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● *Original Contribution*

POTENTIAL VALUE OF CONVENTIONAL ULTRASOUND IN ESTIMATION OF BONE AGE IN PATIENTS FROM BIRTH TO NEAR ADULTHOOD

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Abstract—We aimed to assess the relationship between standard bone age (BA) stratification obtained using plain radiography and that obtained using ultrasound determination of ossification ratio (OR) as a novelty in patients from birth to near adulthood. The ratio of diameters of the ossification center and epiphysis was calculated to evaluate the OR of bones. The ORs of the bones assigned to different weight coefficient were then summed as the skeletal maturity score (SMS). Pearson's correlation *r* between SMSs derived from ORs and BAs was 0.97 in girls ($p < 0.001$) and 0.97 in boys ($p < 0.001$), respectively. There are significant positive correlations between SMSs measured by conventional ultrasound imaging and BAs obtained by radiography of the hand and wrist in patients from birth to near adulthood. The scoring system may potentially provide a quantitative modality to estimate BA by conventional ultrasound. (E-mail: zhangchao_tj@hust.edu.cn)

Key Words: **Ultrasound, Bone age, Epiphysis, Ossification center, Hand, Wrist.**

INTRODUCTION

Many factors influence the progression of skeletal development, including metabolism (Pinhas-Hamiel et al. 2014), endocrine activity (Correa et al. 2017), inflammation (Hill et al. 2009), exercise (Malina et al. 2018), nutrition (Fleshman 2000) and genetics (Creo and Schwenk 2017). The bone age (BA) of a child is an important indicator in growth studies, and has provided useful information in various clinical settings. Bone age has been assessed by means of a hand and wrist radiograph since 1898 (Martin et al. 2011). The Greulich−Pyle (GP) atlas based on American children (Greulich and Pyle 1959) and Tanner−Whitehouse (TW) atlas based on British children (Tanner 1962) are the two most commonly used methods for estimation of BA. The GP method is easy to learn but standards do not exist for weights of different bones, which makes it more reviewer dependent. The third edition of the TW (TW3) may be more accurate but it is more complicated and time consuming (7.9 min) (Creo and Schwenk 2017). Automatic BA assessments, which are usually based on TW methods, have been studied recently. The BoneXpert system (Thodberg et al. 2009) using a unified model combining the TW and GP methods seems an efficient and reliable automated method for evaluation of bone age. However, the usability of the system is still under evaluation (De Sanctis et al. 2014), and high-quality images are needed to obtain reliable results (Spampinato et al. 2017). Some studies have aimed to perform automatic BA assessment using deep-learning methods; these are still in an early phase of development (Mutasa et al. 2018; Booz et al. 2019; Tajmir et al. 2019). What's more, the continuous growth process of bone development was arbitrarily divided into several osseous stages in TW or several developmental levels by the maturational indicators of each bone in the GP atlas. A scoring system based on the continuous growth process of bones will be more promising.

Along with conventional radiography, low-radiation dual-energy X-ray absorptiometry (DXA) and non-radiative magnetic resonance imaging (MRI) and

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ultrasonography (US) have been used to evaluate BA. DXA is the modality used to diagnose osteoporosis. Hand-and-wrist scans by DXA were used to evaluate BA, with radiation doses lower than those of conventional radiography (Pludowski et al. 2005). However, the resolution of DXA hand scans was not high enough to assess all required anatomic details for evaluation of BA with the TW method (Hoyer-Kuhn et al. 2016). Tomei et al. (2014) aimed to evaluate BA using MRI of the hand and wrist. They drew the conclusion that determination of BA with MRI is feasible. Motion artifact and increased cost are the drawbacks to using MRI (Terada et al. 2014; Creo and Schwenk 2017).

Ultrasound is a non-invasive, non-ionizing, accessible and cost-effective imaging modality widely used in clinical work. Bilgili et al. (2003) described a sonographic version of the GP atlas for healthy children from birth to 6 y of age without diseases definitely known to delay or accelerate skeletal maturation. Sonographic scans were targeted on the hyper-echoic ossification centers in the epiphyses of the metacarpals and phalanxes. Each visible carpal bone and the ossification centers were noted on a prepared hand and wrist US chart. Also noted was whether the width of the epiphyses of the phalanxes equaled half the width of the adjacent margins of their shafts. The hand and wrist US chart was then interpreted on the basis of a criterion derived from the GP atlas. The estimated age evaluated with hand and wrist US chart had an excellent correlation with the BA estimated with plain radiography. A similar method was adopted by Hajalioghli et al. (2015) to detect BA abnormalities in children younger than 7 y of age. The study confirmed that the conventional radiographic technique for determining BA abnormalities could be replaced by US; however, both of these studies focused on the patients younger than 6−7 y of age.

The contour of the epiphysis could not be imaged by radiography completely except for the ossification center but could be imaged by ultrasound (Bilgili et al. 2003; Hajalioghli et al. 2015). In this study, we hypothesized that the ossification ratio (OR, ratio of diameter of the ossification center to that of the epiphysis) of long bones in the wrist and hand might be a good parameter in the estimation of BA. We aimed to find the relationship between the ORs of bones and BA in patients from birth to near adulthood and, potentially, provide a quantitative modality for estimation of BA by conventional ultrasound.

METHODS

Patients and instruments

A total of 172 consecutive patients (94 girls and 78 boys) were enrolled from the pediatric outpatient service in our medical institute from March 2017 to December 2018. Informed consents from guardians of the patients were obtained. The ethics committee of the institution approved this study. The study population was selected on the basis of the following inclusion criteria: age <20 y, absence of pathologic modification of the hand and wrist (no direct acute trauma, infection, arthritis, or dysplasia). Three patients were excluded: 2 with hermaphroditism and 1 with congenital polydactyly based on the medical history. Patients with hermaphroditism were excluded because their classification in the male or female group is a thorny problem. The patients complained of mammary development ($n = 79$), short status ($n = 59$), obesity ($n = 20$), irregular menses ($n = 5$), vaginal discharge ($n = 5$), gynecomastia ($n = 3$) and small testicle ($n = 1$). The chronologic age of the patients was 8.4 ± 3.5 y (1.3−18.7 y) for girls and 7.8 ± 5.0 y (0.1−19 y) for boys. The patients underwent left hand and wrist radiography and ultrasonographic examination for BA assessment. Additional information such as sex, date of birth, height and weight, complaints and medical history was gathered from the electronic medical records.

Radiographs of the left hand and wrist were taken according to the instructions in TW3 with a tube−film distance of 91.4 cm. The results were then interpreted with the TW3 method (amended by Zhang et al. (2008) for the Chinese population) by two radiologists who were unaware of the patients' chronologic ages. When different BAs were evaluated, the radiographs were read again by the two radiologists to reach a consensus.

Ultrasound imaging of the left hand and wrist was performed with commercial sonographic machines (LOGIQ e9, GE Medical Systems, Waukesha, WI, USA, or ALOKA Grosound f75, Hitachi Medical Co., Hitachi, Ibaraki, Japan) equipped with a 12- or 10-MHz transducer by one sonographic imaging specialist who was unaware of the plain radiography results.

Ultrasound scanning and measurement

Ultrasonographic scans were targeted at 13 ossification centers and epiphyses of the distal radius and ulna; the first, third and fifth metacarpals; and phalanx. These bones were selected for ultrasonic scans according to TW3-RUS (Tanner et al. 2001), where the 13 bones were assessed for evaluation of BA. Carpal bones are not included in this study because they are irregular in shape, and it is relatively difficult to obtain a standard section for measurement by ultrasound imaging.

The ultrasonic probe was placed on the styloid process of the radius in the coronal plane for imaging of the radius. The probe was placed on the styloid process of the ulna in the coronal plane for imaging of the ulna. The metacarpals and phalanxes were scanned in the sagittal plane from the palmar side of the corresponding bones. The outlines of epiphyses and ossification centers of each bone should appear sharp (Fig. 1).

The diameter of each epiphysis and ossification center was measured. For the radius, ulna and phalanxes, the maximum diameter of the epiphysis was measured from the connection point of the epiphysis and diaphysis to the distal end of the epiphysis along the long axis of the bone. The projection of the ossification center on the aforementioned line of the epiphysis was then measured. To measure the diameter of the metacarpal epiphysis, the start point was the connection point of the epiphysis and diaphysis. The endpoint was the tangency between the line vertical to the long axis of the metacarpal and the curved surface of the epiphysis. The projection of the ossification center on the line of the epiphysis was measured. The OR, described as the ratio of the diameter of the ossification center to that of the epiphysis (d/D), for each bone, was then calculated (Fig. 2; Supplementary Fig. S1, online only).

The skeletal maturity score (SMS) of a subject was calculated with the simple formula

$$\text{SMS} = \sum 100 * (d/D)_i * W_i$$

where d = diameter of the ossification center, D = diameter of the epiphysis, W = weight coefficient and i = 13 epiphyses, because each bone matures at a different rate during children's growth and contributes differently to BA. Therefore, the real BA was defined as summation of the scores of each bone weighted by different coefficients (Hsieh et al. 2011; Tanner et al. 2001). With TW3 (Tanner et al. 2001) as the reference, a different weight coefficient was assigned to each of the 13 bones: 2 for the radius and ulna, 0.67 for the first metacarpal and the two first phalanxes, 0.5 for each of all the other third and fifth metacarpals and phalanxes.

Inter- and intra-observer reliability

The ultrasound images of 30 cases were randomly selected and scored by three radiologists respectively to analyze the reliability of the method used to calculate SMS by the different radiologists; the same 30 cases were also evaluated by the same radiologist twice at a 2-mo interval to analyze intra-observer reliability. Thirty patients were imaged by three different radiologists (with experience in musculoskeletal ultrasound for 1, 2 and 3 y, respectively, trained with the aforementioned scanning protocol) alternatively for data collection. The images were then read and measured by the radiologists to analyze the reliability of data collection and measurement by different operators. All observers were blinded to the patients' clinical data.

Statistical analysis

Pearson's correlation r was calculated to assess the degree of linear association between data calculated from the ultrasound image and BA derived from plain radiograph. The intraclass correlation coefficient (ICC) (Koo and Li 2016) was used to analyze the inter- and intra-observer reliability of US in calculation of SMS. The SPSS software package, Version 22.0 (IBM, Armonk, NY, USA), and Microsoft Excel 2013 (Microsoft, Seattle, WA, USA) were used for statistical analysis. Differences were considered statistically significant at $p < 0.05$.

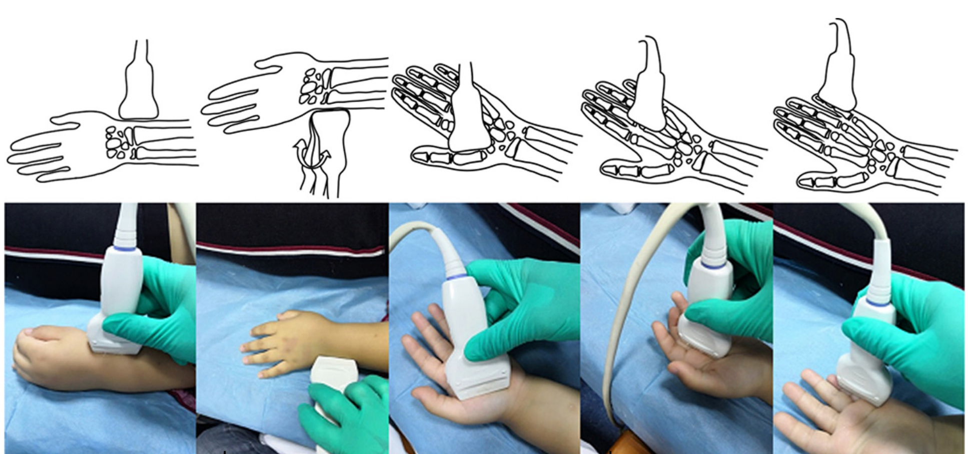

Fig. 1. Scanning skills for hand and wrist imaging by ultrasound to evaluate bone age. (a) The probe was set on the radial styloid process in the coronal plane to image the epiphysis of the radius. (b) The probe was set on the ulna styloid process in the coronal-to-sagittal plane to image the epiphysis of the ulna. (c) The probe was set on the oblique position to image the epiphyses of the first metacarpal and phalanxes. (d, e) The probe was set on the sagittal plane to image the epiphyses of the third and fifth metacarpals and phalanxes.

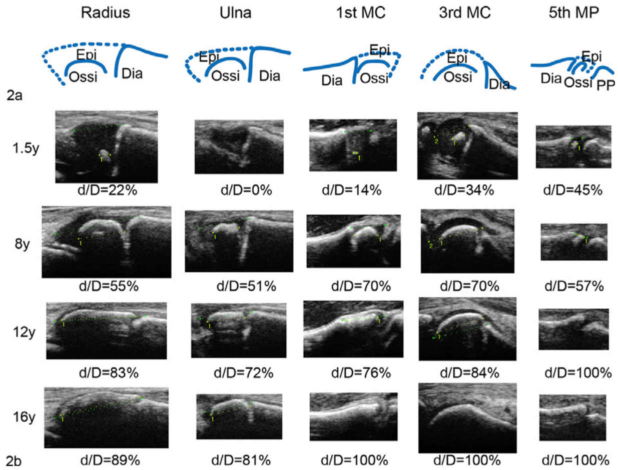

Fig. 2. Sonographic findings of hand and wrist in patients of various ages (girls in this figure). (a) Sketch maps of the distal radius and ulna, metacarpal and phalanx. The epiphysis is delineated by a *dotted line*. The hyper-echoic surface of ossification center and the cortex of the diaphysis are delineated by *solid lines*. (b) Sonographic findings for radius, ulna, metacarpals and phalanx; the *dotted lines* represent measurements of the diameters of the epiphysis and ossification center. *d*/*D* = ratio of the diameter of the ossification center to that of the epiphysis. The value of *d*/*D* was 0% when no ossification center emerged and 100% when the ossification center fused with the diaphysis and no hypo-echoic epiphyseal plate between them could be identified. Dia = diaphysis; Epi = epiphysis; MC = metacarpal; Med = medial; MP = middle phalanx; Ossi = ossification center; PP = primary phalanx.

RESULTS

The epiphyses of all 13 bones in this study could be imaged by ultrasound as a hypo-echoic area with sharp outline at the end of bones. The ossification centers of bones could be imaged by ultrasound as different sizes of the hyper-echoic spot surrounded by the hypo-echoic epiphyses. Marked acoustic shadowing behind the hyper-echoic spot could usually be found if the ossification center was not too small (Fig. 2). The average time to scan 13 bones in each patient by ultrasound was about 4–5 min.

The correlation between the estimated BA derived from the plain radiograph and the ossification center/epiphysis diameter ratio, *d*/*D*, of each bone were analyzed. There was a low correlation between the diameter of the epiphysis and BA (Pearson's r ranged from 0.22–0.59, $p < 0.001$, n = 71). There was moderately high correlation between the diameter of the ossification center and BA (Pearson's r ranged from 0.47–0.83 for a single bone, increased to 0.89 when summed altogether or summed between the radius and ulna, $p < 0.001$, n = 71). There was a moderately high correlation between *d*/*D* and BA (Pearson's r ranged from 0.77–0.93 in girls, $p < 0.001$, n = 94, and from 0.77–0.93 in boys, $p < 0.001$, n = 78). Very high correlation was found between the SMS and BA (Pearson's r = 0.97 in girls, $p < 0.001$, n = 94, and 0.97 in boys, $p < 0.001$, n = 78) (Fig. 3, Table 1).

The correlation between BA and patient height or weight was analyzed (Pearson's r = 0.85 and 0.68 respectively, $p < 0.001$, n = 94). The correlation between the summation of the diameters of ossification centers and BAs of patients was also analyzed (Pearson's r = 0.89, $p < 0.001$, n = 94). The correlations of *d*/*D* and SMS with chronologic age were also analyzed (Supplementary Table S1, online only).

The ORs of long bones in the hand and wrist and the SMSs of the girls and boys with different BAs are listed respectively in Tables 2 and 3.

The frequencies of the delayed and advanced BA in the patients are summarized in Supplementary Table S2 (online only).

Intra- and inter-observer reliability

The intra-radiologist retest revealed excellent repeatability (ICC = 0.95 [95% confidence interval: 0.91, 0.99], $p < 0.001$). Inter-observer repeatability among the three radiologists was high (ICC = 0.89 [95% confidence

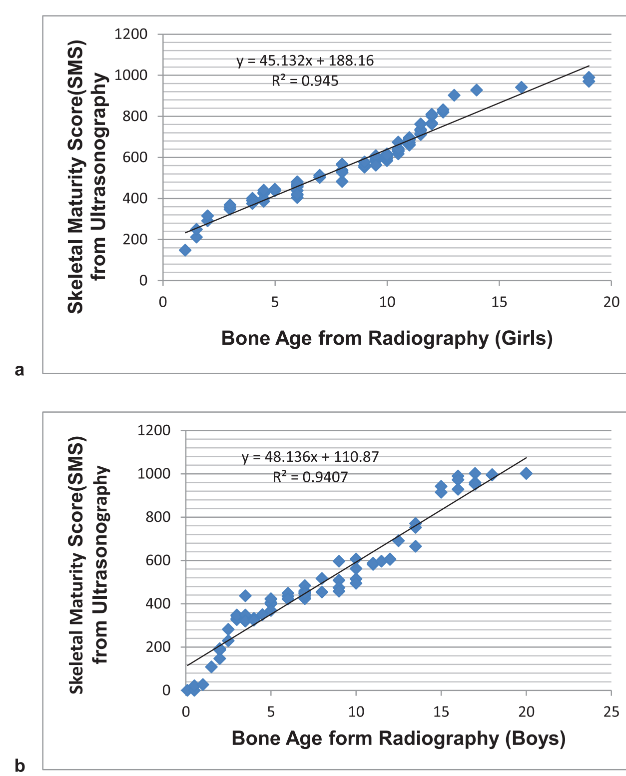

Fig. 3. Linear regression between skeletal maturity score (SMS) calculated from ultrasound images and bone age estimated from radiographs in (a) girls (n = 94) and (b) boys (n = 78).

Table 1. Pearson linear correlation coefficients (r) between bone age and diameter of epiphysis, ossification center and ossification ratio of the 13 bones in the hand and wrist

	Radius	Ulna	MC1	PP1	DP1	MC3	PP3	MP3	DP3	MC5	PP5	MP5	DP5	SUM	Radius + ulna	SMS
Epi*	0.59	0.31	0.49	0.46	0.15	0.14	0.23	0.40	0.36	0.25	0.22	0.22	0.44	0.61	0.57	-
Ossi*	0.75	0.83	0.69	0.60	0.52	0.58	0.51	0.47	0.64	0.62	0.53	0.53	0.64	0.89	0.89	-
d/D†	0.89	0.93	0.77	0.82	0.82	0.80	0.77	0.78	0.79	0.78	0.75	0.79	0.85	0.95	0.95	0.97
d/D‡	0.93	0.92	0.87	0.89	0.91	0.85	0.86	0.83	0.77	0.80	0.79	0.81	0.90	0.96	0.95	0.97

Epi = epiphysis; Ossi = ossification center; d/D = ratio of diameters of ossification center and epiphysis; MC1 = first metacarpal; PP1 = first proximal phalanx; DP1 = first distal phalanx; MC3 = third metacarpal; PP3 = third proximal phalanx; MP3 = third middle phalanx; DP3 = third distal phalanx; MC5 = fifth metacarpal; PP5 = fifth proximal phalanx; MP5, the 5 th middle phalanx; DP5 = fifth distal phalanx; SUM = summation of data from all 13 bones; SMS = skeletal maturity score.

* n = 71 (girls without coagulation of epiphysis and diaphysis).

† girls, n = 94.

‡ boys, n = 78, $p < 0.001$.

interval: 0.62, 0.97], $p < 0.001$). Inter-operator repeatability among the three radiologists was high (ICC = 0.85 [95% confidence interval: 0.58, 0.90], $p < 0.001$) (Table 4)

DISCUSSION

Bone age is considered an important indicator of biological maturity routinely used in different pediatric sections such as orthopedics (Schlégl et al. 2017), endocrinology (Ferris and Geffner 2017) and rheumatology (Martin et al. 2011). There have been attempts to determine BA with conventional ultrasound or with specifically designed sonographic devices. Castriota-Scanderbeg et al. (1998) assessed BA based on sonographic evaluation of the thickness of femoral head articular cartilage, but compared with GP and TW2. its low accuracy made it unsuitable for clinical use. Bilgili et al. (2003) used the ultrasonographic version of the GP atlas to estimate BA with high correlation to plain radiography; however, the patients were children from birth to 6 y. An ultrasound instrument called BonAge (Sunlight Medical Ltd, Tel Aviv, Israel) was used to evaluate BA by calculating sound velocity when ultrasonic waves pass through the subject's distal radius and ulnar epiphysis. Mentzel et al. (2005) reported that there were high correlations between the BA evaluated by BonAge and that evaluated with the GP or TW2 method; however, a more recent study (Khan et al. 2009) concluded that BonAge had poor positive and negative predictive value for identification of a normal or delayed BA and should not yet be considered a valid replacement for radiographic BA determination.

In this study with conventional ultrasound, we considered the maturity of bone as a process of the OR developed from 0%−100%. The OR, calculated as the ratio of the diameter of the ossification center to that of the epiphysis of bones (d/D) in the hand and wrist, was supposed to be a good parameter to estimate BA. The d/D values of the 13 bones were weighted and summed together to obtain the SMS, which was highly correlated with BA estimated by radiography (Pearson's $r = 0.97$ and 0.97 for girls and boys, respectively). The scoring system SMS was based on the continuous growth process of bones. Serial monitoring of BA quantitatively may be achieved with radiation-free ultrasound imaging. What's more, the study was performed in patients aged from 0.1−19 y; this may extend the use of conventional ultrasound to a more practical extent in evaluation of BA as there are more pubertal patients older than 6 y (Bilgili et al. 2003; Daneff et al. 2015; Hajalioghli et al. 2015; Windschall et al. 2016) with various diseases in clinical work that requires evaluation of BA.

Choi et al. (2018) measured the areas of the capitate and hamate on plain radiographs. There was no significant difference in accuracy between capitohamate planimetry (84.39%−84.46%) and the GP method (85.15%−87.66%) ($p \geq 0.0867$). They concluded that capitohamate planimetry may be a reliable method for BA assessment. In our study, there was a relatively high correlation between the diameter of the ossification center and BA (Pearson's $r = 0.89$ for the summation of the diameters of the ossification centers in our study). We did not measure the size of the capitate and hamate. But we are inclined to believe that due caution should be exercised in estimating BA from the size of bones. Just as height (Pearson's $r = 0.85$ between height and BA in our study) or other anthropometric indicators cannot be used to estimate BA because their definite values after maturity vary individually, neither does the size of the ossification center of bones.

The high correlation between the summation of d/D values of the radius, ulna and BA (Pearson's $r = 0.95$ and 0.95 for girls and boys, respectively) revealed the importance of the radius and ulna in estimation of BA. The summation of d/D values of the radius and ulna will be a

Table 2. Ossification ratios of long bones in hand and wrist and skeletal maturity scores from ultrasonography in girls with bone ages ranging from 1−19*

BA	N	Radius	Ulna	MC1	PP1	DP1	MC3	PP3	MP3	DP3	MC5	PP5	MP5	DP5	SMS
1.0	1	0.0	0.0	24.0	15.0	48.0	36.0	30.0	30.0	38.0	0.0	30.0	14.0	0.0	147.2
1.5	2	18.0	0.0	24.5	29.0	43.0	39.5	42.0	39.5	37.5	30.0	39.0	23.0	9.0	230.4
		(5.6)	(0.0)	(14.8)	(11.3)	(1.4)	(7.7)	(5.6)	(7.7)	(7.7)	(4.2)	(5.6)	(32.5)	(12.7)	(26.1)
2.0	2	38.0	0.0	(38.5)	17.0	44.5	48.5	49.0	33.0	40.5	53.5	34.0	38.5	22.5	302.7
		(7.0)	(0.0)	(7.7)	(8.4)	(6.3)	(2.1)	(4.2)	(2.8)	(.7)	(7.7)	(5.6)	(7.7)	(3.5)	(16.8)
3.0	3	40.6	0.0	52.6	34.6	42.0	63.3	44.6	42.0	44.3	62.0	44.0	35.0	43.0	357.1
		(4.9)	(0.0)	(13.0)	(2.8)	(7.2)	(7.0)	(4.1)	(5.5)	(12.5)	(9.5)	(4.5)	(2.6)	(13.1)	(10.8)
4.0	4	41.7	0.0	57.0	39.7	50.5	72.0	52.2	44.0	50.5	60.2	51.0	44.0	43.5	390.9
		(6.5)	(0.0)	(4.6)	(5.9)	(7.8)	(5.3)	(7.5)	(4.8)	(1.9)	(14.2)	(17.7)	(6.1)	(4.4)	(11.6)
4.5	5	43.6	0.0	63.8	48.4	63.4	68.8	51.6	44.4	53.0	65.0	43.4	45.8	48.4	415.0
		(5.1)	(0.0)	(5.8)	(11.4)	(12.1)	(7.8)	(7.9)	(4.2)	(6.7)	(6.1)	(4.5)	(9.8)	(7.4)	(22.1)
5.0	5	48.8	0.0	63.6	46.6	64.0	72.2	55.2	50.8	51.6	66.2	45.0	47.4	51.2	434.1
		(4.8)	(0.0)	(6.8)	(6.5)	(5.5)	(5.2)	(6.1)	(4.4)	(8.6)	(2.2)	(6.3)	(4.3)	(3.7)	(14.9)
6.0	10	49.2	0.7	64.9	49.1	64.9	75.0	55.0	46.0	55.5	70.5	49.0	51.1	58.0	450.2
		(3.6)	(2.4)	(8.0)	(11.0)	(7.5)	(7.0	(6.9)	(7.4)	(9.9)	(7.1)	(6.0)	(7.9)	(5.6)	(26.6)
7.0	3	45.6	23.3	64.3	59.6	60.6	76.0	55.0	44.6	64.6	70.0	52.6	63.0	62.0	505.7
		(1.5)	(2.0)	(5.5)	(6.8)	(7.5)	(2.6)	(5.2)	(2.0)	(6.8)	(0.0)	(2.0))	(7.0)	(2.6)	(5.8)
8.0	7	55.4	28.1	66.5	56.5	66.5	76.1	55.2	48.4	59.4	71.0	49.5	56.1	60.0	532.2
		(3.9)	(10.0)	(5.5)	(9.2)	(9.0)	(4.6)	(5.4)	(7.3)	(5.7)	(4.5)	(5.3)	(6.6)	(5.1)	(28.4)
9.0	5	53.8	46.2	67.8	51.2	69.4	74.8	55.8	46.6	63.4	74.4	49.4	50.0	62.8	564.8
		(4.3)	(5.6)	(6.5)	(5.7)	(6.5)	(2.8)	(8.8)	(3.8)	(9.0)	(3.2)	(11.0)	(8.5)	(6.0)	(10.9)
9.5	9	55.7	48.2	68.4	56.4	71.8	78.5	55.0	45.0	61.3	78.1	49.8	56.0	63.8	583.7
		(2.8)	(8.2)	(5.8	(10.7)	(4.6)	(4.4)	(4.3)	(8.3)	(6.7)	(5.3)	(9.0)	(8.9)	(8.2)	(17.5)
10.0	5	57.8	56.0	71.0	53.8	69.0	81.8	55.2	54.6	60.4	73.8	45.4	54.4	64.0	602.2
		(6.1)	(9.1)	(9.0)	(6.9)	(6.2)	(3.9)	(7.4)	(8.1)	(5.9)	(2.7)	(8.7)	(4.0)	(8.7)	(13.1)
10.5	8	62.4	59.4	70.3	66.2	73.7	80.0	58.2	57.2	62.8	76.2	56.4	57.8	62.5	640.4
		(5.7)	(9.9)	(7.4)	(11.5)	(10.6)	(3.8)	(8.3)	(5.5)	(11.7)	(4.8)	(9.3)	(6.9)	(5.4)	(20.1)
11.0	8	65.0	69.5	73.6	66.5	76.2	82.2	66.2	57.6	67.6	74.7	58.3	60.5	67.2	681.4
		(9.7)	(8.5)	(5.7)	(8.1)	(7.3)	(3.8)	(4.8)	(4.2)	(6.9)	(4.5)	(5.6)	(9.8)	(6.7)	(13.1)
11.5	6	70.1	70.3	73.1	76.0	88.8	83.8	70.1	68.3	77.5	79.5	69.0	69.5	72.8	735.7
		(3.9)	(6.7)	(5.8)	(8.8)	(9.1)	(3.1)	(8.0)	(4.5)	(11.9)	(3.5)	(3.6)	(10.8)	95.2)	(22.2)
12.0	4	77.5	72.2	75.2	76.7	100.0	80.7	69.7	79.7	94.5	85.2	71.7	65.2	86.0	784.8
		(4.1)	(9.1)	(1.7)	(7.6)	(0.0)	(8.5)	(7.7)	(14.6)	(11.0)	(4.4)	(4.6)	(4.8)	(16.6)	(23.9)
12.5	2	79.0	78.5	93.5	79.0	100.0	83.5	70.5	73.5	100.0	81.0	78.0	69.5	100.0	825.5
		(9.8)	(4.9	(9.1)	(1.4)	(0.0)	(3.50	(2.1)	(7.7)	(0.0)	(4.2)	(2.8)	(4.9)	(0.0)	(7.7)
13.0	1	85.0	87.0	100.0	100.0	100.0	88.0	82.0	90.0	100.0	85.0	87.0	83.0	100.0	902.5
14.0	1	90.0	79.0	100.0	100.0	100.0	90.0	100.0	100.0	100.0	87.0	100.0	100.0	100.0	927.5
16.0	1	89.0	81.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	941.0
19.0	2	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	1000.0
		(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)

MC1 = first metacarpal; PP1 = first proximal phalanx; DP1 = first distal phalanx; MC3 = third metacarpal; PP3, the 3 rd proximal phalanx; MP3 = third middle phalanx; DP3 = third distal phalanx; MC5 = fifth metacarpal; PP5 = fifth proximal phalanx; MP5 = fifth middle phalanx; DP5 = fifth distal phalanx; SMS = skeletal maturity score.

* Values are given as the mean (standard deviation).

more convenient method for estimating BA. Although there is an increased risk associated with estimating BA with only one or two bones, especially for young children (<6 or 7 y for girls and boys) in whom the ossification center of the ulna has not emerged.

It is well known that data collection in ultrasound imaging is operator dependent. In this study, a standardized scanning protocol was developed to ensure that images on relatively the same specific sections could be collected even by different sonographers. The method used to measure the diameters of the ossification center and epiphysis was also settled. The ICC values (0.85−0.95 for inter-operator and intra-radiologist studies, respectively) indicated good to excellent reliability of the scoring method (Tanner et al. 2001).

This study has several limitations. It was performed at a single institution with a moderate sample size. And it was, to some extent, time consuming with respect to image acquisition and evaluation of the 13 bones. Fewer bones will be tested for a larger collective as well in future work.

Table 3. Ossification ratios of long bones in hand and wrist and skeletal maturity scores from ultrasonography in boys with bone age ranging from 0.1−19*

BA	N	Radius	Ulna	MC1	PP1	DP1	MC3	PP3	MP3	DP3	MC5	PP5	MP5	DP5	SMS
0.1	1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
		.	.	.	.	.	.		.		.	.	.	.	.
0.5	2	0.0	0.0	0.0	0.0	15.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10.3
		(0.0)	(0.0)	(0.0)	(0.0)	(21.9)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	14.6
1.0	1	0.0	0.0	0.0	0.0	30.0	0.0	13.0	0.0	0.0	0.0	0.0	0.0	0.0	26.6
		.	.	.	.	.	.	.	.	.	.	.	.	.	.
1.5	1	13.0	0.0	0.0	0.0	52.0	14.0	30.0	28.0	22.0	0.0	0.0	0.0	0.0	107.8
		.	.	.	.	.	.	.	.	.		.	.		.
2.0	4	26.7	0.0	11.5	0.0	41.5	21.2	44.2	34.7	29.0	16.5	22.2	3.2	8.2	178.7
		(9.1)	(0.0	(13.6)	(0.0)	(10.7)	(14.2)	(3.2)	(6.2)	(3.3)	(19.4)	(15.1)	(6.5)	(16.5)	(21.9)
2.5	2	26.0	0.0	21.0	22.0	41.5	53.5	49.0	35.5	31.0	36.0	37.0	29.0	21.5	254.8
		(16.9)	(0.0	(12.7)	(11.3)	(9.1)	(12.0)	(0.0)	(6.3)	(11.3)	(5.6)	(4.2)	(9.8)	(13.4)	(36.6)
3.0	4	38.2	0.0	32.4	33.8	44.6	52.6	51.4	34.2	44.6	48.4	44.4	33.0	33.2	321.5
		(5.6)	(0.0)	(18.9)	(13.7)	(8.3)	(3.7)	(6.7)	(8.2)	(9.4)	(5.0)	(7.7)	(11.7)	(11.4)	(35.5)
3.5	5	39.8	0.0	40.0	28.5	58.1	57.3	50.6	37.3	47.0	52.0	43.1	32.0	39.5	344.0
		(2.3)	(0.0)	(17.2)	(13.3)	(9.3)	(5.0)	(7.)	(8.1)	(9.4)	(11.8)	(7.8)	(13.3)	(8.3)	(46.3)
4.0	3	42.0	0.0	33.3	29.0	52.3	57.0	51.6	41.6	51.3	44.6	41.0	28.0	20.0	328.4
		(3.0)	(0.0)	(11.5)	(13.4)	(13.6)	(7.8)	(5.8)	(8.0)	(1.5)	(4.9)	(4.5)	(24.3)	(18.3)	(4.4)
4.5	1	37.0	0.0	35.0	36.0	48.0	61.0	51.0	43.0	58.0	48.0	46.0	38.0	46.0	349.2
		.	.	.	.	.	.		.	.	.	.	.		.
5.0	7	42.6	0.0	44.0	39.3	59.6	65.6	60.6	47.3	49.6	59.0	51.5	43.5	46.3	392.9
		(6.0)	(0.0)	(9.1)	(13.0)	(4.8)	(2.2)	(5.5)	(6.5)	(3.8)	(2.9)	(9.0)	(18.2)	(8.1)	(31.4)
6.0	3	52.6	0.0	63.0	42.3	53.3	72.3	62.6	37.3	56.3	65.3	50.3	44.6	57.0	434.6
		(7.5)	(0.0)	(6.2	(20.2)	(13.7)	(4.0)	(4.6)	(3.7)	(9.7)	(3.5)	(4.9)	(14.0)	(7.2)	(13.3)
7.0	11	49.4	2.8	62.0	50.9	62.7	69.7	54.9	48.0	56.3	63.0	49.8	50.7	55.1	446.0
		(5.0)	(6.8)	(8.2)	(10.0)	(9.4)	(4.3)	(5.0)	(6.4)	(7.5)	(5.3)	(3.9)	(8.8)	(9.9)	(17.4)
8.0	2	48.5	12.5	70.0	50.5	59.0	75.0	66.0	51.5	58.0	71.5	57.5	53.5	52.5	485.0
		(6.3)	(17.6)	(7.0)	(9.1)	(2.8)	(2.8)	(11.3)	(10.6)	(2.8)	(0.7)	(6.3)	(13.4)	(4.9)	(44.0)
9.0	4	54.5	20.7	64.7	53.7	69.0	73.0	53.5	51.7	59.0	65.7	50.2	53.0	59.0	508.7
		(4.1)	(17.4	(7.0)	(9.7)	(7.3)	(4.6)	(9.2)	(4.1)	(8.4)	(6.6)	(3.7)	(11.1)	(6.4)	(61.5)
10.0	4	57.5	19.5	71.0	57.0	72.0	77.2	56.0	58.0	74.5	77.2	54.0	53.7	61.0	543.8
		(6.3)	(23.0	(6.0)	(5.8)	(16.3)	(5.3)	(11.6)	(8.4)	(1.7)	(6.9)	(5.9)	(6.9	(2.8)	(49.9)
11.0	3	53.6	44.3	67.6	67.0	73.6	78.0	54.0	59.6	58.6	74.3	51.6	54.3	66.6	584.2
		(7.0)	(11.3)	(1.5)	(5.5)	(2.0)	(1.7)	(2.6)	(6.4)	(4.5)	(5.5)	(5.1)	(5.1)	(1.5)	(2.8)
11.5	1	55.0	57.0	65.0	64.0	66.0	78.0	61.0	50.0	58.0	77.0	48.0	54.0	57.0	596.1
		.	.	.	.	.	.	.	.			.	.	.	.
12.0	3	59.0	48.6	72.0	62.0	74.0	79.3	59.0	55.6	63.0	72.6	47.6	61.0	62.3	605.0
		3.4)	(2.5)	(1.7)	(6.0)	(3.4)	(1.5)	(5.0)	(5.5)	(6.5)	(6.4)	(4.6)	(9.1)	(9.7)	(1.1)
12.5	1	63.0	77.0	73.0	61.0	75.0	83.0	66.0	73.0	57.0	79.0	66.0	53.0	64.0	690.5
		.	.	.	.	.	.	.	.	.	.		.		.
13.5	3	77.3	72.6	68.0	64.3	79.0	80.6	77.3	65.6	71.0	79.3	59.0	67.0	74.3	728.7
		(4.9)	(9.0)	(6.2)	(15.2)	(14.1)	(2.3)	(7.0)	(9.0)	(2.6)	(7.3)	(7.5)	(9.6)	8.3	56.2
15.0	2	89.5	82.5	100.0	100.0	100.0	95.0	93.0	100.0	100.0	90.5	86.5	100.0	100.0	927.5
		(2.1)	(0.7)	(0.0)	(0.0)	(0.0)	(7.0)	(9.8)	(0.0)	(0.0)	(4.9)	(4.9)	(0.0)	.0	19.0
16.0	3	93.3	95.3	100.0	100.0	100.0	94.0	100.0	100.0	92.6	89.3	100.0	100.0	92.6	962.6
		(7.0)	(8.0)	(0.0)	(0.0)	(0.0)	10.3)	(0.0)	(0.0)	(12.7	(9.2)	(0.0)	(0.0)	(12.7)	31.6
17.0	3	94.0	90.6	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	970.3
		(5.5	(8.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	26.8
18.0	2	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	87.5	994.7
		(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(2.1)	(1.0)
19.0	2	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	1000.0
		(0.0	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)

MC1, the 1st metacarpal; PP1, the 1st proximal phalanx; DP1, the 1st distal phalanx; MC3, the 3rd metacarpal; PP3, the 3rd proximal phalanx; MP3, the 3rd middle phalanx;DP3, the 3rd distal phalanx; MC5,the 5th metacarpal; PP5, the 5th proximal phalanx; MP5, the 5th middle phalanx; DP5, the 5th distal phalanx; SMS, skeletal maturity score.

* Values were mean and standard deviation.

Table 4. Intraclass correlation coefficient

	Intraclass correlation	95% Confidence interval	*p*-Value
Inter-radiologist	0.89	0.62−0.97	<0.001
Intra-radiologist	0.95	0.91−0.99	<0.001
Inter-operator	0.85	0.58−0.90	<0.001

CONCLUSIONS

There are significant positive correlations between ORs measured by conventional ultrasound imaging and BAs obtained from radiography of the hand and wrist in patients from birth to near adulthood. These findings warrant assessment in larger prospective studies. The scoring system may potentially provide a quantitative modality for estimation of BA with conventional ultrasound.

DECLARATION OF COMPETING INTEREST

The authors declare no competing interests.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ultrasmedbio.2019.07.681.

REFERENCES

Bilgili Y, Hizel S, Kara SA, Sanli C, Erdal HH, Altinok D. Accuracy of skeletal age assessment in children from birth to 6 years of age with the ultrasonographic version of the Greulich−Pyle atlas. J Ultrasound Med 2003;22:683–690.

Booz C, Wichmann JL, Boettger S, Al Kamali A, Martin SS, Lenga L, Leithner D, Albrecht MH, Ackermann H, Vogl TJ, Bodelle B, Kaltenbach B. Evaluation of a computer-aided diagnosis system for automated bone age assessment in comparison to the Greulich−Pyle atlas method: A multireader study. J Comput Assist Tomogr 2019;43:39–45.

Castriota-Scanderbeg A, Sacco MC, Emberti-Gialloreti L, Fraracci L. Skeletal age assessment in children and young adults: Comparison between a newly developed sonographic method and conventional methods. Skeletal Radiol 1998;27:271–277.

Choi JA, Kim YC, Min SJ, Khil EK. A simple method for bone age assessment: The capitohamate planimetry. Eur Radiol 2018;28:2299–2307.

Correa FA, França MM, Fang Q, Ma Q, Bachega TA, Rodrigues A, Ozel BA, Li JZ, Mendonca BB, Jorge AAL, Carvalho LR, Camper SA, Arnhold IJP. Growth hormone deficiency with advanced bone age: Phenotypic interaction between GHRH receptor and CYP21A2 mutations diagnosed by sanger and whole exome sequencing. Arch Endocrinol Metab 2017;61:633–636.

Creo AL, Schwenk WF, II. Bone age: A handy tool for pediatric providers. Pediatrics 2017;140 e20171486.

Daneff M, Casalis C, Bruno CH, Bruno DA. Bone age assessment with conventional ultrasonography in healthy infants from 1 to 24 months of age. Pediatr Radiol 2015;45:1007–1015.

De Sanctis V, Soliman AT, Di Maio S, Bedair S. Are the new automated methods for bone age estimation advantageous over the manual approaches? Pediatr Endocrinol Rev 2014;12:200–205.

Ferris JA, Geffner ME. Are aromatase inhibitors in boys with predicted short stature and/or rapidly advancing bone age effective and safe?. J Pediatr Endocrinol Metab 2017;30:311–317.

Fleshman K. Bone age determination in a paediatric population as an indicator of nutritional status. Trop Doct 2000;30:16–18.

Greulich WW, Pyle SI. Radiographic atlas of skeletal development of the hand and wrist. 2nd edition Stanford, CA: Stanford University Press; 1959.

Hajalioghli P, Tarzamni MK, Arami S, Fouladi DF, Ghojazadeh M. The utility of ultrasonographic bone age determination in detecting growth disturbances: A comparative study with the conventional radiographic technique. Skeletal Radiol 2015;44:1351–1356.

Hill RJ, Brookes DS, Lewindon PJ, Withers GD, Ee LC, Connor FL, Cleghorn GJ, Davies PS. Bone health in children with inflammatory bowel disease: Adjusting for bone age. Pediatr Gastroenterol Nutr 2009;48:538–543.

Hoyer-Kuhn H, Knoop K, Semler O, Kuhr K, Hellmich M, Schoenau E, Koerber F. Comparison of DXA scans and conventional X-rays for spine morphometry and bone age determination in children. J Clin Densitom 2016;19:208–215.

Hsieh CW, Liu TC, Wang JK, Jong TL, Tiu CM. Simplified radius, ulna, and short bone-age assessment procedure using grouped-Tanner-Whitehouse method. Pediatr Int 2011;53:567–575.

Khan KM, Miller BS, Hoggard E, Somani A, Sarafoglou K. Application of ultrasound for bone age estimation in clinical practice. J Pediatr 2009;154:243–247.

Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. J Chirop Med 2016;15:155–163.

Malina RM, Coelho-E-Silva MJ, Figueiredo AJ, Philippaerts RM, Hirose N, Peña Reyes ME, Gilli G, Benso A, Vaeyens R, Deprez D, Guglielmo LGA, Buranarugsa R. Tanner−Whitehouse skeletal ages in male youth soccer players: TW2 or TW3? Sports Med 2018;48:991–1008.

Martin DD, Wit JM, Hochberg Z, Savendahl L, van Rijn RR, Fricke O, Cameron N, Caliebe J, Hertel T, Kiepe D, Albertsson-Wikland K, Thodberg HH, Binder G, Ranke MB. The use of bone age in clinical practice: Part 1. Hormone Res Paediatr 2011;76:1–9.

Mentzel HJ, Vilser C, Eulenstein M, Schwartz T, Vogt S, Bottcher J, Yaniv I, Tsoref L, Kauf E, Kaiser WA. Assessment of skeletal age at the wrist in children with a new ultrasound device. Pediatr Radiol 2005;35:429–433.

Mutasa S, Chang PD, Ruzal-Shapiro C, Ayyala R. MABAL: A novel deep-learning architecture for machine-assisted bone age labeling. J Digital Imaging 2018;31:513–519.

Pinhas-Hamiel O, Benary D, Mazor-Aronovich K, Ben-Ami M, Levy-Shraga Y, Boyko V, Modan-Moses D, Lerner-Geva L. Advanced bone age and hyperinsulinemia in overweight and obese children. Endocr Pract 2014;20:62–67.

Pludowski P, Lebiedowski M, Lorenc RS. Evaluation of practical use of bone age assessments based on DXA-derived hand scans in diagnosis of skeletal status in healthy and diseased children. J Clin Densitom 2005;8:48–56.

Schlégl ÁT, O'Sullivan I, Varga P, Than P, Vermes C. Determination and correlation of lower limb anatomical parameters and bone age during skeletal growth (based on 1005 cases). J Orthop Res 2017;35:1431–1441.

Spampinato C, Palazzo S, Giordano D, Aldinucci M, Leonardi R. Deep learning for automated skeletal bone age assessment in X-ray images. Med Image Anal 2017;36:41–51.

Tajmir SH, Lee H, Shailam R, Gale HI, Nguyen JC, Westra SJ, Lim R, Yune S, Gee MS, Do S. Artificial intelligence-assisted interpretation of bone age radiographs improves accuracy and decreases variability. Skeletal Radiol 2019;48:275–283.

Tanner JM. Growth at adolescence: With a general consideration of the effects of hereditary and environmental factors upon growth and maturation from birth to maturity. 2nd edition Springfield, IL: Blackwell Scientific; 1962.

Tanner JM, Healy MJR, Goldstein H, Cameron N. Assessment of skeletal maturity and prediction of adult height (TW3 method). 3rd edition London: Saunders; 2001. p. 1–49.

Terada Y1, Kono S, Uchiumi T, Kose K, Miyagi R, Yamabe E, Fujinaga Y. Yoshioka H Improved reliability in skeletal age assessment using a pediatric hand MR scanner with a 0.3 T permanent magnet. Magn Reson Med Sci 2014;13:215–219.

Thodberg HH, Kreiborg S, Juul A, Pedersen KD. The BoneXpert method for automated determination of skeletal maturity. IEEE Trans Med Imaging 2009;28:52–66.

Tomei E, Sartori A, Nissman D, Al Ansari N, Battisti S, Rubini A, Stagnitti A, Martino M, Marini M, Barbato E, Semelka RC. Value of MRI of the hand and the wrist in evaluation of bone age: Preliminary results. J Magn Reson Imaging 2014;39:1198–1205.

Windschall D, Pommerenke M, Haase R. Ultrasound assessment of the skeletal development of the proximal tibial, proximal femoral, and distal femoral epiphyses in premature and mature newborns. Ultrasound Med Biol 2016;42:451–458.

Zhang SY, Liu LJ, Wu ZL, Liu G, Ma ZG, Shen XZ, Xu RL. Standards of TW3 skeletal maturity for Chinese children. Ann Hum Biol 2008;35:349–354.