

# Bone Mineral Density and its Influencing Factors in Chinese Children with Spinal Muscular Atrophy types 2 and 3

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## Research Article

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# Abstract

**Background:** Patients with spinal muscular atrophy (SMA) are at risk of decreased bone mineral density (BMD). The bone status of Chinese patients with SMA has been poorly studied. We aimed to describe bone health of children with SMA types 2 and 3 in mainland China and to investigate the associated factors that influence BMD.

**Methods:** Forty patients with a mean age of 5.5 years affected by SMA types 2 and 3 (n = 22 and n = 18, respectively) were enrolled between September 2017 and May 2019. Total body less head (TBLH) BMD, lumbar spine (LS) BMD, and body composition were measured using dual-energy X-ray absorptiometry. Serum bone metabolism markers and complete spinal radiographs were assessed. We utilized a linear regression model to explore the correlations between BMD and its related factors.

**Results:** A total of 67.5% (27/40) patients were diagnosed with low BMD, 2.5% (1/40) were diagnosed with osteoporosis, and 5.0% (2/40) had low-trauma fractures. The mean Z-score was  $-3.0 \pm 1.8$  for TBLH BMD and  $-1.3 \pm 1.4$  for LS BMD. The TBLH BMD and LS BMD Z-scores in children with SMA type 2 were significantly lower than those with SMA type 3 (t = 3.344, P = 0.002; t = 3.266, P = 0.002, respectively). Vitamin D insufficiency and deficiency was found in 37.5% (15/40) of the patients. Phenotype and serum parathormone (PTH) levels were the factors associated with the TBLH BMD Z-scores (t = 2.847, P = 0.008; t = 2.572, P = 0.015, respectively), and the phenotype severity was the factor associated with the LS BMD Z-scores (t = 2.762, P = 0.009).

**Conclusions:** Low BMD was highly prevalent in mainland Chinese children with SMA type 2 or 3. Phenotype and serum PTH levels were the factors associated with BMD. More than one-third of our patients also had vitamin D insufficiency or deficiency, which indirectly affected BMD despite their serum PTH levels being normal. We consider it to be necessary to carry out bone health screening in this population.

## 1. Introduction

Spinal muscular atrophy (SMA) is a rare neurodegenerative disease characterized by the degeneration of the anterior horn of the spinal cord and medullary motor neurons, leading to progressive, symmetrical muscle weakness and muscle atrophy of the proximal limbs and trunk. Approximately 1 in 11,000 people are affected by the disorder, and it is a common genetic cause of early infant mortality [1, 2]. The pathogenic mutation of survival motor neuron gene 1 (*SMN1*) located on chromosome 5q causes 5q SMA [3]. Its phenotype is classified into four types (1 to 4) based on the age at onset and the maximum motor function achieved. SMA type 1, the most severe form, appears within 6 months after birth; the affected infants are unable to sit unsupported, and it is usually lethal by the age of 2 years [4]. SMA type 2 often appears between 6–18 months after birth; these patients can sit upright but cannot stand or walk independently. SMA type 3 is the mild form; the age at onset is usually after 18 months, and patients can walk independently. SMA type 4 is an adult-onset disease with mild muscle weakness [5]. The clinical

severity of SMA is highly variable and negatively correlated with the copy number of the survival motor neuron gene 2 (*SMN2*) [6]. Most patients with SMA type 1 have two copies of *SMN2*, those with type 2 usually have three copies, and most patients with types 3 and 4 have three or four copies.

Muscular dystrophy and chronic immobility may lead to low bone mineral density (BMD), osteoporosis, and an increased risk of fractures. Therefore, skeletal system abnormalities are some of the most significant complications and key factors in limiting the quality of life of children affected by SMA type 2 or 3. The development of multidisciplinary management methods can address this issue, and BMD should be studied in patients with SMA. Periodic BMD analysis in patients with SMA has been carried out in other countries, and physicians have implemented interventions to improve the prognosis for complications such as osteoporosis. To date, very limited data are available on bone health assessment in Chinese pediatric patients with SMA.

Our study aimed to assess BMD ( $\text{g}/\text{cm}^2$ ), fractures, and serum bone metabolism markers in 40 children affected by SMA types 2 and 3 and to analyze the related factors that influence BMD. We used dual-energy X-ray absorptiometry (DXA), the "gold standard" technology for BMD assessment [7]. Our goal was to provide a basis for the study of bone health among mainland Chinese children with SMA to improve the management and evaluate the efficacy of new drugs that have been approved for SMA treatment.

## 2. Methods

### 2.1 Study subjects

We enrolled children who were genetically confirmed to have 5q SMA with a homozygous deletion of exon 7 or 8, or both, at the Department of Neurology in Children's Hospital Affiliated to the Capital Institute of Pediatrics between September 2017 and May 2019. The included patients had to meet the following criteria: (1) no history of previous spinal trauma; (2) ability to complete the DXA measurement in the required horizontal position; and (3) no gene therapy. The exclusion criteria were: (1) treatment with drugs that affect bone metabolism (e.g., valproic acid, glucocorticoids, bisphosphonates); and (2) concomitant chronic disease that could affect bone metabolism (e.g., inflammatory bowel disease, pituitary disorders). This study was approved by the Ethics Committee of the Capital Institute of Pediatrics (No. SHERLL2017007). Written informed consent documents for the participating children were obtained from their parents or guardians. All methods were carried out in accordance with relevant guidelines and regulations.

### 2.2 Study design

#### 2.2.1. Collection of clinical data

The attending physicians of the research team conducted detailed medical history consultations for the participants, which included the assessment of the symptom onset time, the maximum motor function that could be achieved, number and location of previous fractures (confirmed on bone radiographs and

clinical records), medications, use of vitamin D and calcium (Ca) in the past 3 months, rehabilitation, and family history.

## 2.2.2 Anthropometry

Weight was measured to the nearest 0.1 kg in lightweight clothing without shoes on a calibrated digital scale. Standing height was measured with a stadiometer. A measuring board was used for patients unable to stand as follows: the child was helped by a technician to lie supine, with the legs straight and well-aligned with the body, and the ankles as close together as possible. The footboard-headboard distance was accurately measured.

## 2.2.3. Genetic testing

Genomic DNA was extracted, and the multiplex ligation-dependent probe amplification technique (P060 kit, MRC, Amsterdam, The Netherlands) was used to detect the copy numbers of *SMN1* and *SMN2*.

## 2.2.4 DXA scanning

Whole-body scanning was performed using Hologic Discovery (A, W, and Wi) fan-beam densitometers (Hologic, Bedford, MA, USA). The coefficient of variation (CV) was used as a quality control procedure. The CVs of A, W, and Wi were 0.471%, 0.302%, and 0.358%, respectively. Measurement reports were prepared by a technician with DXA-training certification. All DXA values were analyzed using Hologic Apex version 4.0 following the manufacturer's guidelines.

2.2.4.1 We measured values (based on the recently published reference standards of BMD and body composition for Chinese children aged 3–18 years [8, 9]) as follows:

(1) BMD ( $\text{g}/\text{cm}^2$ ): Total body less head (TBLH) BMD and lumbar spine (LS) (L1–L4) BMD were measured according to the International Society for Clinical Densitometry (ISCD) recommendation. For most pediatric and adolescent patients, the posterior-anterior spine and TBLH are the preferred skeletal sites for measuring BMD using DXA [7]. TBLH BMD Z-scores (the number of standard deviations that a patient's BMD differs from the average of a healthy control population of the same age and sex) were calculated under the 2017 "Bone mineral density reference standards for Chinese children aged 3–18" [8]. LS BMD Z-scores were determined with DXA using standards for American children [10] because there are no Chinese standards. Height Z-scores were calculated according to the growth standard value of Chinese children [11]. If a patient's height Z-score was  $< -1$ , the BMD Z-score was also corrected for the height Z-score, according to the ISCD indication for the measurement of pediatric BMD [12].

(2) Body composition: Appendicular skeletal muscle mass (ASM), total mass (TM), and ASM weight ratio (ASMR) were calculated using the formula  $\text{ASMR} = \text{ASM}/\text{TM}$ . ASMR Z-scores were calculated according to a healthy control population of the same ethnicity, sex, and age [9].

### 2.2.4.2 Criteria for BMD determination

Decreased BMD in children can be classified as osteoporosis or low BMD according to the standards established by the ISCD in 2019 [13]. Diagnostic criteria for osteoporosis were: (1) the finding of one or more vertebral compression (crush) fractures in the absence of local disease or high-energy trauma; or (2) BMD Z-score  $\leq -2.0$ , and two or more long bone fractures by 10 years of age, or three or more long bone fractures up to 19 years of age. The diagnostic criterion for low BMD was a BMD Z-score  $\leq -2.0$ .

## 2.2.5 Laboratory examinations

Fasting blood collection was used to determine serum bone metabolism markers, including blood Ca, phosphorus (P), alkaline phosphatase (ALP), parathormone (PTH), and 25-OH-D (vitamin D) concentrations. In accordance with the American Academy of Pediatrics [14], serum 25-OH-D concentrations were defined as follows: sufficiency ( $> 50.0$  nmol/L), insufficiency (37.5–50.0 nmol/L), deficiency ( $\leq 37.5$  nmol/L), and severe deficiency ( $\leq 12.5$  nmol/L) in the pediatric population.

## 2.2.6 Radiographic examination

Frontal and lateral images of the entire spinal column were obtained to evaluate compression fractures of the spine. Radiographs were evaluated by two pediatric radiologists.

## 2.3 Statistical methods

The mean  $\pm$  standard deviation values were used to describe quantitative data with a normal or symmetrical distribution, and the median (P25, P75) was used to describe data with a non-normal distribution. A Student's t-test or corrected t-test was used for comparisons between two groups. Proportions or percentages were used to describe qualitative data, and a chi-square, corrected chi-square, or exact probability test was used for comparisons between the two groups. A multiple linear regression model was built to explore related factors of BMD including sex, age at DXA scanning, disease course, phenotype, serum bone metabolic markers (PTH, 25-OH-D), and ASMR Z-values, in which the TBLH BMD and LS BMD Z-values were included in the model separately. A collinearity diagnosis was carried out during the process of regression with a tolerance higher than 0.1.  $P < 0.05$  being considered significant. Data were processed with SPSS (version 23.0, IBM Corp., Armonk, NY, USA).

## 3. Results

### 3.1 Demographic data and clinical characteristics

A total of 51 children with SMA were evaluated at our institution between September 2017 and May 2019; 40 patients met the inclusion criteria (male:  $n = 19$ ; female:  $n = 21$ ) and 11 patients were excluded (five were unable to complete the DXA measurement in the required horizontal position, three refused to undergo blood tests, and three dropped out). The demographics and clinical characteristics of the sample by SMA subtype are shown in Table 1. The sex distribution, age at DXA scanning, and disease course were similar between SMA types 2 and 3. No patient had used vitamin D and Ca supplements regularly in the previous 3 months. Only 30% (12/40) of patients had carried out formal rehabilitation training.

Table 1  
Demographics and BMD data of patients with SMA

	SMA 2	SMA 3	Total	t	P
Number	22	18	40		/
Sex (male/female)	8/14	11/7	19/21		/
Age (y) at DXA	5.5 (4.1, 9.5)	5.4 (4.3, 3.9)	5.5 (4.2, 8.7)	-0.420*	0.677
Disease course (y)	4.5 (3.2, 8.9)	3.9 (2.1, 5.4)	4.2 (3.1, 6.8)	1.465*	0.151
<i>SMN2</i> gene copy number (3/4)	22/0	12/6	34/6		/
TBLH BMD Z-scores	-3.7 ± 1.6	-2.0 ± 1.7	-3.0 ± 1.8	3.344*	0.002
<i>SMN2</i> gene 3 copy		-2.3 ± 1.7		0.912*	0.375
<i>SMN2</i> gene 4 copy		-1.5 ± 1.6			(3 copy vs. 4 copy)
LS BMD Z-scores	-1.9 ± 1.2	-0.6 ± 1.4	-1.3 ± 1.4	3.266*	0.002
<i>SMN2</i> gene 3 copy		-0.6 ± 1.5		0.000*	1.000
<i>SMN2</i> gene 4 copy		-0.6 ± 1.0			(3 copy vs. 4 copy)
Low BMD (n%)	19 (86%)	8 (44%)	27 (68%)		/
ASMR Z-scores	-3.6 ± 1.1	-2.7 ± 1.3	-3.2 ± 1.2	2.476*	0.018
Data are shown as mean ± standard deviation, n (%), or median (range). *Student's t-tests or corrected t-tests. ASMR: appendicular skeletal muscle mass weight ratio; BMD: bone mineral density; DXA: dual-energy X-ray absorptiometry; LS: lumbar spine; SMA: spinal muscular atrophy; <i>SMN2</i> : survival motor neuron gene 2; TLBH: total body less head; /: not applicable.					

### 3.2 Prevalence of low BMD by SMA subtype

DXA data were available for all included patients and are shown in Table 1. According to the 2019 ISCD standard, 67.5% (27/40) of patients were diagnosed with low BMD, 2.5% (1/40) were diagnosed with osteoporosis, and only 30% (12/40) had BMD in the normal range (Fig. 1). The mean TBLH BMD Z-score was  $-3.0 \pm 1.8$ , and the mean LS BMD Z-score was  $-1.3 \pm 1.4$ . Patients with SMA type 2 had significantly lower TBLH BMD and LS BMD Z-scores than those with SMA type 3 ( $t = 3.344$ ,  $P = 0.002$  and  $t = 3.266$ ,  $P = 0.002$ , respectively). In 18 patients with SMA type 3, 12 carried three *SMN2* copies and 6 carried four copies. There were no significant differences between these two groups in terms of TBLH BMD and LS BMD Z-scores ( $t = 0.912$ ,  $P = 0.375$  and  $t = 0.640$ ,  $P = 0.531$ , respectively).

### 3.3 Fractures

None of the 40 children had vertebral fractures as confirmed via spinal radiographs, and 5.0% (2/40) patients with SMA type 3 had a history of long bone fracture, including one child who had two low-trauma fractures in the proximal humerus during activity at the age of 2 years, and one who had a right femur fracture at the age of 8 years.

### 3.4 Body composition

DXA body composition measurements were performed in all 40 patients, and the results are shown in Table 1. Our results showed that the mean ASMR Z-score was  $-3.2 \pm 1.2$ , which was lower than that of the healthy children (ASMR Z-score between  $-2.0$  to  $2.0$ ). Patients with SMA type 2 had significantly lower ASMR Z-scores than those with SMA type 3 ( $t = 2.476$ ,  $P = 0.018$ ).

### 3.5 Serum bone metabolism markers

The mean levels of serum Ca, P, ALP, and PTH are shown in Table 2. The ALP levels were in the normal range in all the children, and serum Ca was slightly below the normal range in only one child (3%). Serum phosphate was slightly above the normal range in five children (13%), and serum PTH was slightly below the normal range in only one child (3%). The mean level of serum 25-OH-D was  $53.93 \pm 19.68$  nmol/L. Among the 40 patients, the levels of serum 25-OH-D fulfilled the criteria for insufficiency (range, 37.5–50.0 nmol/L) in six children (15%) and deficiency ( $\leq 37.5$  nmol/L) in nine children (22.5%), and there was no severe deficiency. In 25 (62.5%) cases, the vitamin D values were within the normal range.

Table 2  
Serum bone metabolism markers in patients with SMA

	Mean	min	max	Reference value	Abnormal values n(%) (n = 40)
Ca (mmol/L)	$2.42 \pm 0.10$	2.21	2.62	2.25 ~ 2.74	1(3%)
P (mmol/L)	$1.78 \pm 0.18$	1.37	2.23	1.29 ~ 1.94	5(13%)
ALP (U/L)	$166.35 \pm 38.97$	91	272	0 ~ 400	0(0%)
PTH (ng/ml)	$27.83 \pm 11.22$	11.3	58.6	14.9 ~ 56.9	1(3%)
25-OH-D (nmol/L)	$53.93 \pm 19.68$	22.4	123.55	75 ~ 200	15(37.5%)

Data are shown as mean  $\pm$  standard deviation, n (%). ALP: alkaline phosphatase; Ca: calcium; Max: maximum value; Min: minimum value; P: phosphorus; PTH: parathormone; SMA: spinal muscular atrophy.

### 3.6 Influencing factors of BMD

Age at DXA scanning, sex, disease course, phenotype, serum bone metabolism markers (PTH, 25-OH-D), ASMR Z-scores, and BMD were evaluated with a linear regression model. The results showed that phenotype and PTH levels were significantly associated with the TBLH BMD Z-scores in patients with

SMA (t = 2.847, P = 0.008 and t = 2.572, P = 0.015, respectively) (Table 3); phenotype was significantly associated with the LS BMD Z-scores (t = 2.762, P = 0.009) (Table 4).

Table 3  
Related factors for TBLH BMD in children with SMA

Model	Unstandardized Coefficients		Standardized Coefficients	t	P
	Beta	Std error	Beta		
Constant	-8.083	2.261		-3.575	0.001
Sex	-0.574	0.608	-0.159	-0.943	0.353
Age at DXA	0.008	0.131	0.014	0.058	0.954
Disease course	-0.149	0.157	-0.238	-0.946	0.351
Phenotype	1.599	0.562	0.441	2.847	0.008
PTH	0.068	0.026	0.417	2.572	0.015
25-OH-D	0.004	0.017	0.040	0.214	0.832
ASMR Z-score	-0.015	0.259	-0.010	-0.057	0.955
R <sup>2</sup> = 0.595					
ASMR: appendicular skeletal muscle mass weight ratio; BMD: bone mineral density; DXA: dual-energy X-ray absorptiometry; PTH: parathormone; SMA: spinal muscular atrophy; TLBH: total body less head.					

Table 4  
Related factors for LS BMD in children with SMA

Model	Unstandardized Coefficients		Standardized Coefficients	t	P
	Beta	Std error	Beta		
Constant	-6.753	1.923	-0.210	-3.511	0.001
Sex	-0.591	0.517	0.130	-1.143	0.262
Age at DXA	0.054	0.111		0.485	0.631
Disease course	0.016	0.134	0.033	0.120	0.905
Phenotype	1.320	0.478	0.466	2.762	0.009
PTH	0.041	0.022	0.326	1.848	0.074
25-OH-D	0.018	0.015	0.249	1.222	0.231
ASMR Z-scores	0.026	0.220	0.022	0.117	0.908

R<sup>2</sup> = 0.327

ASMR: appendicular skeletal muscle mass weight ratio; BMD: bone mineral density; DXA: dual-energy X-ray absorptiometry; LS: lumbar spine; SMA: spinal muscular atrophy; PTH: parathormone.

## 4. Discussion

The evaluation of bone status has become an important part of SMA management due to the availability of the intrathecal treatment, nusinersen, and the clinical development of other systemic approaches. However, in mainland Chinese patients with SMA, the BMD value remains unknown. This was the first evaluation of bone health in Chinese children with SMA based on DXA scanning in 40 patients with SMA type 2 or 3. We obtained baseline data on BMD and analyzed its related factors in this population, which could help to improve bone health management, select appropriate interventions to prevent low-trauma fractures, and evaluate the effects of treatment drugs.

Patients with SMA have an increased probability of pathological low bone mineral content due to muscle atrophy, limited development of gross motor functions, long-term low activity, insufficient vitamin D intake, and osteoporosis, which increases the risk of fragility fractures, severely affecting the quality of life. Skeletal system complications have been previously reported in children with SMA types 1–3. In 1986, Burke et al. [15] presented three cases of children with SMA type 1 with multiple perinatal fractures. Poruk et al. [16] reported that the mean values of whole-body BMD and LS BMD of 47 patients with SMA type 1 were both much lower than those of age-matched healthy controls. In recent years, an increasing number of BMD studies have included children with SMA type 2 or 3. Vai et al. [17] confirmed that LS bone mineral apparent density Z-score significantly decreased below - 1.5 in 50% of children with SMA

type 2 or 3, and fractures occurred in 36.7% of patients including four patients with peripheral fractures and seven with vertebral fractures. Wasserman et al. [18] reported a BMD Z-score below  $-2.0$  in 85% of 62 patients with SMA types 1–3, and osteoporosis was diagnosed in 12.9% of these patients. Furthermore, fractures and osteoporosis could occur even in younger patients aged 3–4 years. In our cohort including patients with SMA type 2 or 3, 67.5% of patients had BMD Z-scores  $\leq -2.0$ , consistent with the results of these previous studies. We suggested that low BMD is also frequently encountered in mainland Chinese patients with SMA, and it is necessary to regularly test and evaluate the bone status of children with SMA.

Our study found that the phenotype was mainly associated with the TBLH BMD and LS BMD Z-scores. Both the TBLH BMD and LS BMD Z-scores of children with SMA type 2 were significantly lower than those of the children with type 3. Wasserman et al. [18] also reported that patients with SMA type 1 had significantly lower BMD Z-scores at all skeletal sites compared to those with SMA type 2 or 3. This study showed that the more severe the phenotype, the lower the BMD Z-score. The effect of the severity of the phenotype on BMD may be related to numerous factors. Low BMD is related to the degree of muscle atrophy and motor function. The more severe the phenotype, the more obvious the muscle atrophy and the lower the motor function scores. Behringer et al. [19] revealed that ASM atrophy in SMA type 2 was more obvious than that in SMA type 3, while weight-bearing activities and traction of muscle could directly affect the increase of BMD. Conversely, the survival motor neuron (SMN) protein may directly influence BMD. Khatri et al. [20] revealed that the reduction of BMD in pediatric patients with SMA tends to be more pronounced than that in patients with other neuromuscular diseases. A previous study confirmed that the SMN protein plays an important role in bone remodeling and affects bone metabolism by regulating the expression of osteoclast stimulating factor by osteoclasts [21]. It has been reported that in patients with SMA, the more severe the phenotype, the lower the amount of the SMN protein. Therefore, a high incidence of low BMD and fractures in patients with SMA may not be simply attributed to muscle weakness and lack of exercise but is one of the primary symptoms of the disease itself [22, 23].

Multiple studies have reported high fracture prevalence in children with SMA, while in our study, only 5% (2/40) of children with SMA children had fractures, which was significantly lower than the fracture rate of 36–46% reported by other studies [17, 24, 25]. The low rate of fractures in our patients may be related to their decreased participation in outdoor activities and rehabilitation. In our cohort, the patients with SMA were over-protected by their parents and seldom went outdoors to avoid possible injury, and only 30% (12/40) of the children visited a formal rehabilitation department for regular physical treatment for 1–3 years. The fractures in our patients occurred in children with regular long-term rehabilitation training and activities. One study has reported that fractures in patients with SMA and osteoporosis may occur in the regular rehabilitation process [26]. With the development of multidisciplinary management and intrathecal administration of nusinersen in China, patients will inevitably face more rehabilitation training and a return to social life, and the proportion of fractures in Chinese patients may increase. Due to the high prevalence of low BMD in this population, we recommend the regular monitoring of BMD for Chinese patients with SMA in the future, and the appropriate exercise and rehabilitation methods must be well arranged according to their BMD data.

A low 25-OH-D level was found in 37.5% of our patients with SMA type 2 or 3, consistent with the findings of studies in other countries [27]. Our study also showed that the serum PTH level was correlated with TBLH BMD in the linear regression model. Since PTH can promote bone resorption, elevated PTH levels can lead to bone density reduction. It is known that there is a negative relationship between vitamin D and PTH levels. Hence, vitamin D deficiency must be corrected to avoid an abnormal increase in bone resorption due to increased PTH secretion. Notably, vitamin D is a steroid hormone that can promote the absorption of Ca and P by small intestinal mucosa cells, thereby increasing blood Ca and P concentrations, which are beneficial to new bone formation and calcification, thus playing an important biological role in bone health. In 2018, international SMA management consensus [28] experts recommended that vitamin D levels and intake should be monitored annually, and supplements should be administered in the presence of low vitamin D levels or osteoporosis. However, in our study, none of the patients used vitamin D and Ca supplements regularly. This indicated that Chinese clinicians should pay more attention to this aspect to promote the bone health status of patients with SMA.

Although our study was the first to report a comprehensive view of BMD and fracture history across pediatric SMA types 2 and 3 in China, there were still several limitations. First, children with SMA type 1 were not included in our study. Second, the small sample size limited any detailed statistical analysis on differences among subtypes. Finally, our report cross-sectionally examined bone mineral density, lacking long-term monitoring and follow-up.

We conclude that low BMD was commonly observed in mainland Chinese patients with SMA and more than one-third of our patients also had vitamin D insufficiency or deficiency. BMD Z-scores at all skeletal sites of patients with SMA type 2 were substantially lower than those of patients with SMA type 3. The SMA phenotype and serum PTH level were the factors associated with the BMD of the patients. Therefore, the regular monitoring of BMD and serum vitamin D levels and timely intervention are of great importance in children with SMA. In a more thorough future investigation, the sample size must be expanded to minimize the bias of BMD data for better multidisciplinary management and individual treatment of patients with SMA.

## Abbreviations

SMA: spinal muscular atrophy; TBLH: total body less head; LS: lumbar spine; BMD: bone mineral density; DXA: dual-energy X-ray absorptiometry; SD: standard deviation; MLPA: multiplex ligation-dependent probe amplification; SMN: survival motor neuron; PTH: serum parathormone; ASM: appendicular skeletal muscle mass; TM: total mass; ASMR: ASM ratios; FMP: fat mass percentage; ISCD: International Society for Clinical Densitometry.

## Declarations

## Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Capital Institute of Pediatrics (No. SHERLL2017007). The written informed consent documents for children were obtained from their parents or guardians. All methods were carried out in accordance with relevant guidelines and regulations.

## **Consent for publication**

Written consent for publication was obtained from the parents of all subjects as part of their written informed consent to participate in this study.

## **Availability of data and materials**

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

## **Competing interests**

The authors declare that they have no competing interests.

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## **Authors' contributions**

XYP drafted manuscript. YJQ critically revised manuscript. JTL contributed to acquisition, analysis, and interpretation of data. XYS and JW collected and analyzed the patient data. XHL, FS contributed to conception and design. All authors reviewed the manuscript.

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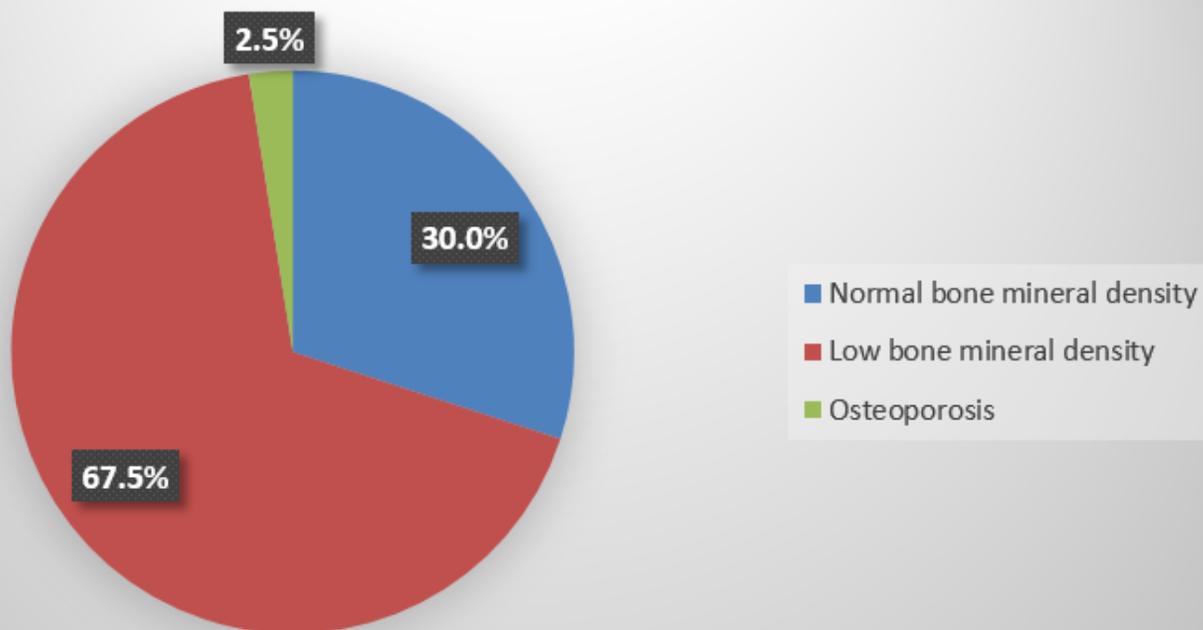
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## Figures

## Bone Mineral Density (Total=40)



**Figure 1**

Distribution of BMD in pediatric patients with SMA type 2 or 3 Based on the 2019 International Society for Clinical Densitometry criteria, 2.5% (1/40) of patients in this study were diagnosed with osteoporosis, and 67.5% (27/40) were diagnosed with low BMD BMD: bone mineral density; SMA: spinal muscular atrophy.