Radiology

Statistical Confirmation of a Method of US Determination of Bone Age

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Conflicts of interest are listed at the end of this article.

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Background: There is limited literature on conventional US to assess bone age.

Purpose: To determine the diagnostic performance of US in the assessment of abnormal bone age in Chinese children.

Materials and Methods: In this prospective study, children and young adults aged between birth and 19 years from a large provincial teaching hospital were enrolled from January to November 2020. Children without clinical diseases potentially affecting skeletal growth were included in the normal-value group. Children with clinically suspected growth disturbances who were undergoing bone age evaluation were included in the validation group. Ossification ratios (ie, the ratio of the height of the epiphyseal ossification center to the entire epiphysis, including the cartilaginous component) of the radius, ulna, and femur from all the children were measured using US. Ultrasonic skeletal maturity scores (ie, the summation of ossification ratios of the radius, ulna, and femur multiplied by 100) collected from children in the normal-value group were used for score-for-age curve fitting through Box-Cox power exponential distribution. Test performance characteristics for the ability of US to help diagnose abnormal bone age were determined using radiographic bone age as a reference standard. Statistically significant difference between groups was determined by using a paired-sample *t* test.

Results: A total of 1089 children (median age, 9 years [interquartile range, 3–14 years]; 578 boys) were enrolled, including 929 children (mean age, 8 years [interquartile range, 4–12 years]; 515 boys) in the normal-value group and 160 children (mean age, 9 years [interquartile range, 7–11 years]; 63 boys) in the validation group. Ultrasonic bone ages in the validation group were evaluated with use of the lists of normal score-for-age values. With radiographic bone age as a reference standard, US could help diagnose abnormal bone age with high sensitivity (93% [14 of 15 participants; 95% CI: 66, 100] for boys, 100% [14 of 14 participants; 95% CI: 73, 100] for girls) and specificity (98% [47 of 48 participants; 95% CI: 88, 100] for boys, 98% [81 of 83 participants; 95% CI: 91, 100] for girls).

Conclusion: The US scoring system established can be used to evaluate bone age with high sensitivity and specificity.

Clinical trial registration no. ChiCTR1900027917

Online supplemental material is available for this article.

Bone age is the degree of maturation of a child's skeleton (1). The assessment of bone age and its comparison with chronological age are particularly useful in pediatric endocrinology for estimations of an individual's final height and to study other growth problems in clinical pediatrics (2,3). The most common bone age assessment methods are the Greulich-Pyle (GP) (4) and Tanner-Whitehouse (TW) (5) methods, both of which involve left hand and wrist radiographs. However, the World Health Organization (6) estimates that a radiography machine may not be available for as much as three-quarters of the world's population. In contrast, US is becoming cheaper and more portable (3). US has been used to assess bone age in infants (7,8), young children (ie, birth to 6 years of age) (3,9–11), and teenagers (10–17 years of age) (12) based on the GP atlas. Yet, all these methods were more complicated and time consuming in image acquisition and interpretation than radiography (3,7–12).

In a recent study, Wan et al (13) attempted to assess bone age based on evaluation of the ossification ratio, which was defined as the ratio of the height of the ossification center to the epiphysis of the bone. The authors considered bone maturation as a process of the ossification ratio from 0%–100%, and the scoring system was based on the continuous bone growth process. There are significant positive correlations between ossification ratios measured with US and bone ages obtained by means of radiography of the hand and wrist (13). However, it was time consuming to image all 13 bones (7–9 minutes for data acquisition and measurement to calculate the ossification ratio) compared with radiography. In a more recent study by the same author group (14), three bones (distal end of the radius, distal end of the ulna, and medial epicondyle of the femur) were imaged with use of US. It took 2–3 minutes for data acquisition and measurement of the ossification ratios of these three bones. The Pearson correlation coefficient (*r* value) between the summation of the ossification ratios of the radius, ulna, and femur and the radiographic bone age was 0.97 in boys and 0.96 in girls. The authors concluded that the summation of the ossification ratios of the radius, ulna, and femur obtained with US has the potential to enable assessment of bone age

Abbreviations

BCPE = Box-Cox power exponential, GP = Greulich-Pyle, TW = Tanner-Whitehouse

Summary

The US scoring system established in this study can be used to diagnose abnormal bone age in children aged from birth to early adulthood with high sensitivity and specificity.

Key Results

- Normal values of ultrasonic skeletal maturity score for age were predicted.
- US helped diagnose abnormal bone age with high sensitivity (93% [14 of 15 participants] for boys, 100% [14 of 14 participants] for girls) and specificity (98% [47 of 48 participants] for boys, 98% [81 of 83 participants] for girls), with radiographic bone age as the reference standard.

quantitatively in an efficient and easy manner. However, no clinically useful normal values of ossification ratios in healthy children were obtained.

In this study, we aimed to acquire normal values of the ultrasonic skeletal maturity score (the summation of ossification ratios of the radius, ulna, and femur multiplied by 100) for age and to determine the diagnostic performances of the method.

Materials and Methods

Study Participants

Our prospective diagnostic accuracy study followed Standards for the Reporting of Diagnostic Accuracy Studies guidelines (15) and was approved by the institutional review board of our hospital. Our study population consisted of a convenience sample of children who met predetermined inclusion criteria. Written informed consent was obtained from the parent(s) or guardian(s) of the participants who could not provide it on their own. Data generated by the authors or analyzed during the study are available at *http://www.chictr.org.cn/showproj.aspx?proj=44293* (Chinese Clinical Trial Registry no. ChiCTR1900027917).

The children, who were residents of the city where our large provincial teaching hospital is located, were evaluated from January to November 2020. Two groups of children (the normal-value group and validation group) were included. Inclusion criteria in the normal-value group were age younger than 19 years and the absence of acute trauma, infection, arthritis, or dysplasia of the hand, wrist, or knee. In this group, we excluded children with clinical diseases potentially affecting skeletal growth. Inclusion criteria in the validation group were children aged between birth and 19 years with clinically suspected growth disturbances. In this group, we excluded children who did not undergo radiography for bone age evaluation within 2 weeks after US evaluation (Fig 1).

US and Radiography Examination

US of the wrist and knee was performed with a conventional ultrasonic machine (Aloka ProSound F75, Hitachi Medical, or Logiq E9, GE Medical Systems) equipped with a 10- or 12-MHz transducer.

The investigators who performed US and interpreted the results consisted of four radiologists (C.Z., Y.Z., Q.F., and P.L., with 20, 6, 5, and 1 year of experience, respectively). Investigators Y.Z., Q.F., and P.L. underwent a 30-minute bone age US training with the protocol by C.Z. (who has evaluated hundreds of bone age US examinations) and finished 20 bone age US examinations under the supervision of C.Z. before the start of the study. Two radiologists (J.W. and C.Z., with 2 and 10 years of experience in bone age radiography evaluation, respectively) interpreted the radiographs.

All children (both in the normal-value group and the validation group) underwent US of the left hand and knee according to the protocol in our study. The children in the validation group underwent left hand and wrist radiographic bone age estimations within 2 weeks of US. In the normal-value group, US imaging was performed by one investigator (C.Z.), and in the validation group, US imaging was performed by one of several investigators (C.Z., Y.Z., Q.F., or P.L.).

The US examinations were performed in compliance with the protocol described in a previous article (14). To summarize briefly, for imaging of the radius, the ultrasonic probe was placed longitudinally oriented along the distal lateral aspect, with the forearm placed in the neutral position to image the styloid process. For imaging of the ulna, the probe was placed longitudinally oriented along the distal lateral aspect in the coronal plane, with pronation of the forearm to image the styloid process. For imaging of the femur, the probe was placed along the medial collateral ligament in the coronal plane to image the medial epicondyle, with the participant lying supine and the limbs in extension. The ratio of the height of the epiphyseal ossification center to the entire epiphysis, including the cartilaginous component, was calculated to obtain the ossification ratio of each of the three bones (Fig 2). The summation of the ossification ratios of the radius, ulna, and femur multiplied by 100 (ie, the ultrasonic skeletal maturity score) was calculated for score-for-age curve fitting. More details on US imaging are described in Appendix E1 (online). The investigators were blinded to the chronological age and other medical information of the children during US scanning and measuring.

Radiographs of the left hand and wrist of the children in the validation group were interpreted with the third edition of the TW method (hereafter referred to as TW3) (16) to obtain radiographic bone age by two investigators (J.W. and C.Z.) who were blinded to the children's medical information. When different bone ages were evaluated by the investigators, the mean value was used to determine the bone age of the child. The radiographs were also interpreted with the GP atlas (for Chinese patients) (17) by two investigators (J.W. and C.Z.) to obtain GP atlas bone age. The mean value was selected when different GP atlas bone ages were evaluated.

Score-for-Age Curves and the Predicted Normal Values

Box-Cox power exponential (BCPE) distribution has been used in growth studies for height-for-age and weight-for-age

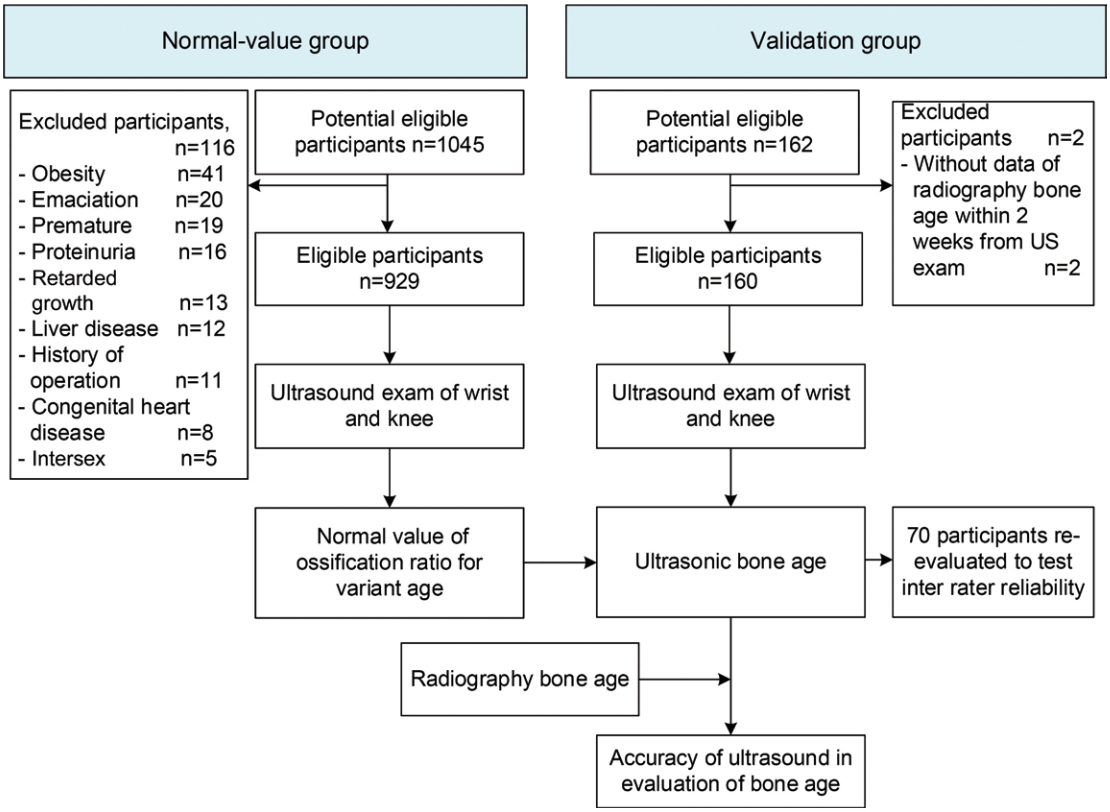


Figure 1: Flowchart of study. A body mass index in the 97th percentile or greater (or weight-for-age Z score ≥3 for children <5 years of age) was defined as obesity; a body mass index in the third percentile or less (or weight-for-age Z score less than or equal to −2 for children <5 years of age) was defined as emaciation.

curve fitting (18–20). BCPE distribution with curve smoothing by cubic splines was selected as the approach for constructing the score-for-age curves in our study. Other distributions (Box-Cox Cole and Green and Box-Cox *t*) were compared with BCPE to confirm the best distribution for the ultrasonic skeletal maturity score for age. The BCPE is a flexible distribution that consists of four parameters denoted as μ (median), σ (coefficient of variation), ν (skewness), and τ (kurtosis). Smooth centile curves of the ultrasonic skeletal maturity score were obtained by modeling each of four parameters (μ, σ, ν, and τ) of the distribution as a cubic spline function of chronological age. The model with the smallest generalized Akaike information criterion, or GAIC (3), value was obtained for optimal fit. Worm plots and Z statistics were used to test goodness of fit (21). Normal values and percentiles of score for age were predicted through the selected model. Score increments for age were obtained as the increments of score per year.

Diagnostic Performances and Interrater Reliability

Ultrasonic bone ages of the children in the validation group were evaluated with use of the lists of normal values of score for age. The ultrasonic bone age is defined as the age of boys (or girls) for whom that the score lies on the 50th percentile (22). The agreement and differences between ultrasonic bone age and radiographic bone age were assessed.

In this study, skeletal maturity scores between the 2.5th percentile and 97.5th percentile were considered normal, while scores less than the 2.5th percentile or greater than the 97.5th percentile were considered abnormal. Test performance characteristics for the ability of US to help diagnose abnormal bone age, including sensitivity and specificity, were determined using radiographic bone age as the reference standard. To examine the effect of experience on diagnostic performance, a subgroup analysis in the validation group stratified by less experienced investigators (Y.Z., Q.F., and P.L.) and a more experienced investigator (C.Z.) was performed.

To confirm the reliability of assessment of ultrasonic bone age, US images in children evaluated by the less experienced investigators were re-evaluated by the more experienced investigator. Interrater reliability was calculated (intraclass correlation coefficient).

Statistical Analysis

Score-for-age curves were fitted with the generalized additive model for location, scale, and shape package, or GAMLSS, in R 3.6.3 (The R Foundation for Statistical Computing). Statistical analyses were performed using SPSS 22.0 (IBM) and Prism 8.0 (GraphPad). The agreement between ultrasonic bone age and radiographic bone age was analyzed with use of Bland-Altman analysis. A linear regression model was used for the assessment of correlation between ultrasonic bone age and radiographic bone age. Statistical significance between groups was determined by using a paired-sample *t* test. $P < .05$ was considered to indicate a statistically significant difference.

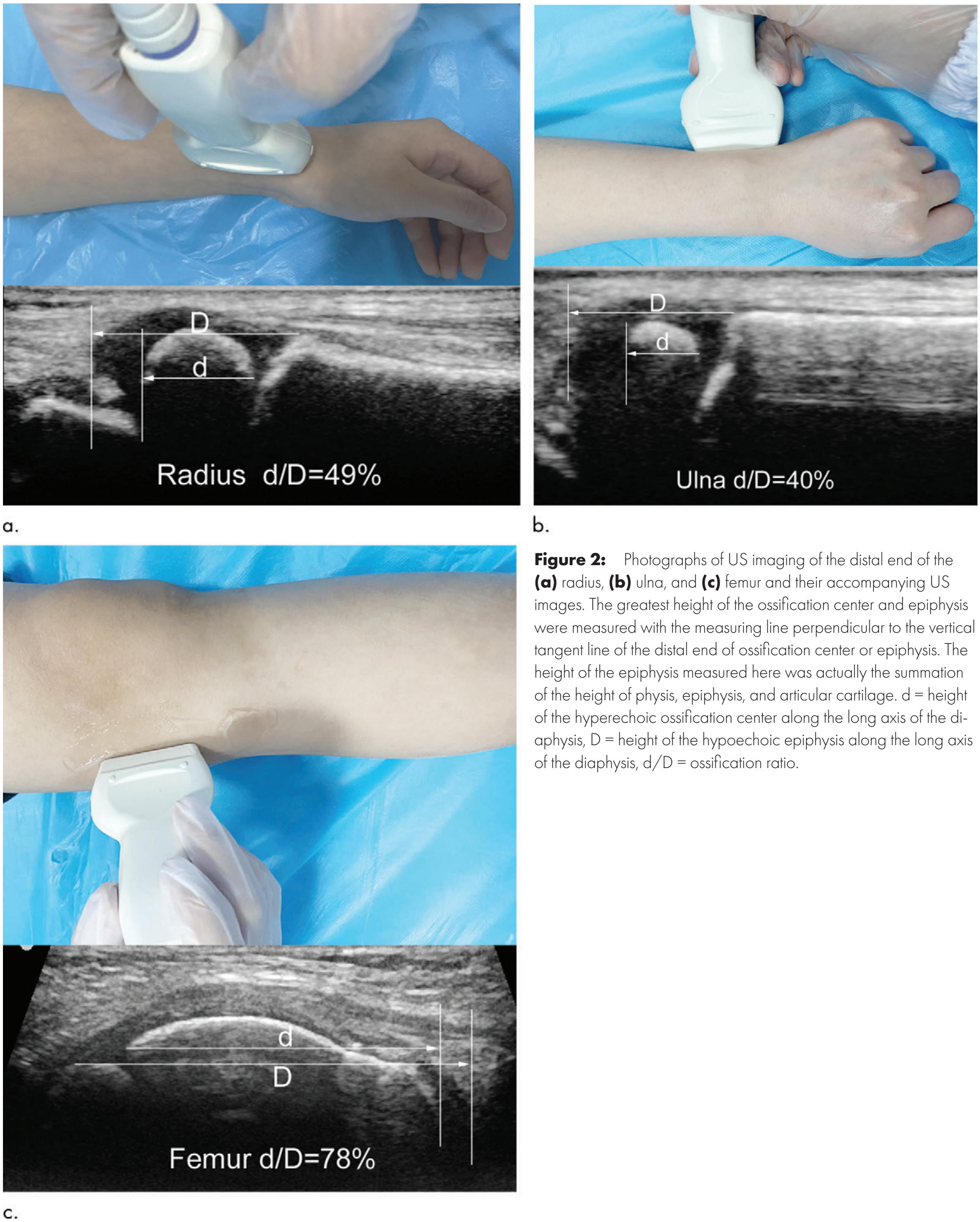


Figure 2: Photographs of US imaging of the distal end of the **(a)** radius, **(b)** ulna, and **(c)** femur and their accompanying US images. The greatest height of the ossification center and epiphysis were measured with the measuring line perpendicular to the vertical tangent line of the distal end of ossification center or epiphysis. The height of the epiphysis measured here was actually the summation of the height of physis, epiphysis, and articular cartilage. d = height of the hyperechoic ossification center along the long axis of the diaphysis, D = height of the hypoechoic epiphysis along the long axis of the diaphysis, d/D = ossification ratio.

Results

Participant Characteristics

The parents or guardians of 1207 children were approached for the enrollment of their child. Then, 118 potentially eligible participants were excluded. A total of 1089 children (median age, 9 years [interquartile range, 3–14 years]; 578 boys) were enrolled into the study (Fig 1), with 929 children (median age, 8 years [interquartile range, 4–12 years]; 515 boys) in the normal-value group and 160 children (median age, 9 years [interquartile range, 7–11 years]; 63 boys) in the validation group.

Score-for-Age Curves and the Predicted Normal Values

The automated function lms() confirmed BCPE was the best distribution (compared with Box-Cox Cole and Green and Box-Cox *t*) for ultrasonic skeletal maturity score for age. For boys, the selected model for constructing the score-for-age curves was as

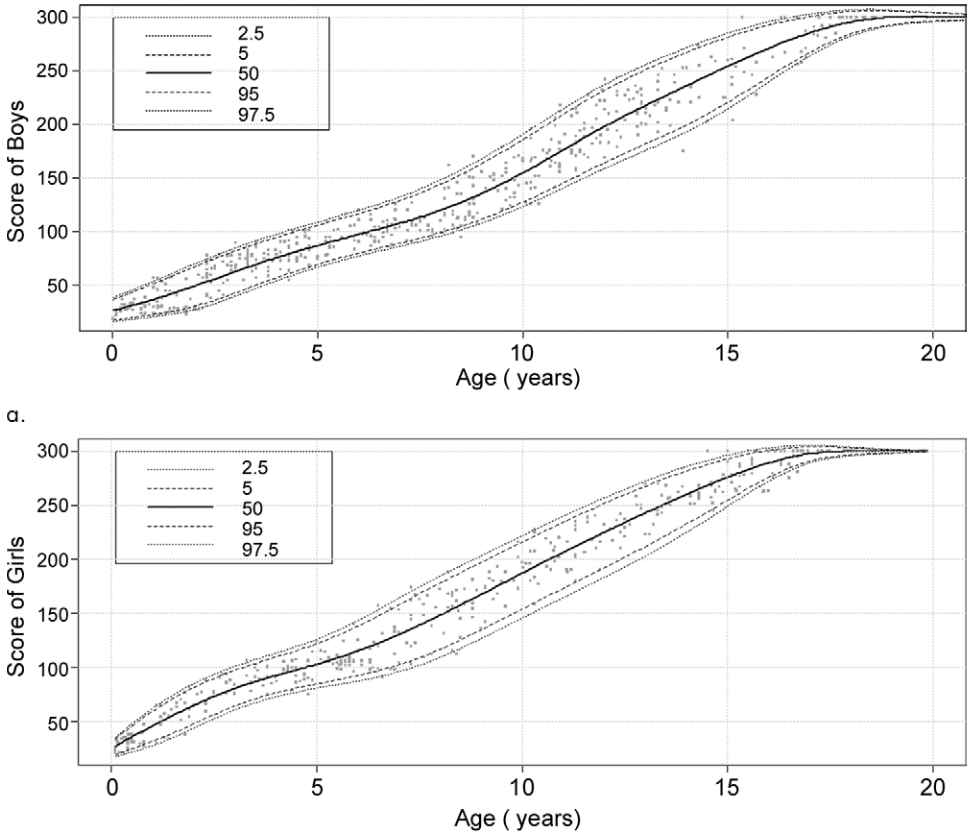


Figure 3: Centile curves using Box-Cox power exponential distribution for the ultrasonic skeletal maturity score of **(a)** boys and **(b)** girls.

follows: BCPE [λ = 0.90, $df(\mu)$ = 6.6, $df(\sigma)$ = 3.9, $df(\nu)$ = 2.0, τ = 1]; for girls, BCPE [λ = 0.65, $df(\mu)$ = 7.1, $df(\sigma)$ = 4.3, $df(\nu)$ = 1.7, τ = 1], where λ is the power of the transformation applied to age before fitting the model, $df(\mu)$ the degree of freedom for the cubic splines fitting the median (μ), $df(\sigma)$ the degree of freedom for the cubic splines fitting the coefficient of variation (σ), $df(\nu)$ the degree of freedom for the cubic splines fitting the skewness (ν), and τ the parameter related to the kurtosis (20).

The fitting curves are shown on Figure 3. The worm plots for the selected models implied that the fit was adequate. The results of Z statistics showed that almost all the absolute values of z were smaller than two. This was considered indicative of fit in the variance of the residuals in the model. The predicted normal values and percentiles of score for age with the selected model are listed in Table 1. The ages attaining a full score of 300 were 19 years for boys and 18 years for girls (Fig 3, Table 1).

Reference values of the increments of the 50th percentile of score for age were calculated and are presented in Figure 4.

Table 1: Predicted Normal Values and Percentiles of the Ultrasonic Skeletal Maturity Score for Age

	Boys			Girls		
Age (y)	C2.5	C50	C97.5	C2.5	C50	C97.5
1	21	37	54	29	46	61
2	28	49	70	45	65	84
3	41	63	85	61	80	100
4	55	76	97	74	92	112
5	68	87	108	82	103	125
6	78	98	119	89	115	142
7	87	108	132	98	130	162
8	97	120	147	111	148	183
9	109	136	167	129	167	202
10	124	155	190	148	187	220
11	142	177	214	167	206	238
12	161	198	236	186	225	256
13	178	218	255	205	243	271
14	195	236	271	227	260	285
15	216	254	285	250	276	296
16	241	272	295	273	289	303
17	265	286	303	289	298	305
18	283	296	307	296	300	304
19	293	300	307	298	300	302

Note.—Data are the ultrasonic skeletal maturity score for age. C = centile.

Diagnostic Performances and Interrater Reliability

The mean differences between ultrasonic bone age and radiographic bone age are shown in Figure 5. The differences between ultrasonic bone age and radiographic bone age (evaluated with the TW3 method) were calculated. Ultrasonic bone age and radiographic bone age correlated well in both boys (R^2 = 0.95, P < .001) and girls (R^2 = 0.95, P < .001). There were no differ-

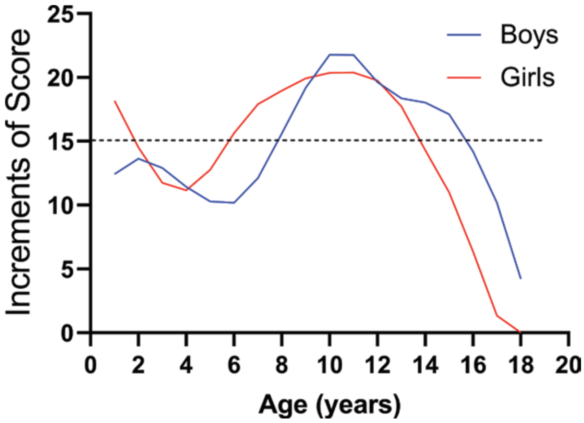


Figure 4: Graph shows increments of score according to age. Increments of the ultrasonic skeletal maturity score were obtained as the increments of score per year. The predicated median values (50th percentile) of the scores were used for the calculation of increments. The ages during which relatively high increase in score (eg, >15 points) occurred were 0–2 years and 6–14 years of age for girls and 8–16 years for boys. For boys, the score increased slowly during 0–8 years of age (12 points per year). Then, the fastest increase could be observed during 8–16 years of age (18 points per year), followed by the slowing down of the rate of increase during 17–18 years of age (10 points per year). For girls, a rapid growth of score could be observed in the first 2 years of life (18 points per year), followed by a slowdown during 3–6 years of age (10 points per year). The fastest growth rate came during 6–14 years of age (18 points per year), followed by the slowest growth rate during 15–18 years of age (6 points per year).

ences between the value of the slope and 1 in boys (slope, 0.99; $P = .80$). The value of the slope in girls was smaller than 1 (slope, 0.95; $P = .02$). There were no differences between the value of the intercept and 0 (intercept, 0.30, $P = .46$ in boys; intercept, 0.37, $P = .07$ in girls). The estimated error about the regression line was 0.75 in boys and 0.53 in girls (Fig 6).

Images from 70 children in the validation group were re-evaluated. The interrater repeatability was high (the intraclass correlation coefficient was 0.97 [95% CI: 0.95, 0.98], $P < .001$).

The prevalence of abnormal bone age (including delayed bone age and advanced bone age), which was confirmed using radiographic bone age, was 24% (15 of 63 participants) for boys and 17% (16 of 97 participants) for girls. Test performance characteristics are given in Table 2.

The mean time ± standard deviation for US examination was 2 minutes ± 2. Among US examinations performed by operators with less experience, the mean examination time was 3 minutes ± 2. Among US examinations performed by the operator with more experience, the mean examination time was 1 minute ± 1.

Discussion

Conventional US has the potential to enable assessment of bone age quantitatively in children from birth to near adulthood in an efficient and easy manner (14). However, no clinically useful normal values have yet been obtained. In this study, normal val-

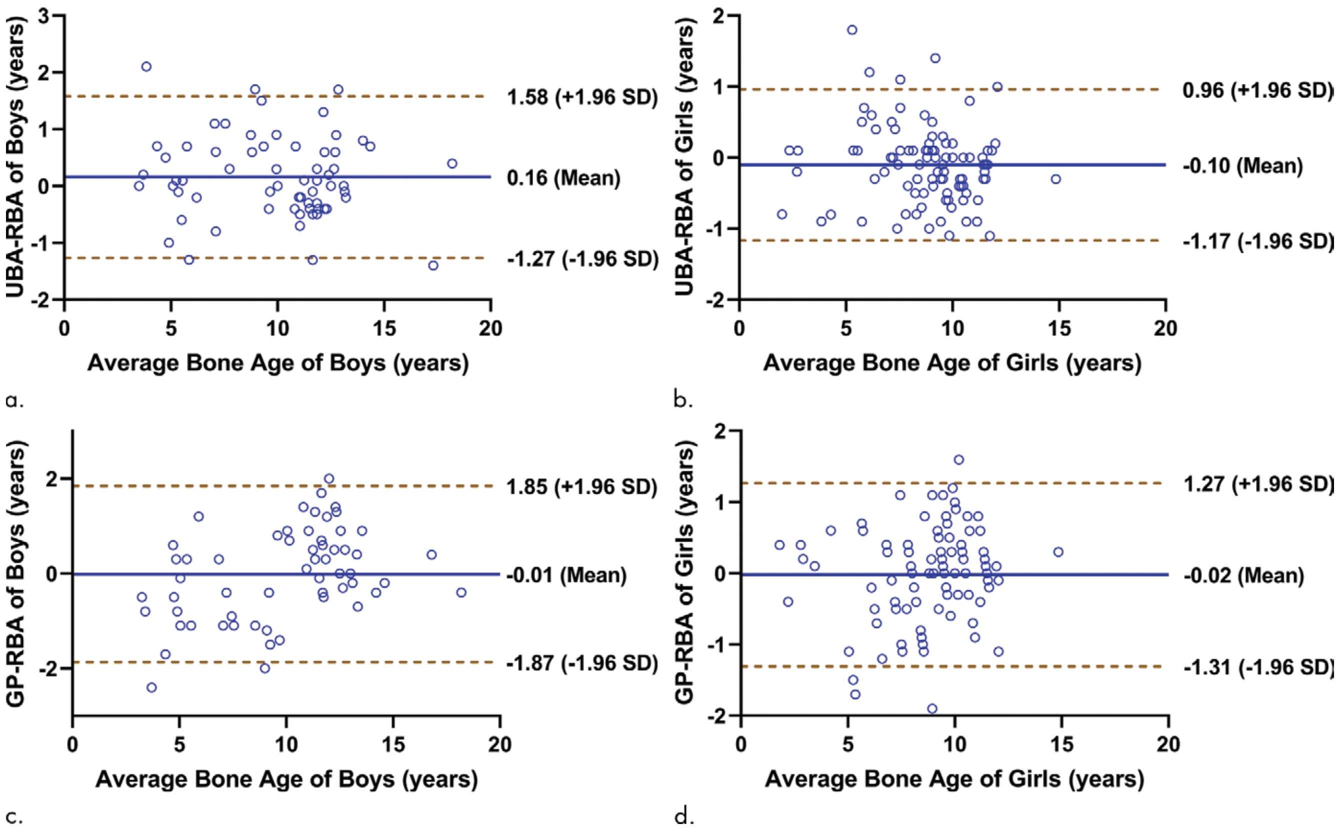
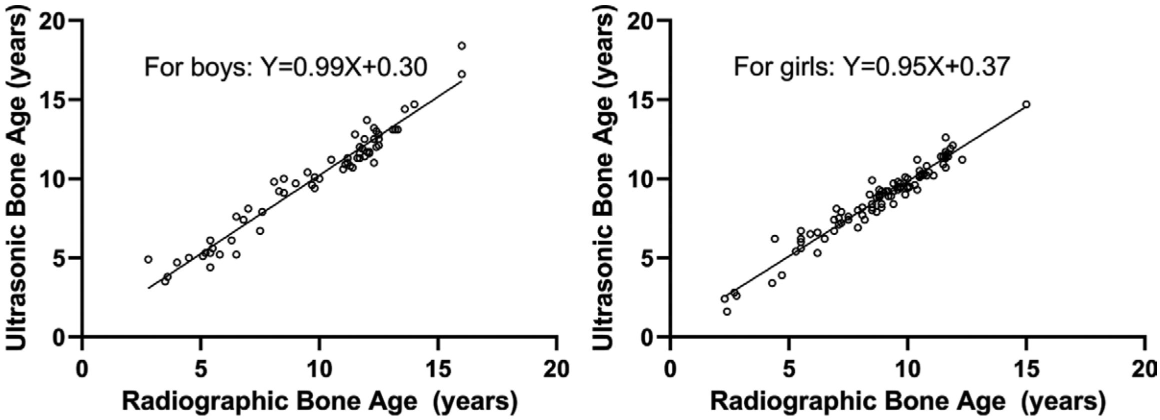


Figure 5: Bland-Altman graphs of age difference versus average age between ultrasonic bone age (UBA) and radiographic bone age (RBA) evaluated with use of the third edition of the Tanner-Whitehouse method for **(a)** boys and **(b)** girls and between radiographic bone age evaluated using the Greulich-Pyle atlas (GP) and radiographic bone age for **(c)** boys and **(d)** girls. SD = standard deviation.



a. b.

Figure 6: Simple linear regressions show the relationship between radiographic bone age (evaluated with use of the third edition of the Tanner-Whitehouse method) and ultrasonic bone age in **(a)** boys and **(b)** girls in the validation group.

Table 2: Test Performance Characteristics in the Validation Group

Variable	Sensitivity	Specificity
Sex		
Boys (*n* = 63)	93 (14/15) [66, 100]	98 (47/48) [88, 100]
Girls (*n* = 97)	100 (14/14) [73, 100]	98 (81/83) [91, 100]
Operator experience		
Evaluation by less experienced operators* (*n* = 70)	92 (12/13) [62, 100]	98 (56/57) [89, 100]
Evaluation by an experienced operator† (*n* = 90)	100 (16/16) [76, 100]	97 (72/74) [90, 100]

Note.—Radiographic bone age was used as the reference standard. Data are percentages, with numbers of participants in parentheses and 95% CIs in brackets.

* Less experienced operators were Y.Z., Q.F., and P.L., with 6, 5, and 1 year of experience, respectively.

† The experienced operator was C.Z., with 20 years of experience.

ues of ultrasonic skeletal maturity scores for age were predicted and used to evaluate ultrasonic bone age. US helped diagnose abnormal bone age with high sensitivity (93% [14 of 15 participants; 95% CI: 66, 100] for boys, 100% [14 of 14 participants; 95% CI: 73, 100] for girls) and specificity (98% [47 of 48 participants; 95% CI: 88, 100] for boys, 98% [81 of 83 participants; 95% CI: 91, 100] for girls), with radiographic bone age as the reference standard. The mean time for US examination was 2 minutes ± 2.

According to the age-specific centile curves of the ultrasonic skeletal maturity score in our study, the score increased sharply during 8–16 years of age for boys. For girls, two sharp increase periods could be observed during 0–2 years and 6–14 years of age. This was similar to findings in the study by Zhang et al (16) that established the standards of TW3 radiographic skeletal maturity for Chinese children. Our results indicate the skeletal maturities of boys lag behind those of girls. The 50th percentile ages at which the full ultrasonic skeletal maturity score (score, 300) was attained were 18 years for girls and 19 years for boys. This was quite different from the study by Zhang et al with the TW3 method, in which the full scores (score 1000) were attained at 15 years of age for girls and 16 years of age for boys. This is because with use of the TW3 method, the full marks of the maturity score were assigned at the moment of the epiphyseal fusion of the bones (5,16). In our study, the full marks were assigned when the ossification center fused with the metaphysis and no hypoechoic physis could be identified on US images. This complete fusion happened around 17 years of age for girls and 18 years of age for boys, consistent with what can be identified in the GP atlas for Chinese children (17).

In our study, the 95% CIs for the differences between ultrasonic bone age and radiographic bone age (with the TW3 method) were −1.27 to 1.58 years for boys and −1.17 to 0.96 years for girls, both of which were smaller than that between the radiographic bone ages interpreted with the GP atlas and with the TW3 method (−1.87 to 1.85 years for boys and −1.31 to 1.27 years for girls). In the study by Bull et al (23), radiographs of the left hand and distal radius were analyzed to compare the GP method and TW2 method in the evaluation of bone age. The 95% CI for the difference between the two methods was −1.52 to 2.28 years. There were relatively smaller intervals for the differences between ultrasonic bone age and radiographic bone age (with the TW3 method) in our study than those between radiographic bone ages interpreted with the GP atlas and with the TW3 method. The high sensitivity and specificity of ultrasonic bone age to help diagnose abnormal bone age also suggest the ultrasonic skeletal maturity scoring system established in our study could be an alternative modality for evaluation of bone age.

Our study has several limitations. First, the children were from outpatient and inpatient departments of a hospital and not from a healthy population. Nonetheless, the children with emaciation, obesity, or any clinical disease potentially affecting skeletal growth were excluded from the normal-value group after assessment of medical history, physical examination, laboratory test results, and imaging results. Second, the children belonged to a single ethnic group (Chinese). The lack of diversity of the study population makes it unclear if the reference standard is applicable to other groups. The results will require validation in a more diverse population to be widely useful.

In summary, the US scoring system established in our study can be used to evaluate bone age and to diagnose abnormal bone age in Chinese children aged from birth to early adulthood with high sensitivity and specificity. Further studies are necessary before the scoring system is applied in other ethnic groups.

Author contributions: Guarantor of integrity of entire study, C.Z.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, J.W., P.L.; clinical studies, Y.Z., Q.F., P.L., K.H., C.Z.; statistical analysis, J.W., P.L., C.Z.; and manuscript editing, J.W.

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