also showed a higher discriminative ability for identifying VCFs than BMD [42].

Spinal deformity is also a common complication of patients with OI [43]. Severe spinal deformity can detrimentally impact the cardiac and respiratory functions, significantly diminishing quality of life and even shortening lifespan. Currently, there is no accurate quantitative marker for monitoring the progression of spinal deformity in patients with OI. Lumbar spine aBMD can be falsely elevated by existing vertebral fractures, which is less reliable in patients with vertebral fractures [11]. Our study found that the TBS Z-score was negatively correlated with the severity of spinal deformity assessed by SDI in patients without obvious densitometric osteoporosis, whereas the Z-score of lumbar spine aBMD was not. A similar outcome also showed that TBS was negatively related to SDI in osteoporotic patients over 50 years old with non-vertebral fractures but without densitometric osteoporosis [41]. Therefore, TBS may be a valuable imaging index for reflecting the progression of spinal deformity in children and adolescents with OI.

The sub-analysis of patients with identified pathogenic variants displayed similar, though less significant, patterns of correlations between TBS, bone mineral density, vertebral compression fracture, and spinal deformity. These results still support TBS as a valuable complementary tool for assessing vertebral fractures and spinal deformities in children and adolescents with OI, confirming the role of TBS as a potential index for bone fragility in genetically confirmed OI patients. In the future, this conclusion needs to be further verified by larger sample studies in patients with OI.

Our study found a good correlation between TBS Z-score and aBMD Z-score in children and adolescents with OI, but TBS Z-score appears to be more accurate than aBMD Z-score to evaluate the risk of VCFs and the progression of spinal deformity, particularly in those without densitometric

osteoporosis. Our results indicated that TBS is well expected to be used for quantitative evaluation of bone quality in OI. However, this study still had a series of limitations. This study was a cross-sectional study, which was difficult to dynamically evaluate the changes of TBS during growth and puberty of children with OI. Longitudinal or prospective studies should be conducted to further explore the clinical utility of TBS in predicting VCFs and spinal deformity. This study did not find correlations between TBS and types of pathogenic gene variants of OI and their impact on collagen metabolism, which may be related to the insufficient sample size for correlation analysis in this study. The effect of puberty on this study was not fully assessed. Also, as patients with OI often exhibit short stature, the interpretation of aBMD may be influenced by body height. Furthermore, the lack of reference data for TBS in healthy Asian children may influence the calculation of the TBS Z-score and lead to the overgeneralization of our findings. Finally, we did not use a TBS software version that accounted for tissue thickness instead of BMI, which is more appropriate for children and adolescents [37].

In conclusion, the current study revealed that TBS is closely correlated to bone mineral density in children and adolescents with OI, which can provide insight into bone quality and improve the evaluation of skeletal phenotype. TBS Z-score may be useful for evaluating the risk of vertebral fractures and the progression of spinal deformity, especially in patients without densitometric osteoporosis.

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**Data Availability** Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

## Declarations

**Conflicts of interest** None.



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