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● *Original Contribution*

SUMMATION OF OSSIFICATION RATIOS OF RADIUS, ULNA AND FEMUR: A NEW PARAMETER TO EVALUATE BONE AGE BY ULTRASOUND

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Abstract—Radiographic bone age (BA) assessment is reviewer dependent or time consuming. We aimed to clarify the correlation between sonographic ossification ratios (ORs, the ratio of ossification center and epiphysis diameters) of bones and radiographic BA and then to develop a repeatable parameter for BA assessment by ultrasound. The distal ends of the radius and ulna, medial epicondyle of the femur, medial tibial condyle, medial malleolus and lateral malleolus in 271 consecutive patients (132 boys and 139 girls) aged 0.1−19.0 y were imaged by ultrasound. The ORs of these bones were measured sonographically. The highest Pearson correlation *r* was that between the sum of the ORs of radius, ulna and femur (RUF) calculated from ultrasound images and the radiographic BA (0.97 in boys and 0.96 in girls). The entire process of collecting data and calculating the ORs of RUF took 2.6 ± 0.6 min. The ORs of RUF obtained with ultrasound have potential as an easy-to-perform and efficient quantitative assessment of BA. (E-mail: zhangchao_tj@hust.edu.cn)

Key words: **Ultrasound, Bone age, Epiphysis, Ossification center, Wrist, Knee.**

INTRODUCTION

An individual undergoes a developmental process from immaturity at birth to maturity. Biological age, instead of chronologic age, has been used to reflect the developmental level of an individual. Bone age (BA) assessed by radiography is the biological age most commonly used in clinical practice to investigate endocrinologic, genetic and growth disorders in children. It is also used in elite sports selection and forensics (Creo and Schwenk 2017; Utczas et al. 2017). Radiographs of bones, especially of the hand and wrist, have usually been studied by the Tanner−Whitehouse (TW) (Tanner et al. 2001) and Greulich−Pyle (GP) (Greulich and Pyle 1959) methods for estimation of BA. The GP method is easy to learn but it is more reviewer dependent. The TW method may be more accurate but it is more complicated and time consuming (Creo and Schwenk 2017). Automatic BA assessment seems to be an efficient and reliable method to evaluate bone age. The usability of the system is still under evaluation (De Sanctis et al. 2014), and high-quality images are required to obtain reliable results (Spampinato et al. 2017). More drawbacks of the radiographic BA assessment method are exposure to ionizing radiation, which is very low (0.00015 mSv), but in many cases repeated annually, and the requirement for specialized personnel to interpret bone appearance (De Sanctis et al. 2014).

A good method for assessing BA should be accurate, tolerable and easy to learn and should not require time-consuming data acquisition or calculation (Choi et al. 2018). Ultrasound is a non-invasive, non-ionizing, accessible and cost-effective imaging modality widely used in clinical work. It has already been used in the evaluation of BA. The ultrasound device BonAge (Khan et al. 2009) was used in an attempt to evaluate BA by identification of the transmission velocity of ultrasound waves in the epiphysis of bones. The ultrasound wave generated from a transducer on the ulnar side were transmitted through the wrist at a frequency of 750 kHz. The wave was then received by another transducer on the radial side of the wrist. The software calculated the speed of sound using the distance between the transducers and an algorithm to provide a numeric result for the BA of patients. However, because of the poor positive and negative predictive values for identification of a

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normal or delayed BA, the device was not considered a valid replacement for radiographic BA determination. A more recent study (Rachmiel et al. 2017) evaluated BA with the device SonicBone, which operates with similar mechanism. The wrist, distal metacarpal and phalanx of 150 children were detected. Speed of sound and time of progression of the ultrasound wave over the distance from the transmitter to the receiver were the two parameters used. The results indicated that SonicBone was comparable with radiography in the assessment of BA; however, no additional relevant studies were published after that.

In addition to the aforementioned ultrasound devices specifically manufactured for BA analysis, conventional ultrasound machines have also been used to analyze BA. Mahony et al. (1985) evaluated the distal femoral epiphyseal secondary ossification center (DFE) sonographically in fetuses. Measurements of the DFE revealed that its size increases linearly: the menstrual age of a fetus whose DFE measured ≥7 mm was most likely ≥37 wk. Leshem et al. (2002) examined neonates within 24 h of birth. The distal femoral epiphysis was imaged on the coronal plane sonogram of the distal femur, and the maximal height of the DFE was recorded. The correlation (r) between DFE height and gestational age was 0.45. The authors suggested performing sonography of the distal femoral epiphysis as a bedside tool for the assessment of skeletal maturity in newborns. Savino et al. (2011) evaluated the DFE volume sonographically in neonates within 48 h of birth and concluded that ultrasound evaluation of DFE volume provided a simple method for assessing bone maturity. Bilgili et al. (2003) scanned the metacarpals and phalanxes of children with conventional ultrasound. The visible hyper-echoic ossification centers were noted on a prepared hand and wrist chart. The chart was then interpreted with a sonographic version of the GP atlas. The estimated age evaluated from the ultrasonography chart correlated excellently with the BA from plain radiography. A similar method was adopted by Hajalioghli et al. (2015) to detect BA abnormalities. Their study confirmed that the conventional radiographic technique for determining BA abnormalities could be replaced by ultrasonography. All of these studies focused on patients younger than 6−7 y (Mahony et al. 1985; Leshem et al. 2002; Bilgili et al. 2003; Savino et al. 2011; Daneff et al. 2015; Hajalioghli et al. 2015). In a recent study by Wan et al. (2019), ossification ratios (ORs, ratio of the ossification center and epiphysis) of 13 bones in the hand and wrist were measured by conventional ultrasound in newborn to near-adult patients. The ORs of the bones assigned to different weight coefficients were then summed to obtain a skeletal maturity score. Pearson's correlation r between skeletal maturity score derived from ORs and BA was 0.97. The scoring system may potentially supply a quantitative modality to estimate BA by conventional ultrasound. It was, however, time consuming to image and calculate data from all 13 bones (4−5 min for data acquisition and another 3−4 min for measurement of skeletal maturity score).

In this study, ORs of bones from the wrist, knee and ankle were measured by ultrasound. The correlations between the sonographic ORs of these bones and the radiographic BA in patients from infants to teenagers was clarified. The ORs from bones with relatively higher correlations to BA were then selected to develop a new parameter to evaluate BA.

METHODS

Patients

Patients were enrolled into this prospective study from the pediatric outpatient service in our general medical institute between May 2017 and March 2019. To be included, patients had to be Chinese and younger than 19 y and have no pathologic modifications (tumor, trauma, infection, surgical fixation) of the wrist, knee and ankle. Patients underwent left hand and wrist radiography and ultrasound examination of the wrist, knee and ankle. Informed consent was obtained from the guardians of all patients. The study was approved by the local institutional review board. The protocol used in this study is illustrated in Figure 1.

Ultrasound and radiographic examination

Ultrasound imaging of the wrist, knee and ankle was performed with a commercial sonographic machine equipped with a 10-MHz transducer (ALOKA ProSound F75, Hitachi Medical Co., Tokyo, Japan). All images were acquired by one operator with 3 y of experience in musculoskeletal ultrasound scanning who was unaware of the chronologic age and other medical information of the patient.

Radiographs of the left hand and wrist were taken with a tube−film distance of 91.4 cm (Tanner et al. 2001). The results then were interpreted with the TW3 method (the third edition of TW 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 by the two radiologists, the average maturity score from the radiologists was selected to evaluate the BA of the subject.

Protocol for ultrasound scanning and measurement

Ultrasonographic scans were targeted on ossification centers and epiphyses of the distal end of the radius, ulna, medial epicondyle of femur, medial tibial condyle, medial malleolus and lateral malleolus. Patients were

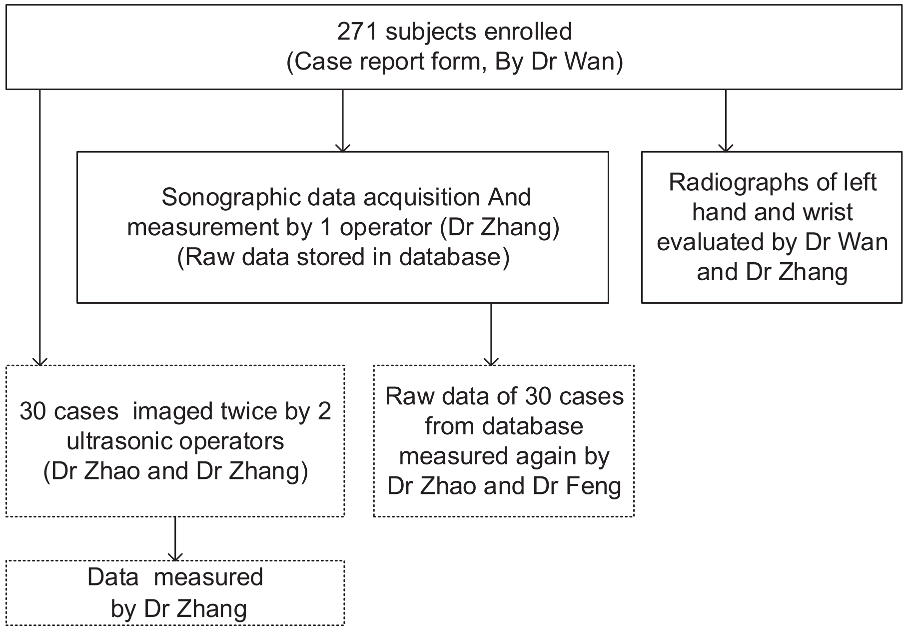

Fig. 1. Flowchart of the study. Clinical data of the patients were entered on the case report form. The data handled by the observers were numbered, and no clinical data of the patients were provided when processing data. The dotted boxes represent the study on inter- and intra-observer reliability.

imaged while in the supine position, with legs spread slightly and knees straight for examination of the knee.

The outlines of the epiphyses and ossification centers of each bone should appear sharp. The ultrasonic probe was placed on the styloid process of the radius (Fig. 2a) or ulna (Fig. 2b) in the coronal plane from the lateral or medial side to image the distal end of the radius or ulna, respectively. The probe was placed on the medial epicondyle of the femur or medial tibial condyle along the medial collateral ligament in the coronal plane (Fig. 2c) to image the distal femur or proximal tibia, respectively. The probe was placed on medial or lateral malleolus in the coronal plane to image the distal tibia or fibula, respectively.

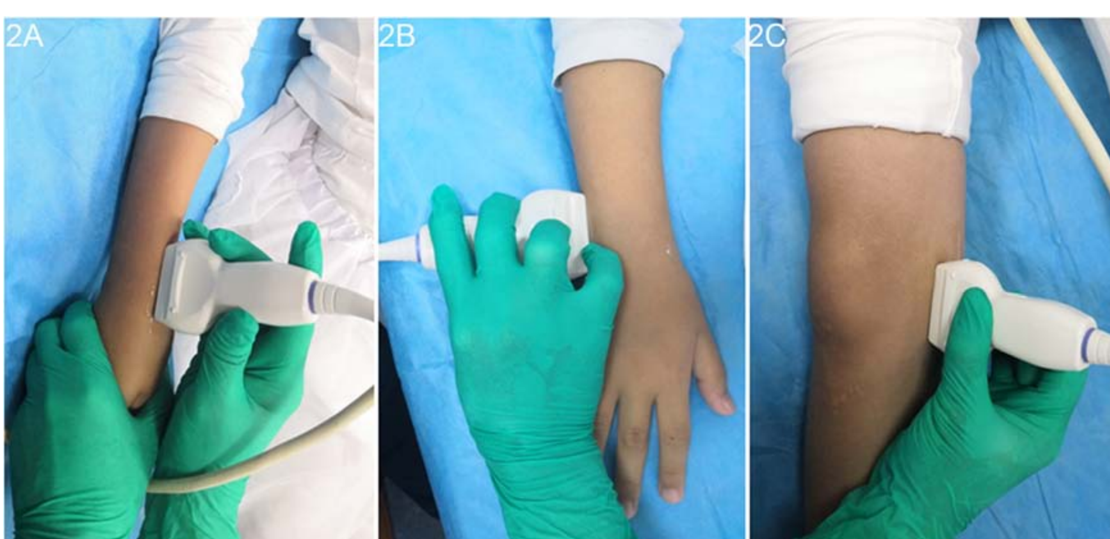

Fig. 2. Scanning skills to image ossifacation centers and epiphyses in the wrist and knee by ultrasound. (a) Probe set on radial styloid process in coronal plane to image the epiphysis of the radius. (b) Probe set on ulna styloid process in coronal-to-sagittal plane to image the epiphysis of the ulna. (c) Probe set on the medial collateral ligament in the coronal plane to image the epiphysis of the medial epicondyle of the femur and the medial tibial condyle.

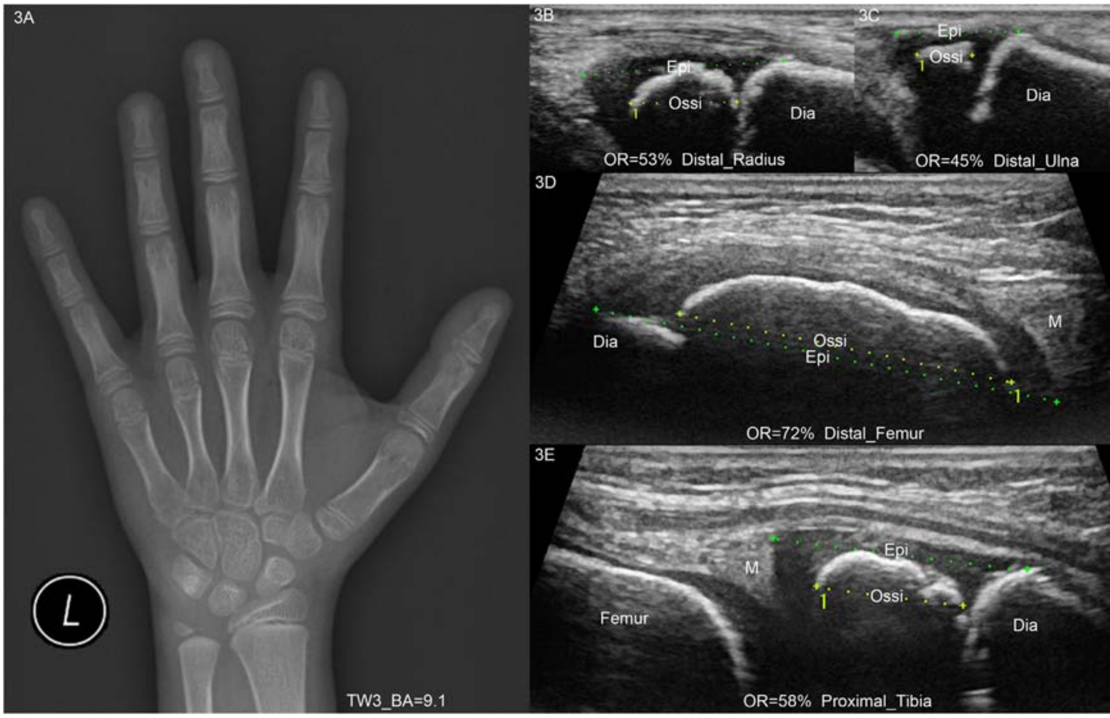

Fig. 3. (a) Radiograph of left hand and wrist. (b−e) Sonographic findings for the distal radius (b), ulna (c), the medial epicondyle of the femur (d) and medial tibial condyle (e) of a 9-y-old girl. Radiographic bone age was 9.1 y after interpreted with TW3 for Chinese population. *The dotted line* represents the measurement of the diameters of the epiphysis and ossification center. OR = ossification ratio defined as the ratio of the ossification center and epiphysis diameters; Epi = epiphysis; Ossi = ossification center; Dia = diaphysis; M = meniscus.

The maximum diameter of the epiphysis was measured from the point where the epiphysis and diaphysis connect 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. The OR, described as the ratio of the diameters of the ossification center and epiphysis was then calculated. The diameters of the epiphysis and ossification center and the OR were measured by the operator immediately after acquisition of the ultrasound images (Fig. 3).

Inter- and intra-observer reliability

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

Statistical analysis

Linear association between the OR calculated from the ultrasound image and BA derived from the plain radiograph was assessed with Pearson's correlation. The inter- and intra-observer reliability of the study was analyzed with the intra-class correlation coefficient (ICC). SPSS Version 22.0 (IBM Corp., Armonk, NY, USA) and Microsoft Excel 2013 (Microsoft Corp., Seattle, WA, USA) were used for statistical analysis. Differences were considered statistically significant at $p < 0.05$.

RESULTS

A total of 271 consecutive patients (132 boys and 139 girls) were finally enrolled. The chronologic age of the patients was 8.9 ± 4.4 y (0.1−18.8 y) for boys and 8.8 ± 4.3 y (0.1−18.9 y) for girls. Patients complained of short status (n = 99), mammary development (n = 82), obesity (n = 48), emaciation (n = 23), irregular menses (n = 9), vaginal discharge (n = 4), gynecomastia (n = 4) and small testicle (n = 2). Ossification centers of bones could be imaged by ultrasound as different sizes of

Table 1. Pearson's linear correlation coefficients (r) between bone age and ossification ratio of the bones in the wrist, knee and ankle

	Radius	Ulna	Femur	Tibia	MM	LM	RU	RUF	RUFT	Total
Boys (n = 132)	0.87 (0.80−0.92)	0.89 (0.81−0.93)	.90 (0.85−0.94)	0.79 (0.74−0.89)	0.75 (0.60−0.84)	0.50 (0.29−0.66)	0.95 (0.91−0.97)	0.97 (0.94−0.98)	0.97 (0.95−0.98)	0.94 (0.90−0.97)
Girls (n = 139)	0.87 (0.81−0.91)	0.88 (0.80−0.93)	0.91 (0.85−0.93)	0.81 (0.73−0.89)	0.78 (0.64−0.88)	0.54 (0.30−0.69)	0.94 (0.90−0.97)	0.96 (0.93−0.98)	0.96 (0.94−0.98)	0.94 (0.91−0.97)

Note. Data in parentheses are 95% confidence intervals.
MM = medial malleolus; LM = lateral malleolus; RU = radius + ulna; RUF, radius + ulna + femur; RUFT = radius + ulna + femur + tibia; Total = sum of ossification ratios from all six bones, $p < 0.001$.

hyper-echoic spots surrounded by hypo-echoic epiphyses (Fig. 3).

The correlation between the ORs and BA of each bone were analyzed. There was a relatively low correlation between ORs of the malleolus and BA (medial malleolus: Pearson's $r = 0.75$ and 0.78 for boys and girls; lateral malleolus: Pearson's $r = 0.50$ and 0.54 for boys and girls, respectively). There ORs of the radius, ulna and femur were highly correlated with BA (Pearson's r ranged from 0.87−0.91). There was a very high correlation between radius, ulna and femur (RUF) (sum of the ORs of the radius, ulna and femur) and BA (Pearson's $r = 0.97$ for boys and 0.96 for girls). No obvious increase in Pearson's r was observed when the OR of the tibia was appended. When the ORs of all the bones were summed, the correlation between OR and BA decreased (Pearson's $r = 0.94$ for boys and girls) (Table 1, Fig. 4).

The ORs of bones of patients with various BAs, expressed as percentages, are listed in Table 2. The ORs of the medial tibial condyle, medial malleolus and lateral malleolus are not listed as these had relatively low correlations with BA. The ORs of the radius, ulna and femur and RUF for infants (BA = 0−1 y) were 4%, 0%, 28.6% and33.6% for boys and 11.8%, 0%, 30.4% and 42.2% for girls, respectively. For patients with a BA >18 y, the OR of each bone and the RUF reached 100% and 300% (Table 2, Fig. 4).

The average time to scan the radius, ulna and femur in each patient by ultrasound was about 1.6 ± 0.5 min (1.0−2.1 min). It took 0.9 ± 0.2 min (0.7−1.2 min) to calculate the ORs of RUF. The entire process of data collection and calculation of RUF took 2.6 ± 0.6 min (1.9−3.1 min).

The inter-operator re-test indicated high repeatability (ICC = 0.83 [95% confidence interval: 0.59, 0.93], $p < 0.001$). Inter-observer repeatability among the three radiologists was high (ICC = 0.93 [95% confidence interval: 0.69, 0.96], $p < 0.001$). The intra-radiologist re-test revealed excellent repeatability (ICC = 0.95 [95% confidence interval: 0.93, 0.99], $p < 0.001$) (Table 3).

DISCUSSION

In this study, radiation-free ultrasound imaging was selected to assess the ORs of bones. There were high correlations between BA and the ORs of the distal end of the radius, ulna and medial epicondyle of the femur. The highest correlation was observed between BA and the OR of RUF, the sum of the ORs of the aforementioned three bones (Pearson's $r = 0.97$ for boys and 0.96 for girls). Moreover, a specific protocol was set for ultrasound scanning of the epiphyses of each bone. For example, the medial epicondyle of the femur was scanned in the coronal plane along the medial collateral ligament,

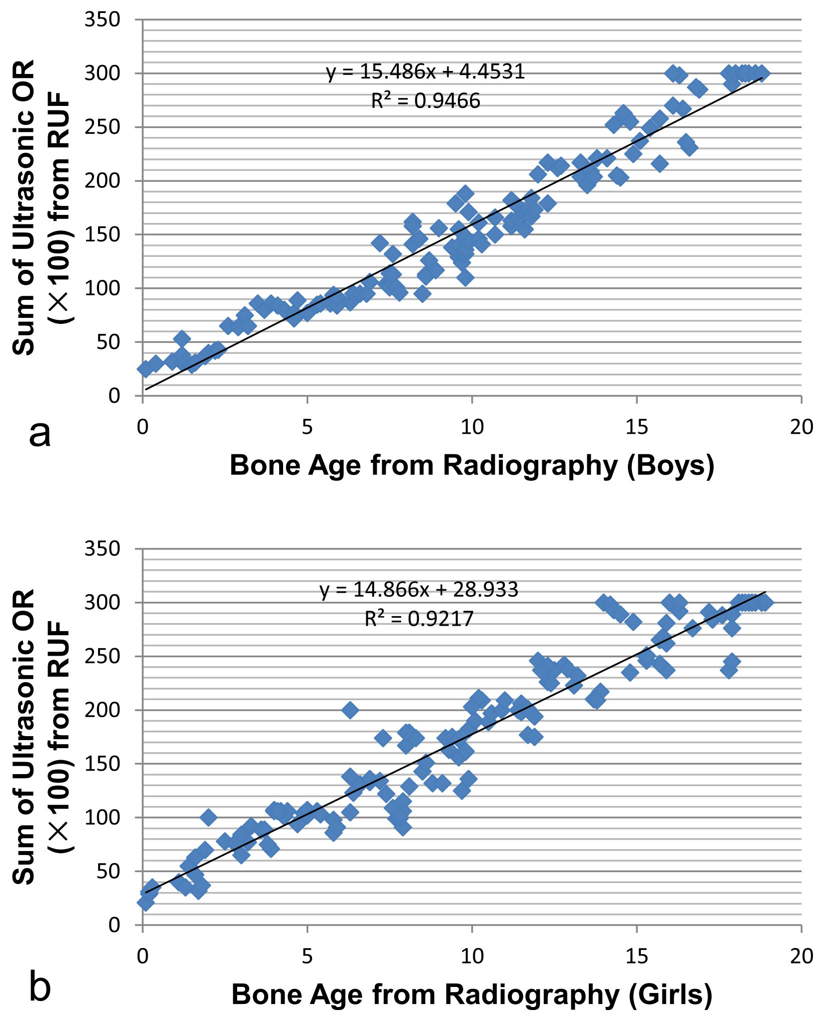

Fig. 4. Linear regression between summation of ossification ratios (shown as percenta‘ge) of radius, ulna, femur calculated from ultrasound images and bone age estimated from radiographs in (a) boys (n = 132) and (b) girls (n = 139). OR = ossification ratio; RUF = radius, ulna and femur.

Table 2. Ossification ratios (× 100) of bones for patients with different bone ages

Bone age	n		Radius		Ulna		Femur		RUF*	
	M	F	M	F	M	F	M	F	M	F
0−1	10	12	4 (8.1)	11.8 (14.0)	0	0	28.6 (3.9)	30.4 (5.3)	33.6 (10.3)	42.2 (17.6)
2−3	10	11	28.1 (8.2)	36.6 (5.1)	0	0	36.3 (5.7)	46.8 (6.2)	64.6 (11.8)	81.6 (10.5)
4−5	13	15	40.5 (5.4)	42.8 (6.1)	0	0	44.9 (7.0)	58.5 (6.8)	84.3 (10.7)	101.4 (9.4)
6−7	15	17	45.1 (5.3)	47.2 (5.4)	2.6 (7.8)	9.2 (9.1)	59.3 (5.0)	66.8 (4.1)	105.9 (10.8)	124.2 (12.1)
8−9	24	20	52.4 (6.8)	52.4 (3.8)	20.1 (6.9)	37.8 (7.9)	67.7 (3.7)	72.7 (2.8)	139.9 (11.2)	157.2 (10.1)
10−11	17	15	54.5 (5.8)	66.8 (7.9)	38.2 (8.6)	56.5 (7.7)	76.1 (3.0)	77.8 (2.9)	164.1 (12.6)	197.4 (12.8)
12−13	11	13	67.2 (9.4)	79.4 (5.7)	59.7 (9.9)	71.4 (7.1)	81.1 (3.1)	85.4 (2.9)	207.2 (13.1)	229.3 (14.5)
14−15	13	15	78 (9.3)	87.6 (7.8)	67.5 (8.6)	83.8 (6.6)	93.1 (5.4)	95.8 (6.0)	238.6 (14.2)	267.2 (12.8)
16−17	10	11	89.4 (11.2)	91.2 (9.2)	89.6 (12.8)	90.8 (11.1)	97.2 (6.3)	97.8 (4.9)	276.3 (19.3)	279.8 (18.4)
>18	9	10	100 (0)	100 (0)	100 (0)	100 (0)	100 (0)	100 (0)	300 (0)	300 (0)

Note. Data are medians, with standard deviation in parentheses.
* RUF = sum of ossification ratios from distal end of radius, ulna and medial epicondyle of femur.

Table 3. Intra-class correlation coefficient

	Intra-class Correlation	95% Confidence interval	*p* Value
Inter-operator	0.83	0.59−0.93	<0.001
Inter-radiologist	0.93	0.69−0.96	<0.001
Intra-radiologist	0.95	0.93−0.99	<0.001

which that familiar to sonographers, especially those who focused on musculoskeletal ultrasound. This will make the scanning method easy to learn. In addition, it took only 1.9−3.1 min for data acquisition and measurement of the OR of the RUF in our study. Wan et al. (2019) took about 7−9 min for data acquisition and measurement of the ORs of 13 bones from the hand and wrist, which is much more time consuming than this study. The method established in this study has the potential to assess BA quantitatively in an efficient and easy manner.

Imaging of the knee instead of the hand and wrist by radiography and magnetic resonance imaging (MRI) for BA estimation has already been studied. In Aicardi et al. (2000), the method used for assessment of skeletal age of the knee on radiographs proved to be less sensitive than the TW hand−wrist method in quantifying maturity advancement or delay. In our study, ORs of the femur ranged from 30.3%−100% for girls with BAs of 1−18 y. The span from 30.3%−100% was narrower than the span from 4%−100% (the ORs of radius) and that from 0%−100% (the ORs of ulna). Whether this narrower span of ORs across variant ages makes the evaluation of BA less sensitive is yet to be proven.

In another study, Pennock et al. (2018) created an atlas of MRI studies of the knee for pediatric and adolescent patients. The patella provided the best age assessment in early childhood. In our pilot study, we found that it was hard to obtain a standardized section by ultrasound to image the patella. Unlike the scans for radius, ulna or femur, there do not exist references such as diaphyses or ligaments when it comes to scans of the patella. We tried to measure the OR of the patella in a section with the maximum diameter of the ossification center, but the values obtained fluctuated greatly even when measured by the same operator. So the patella was not included in our study. The lateral side of the femur and tibia of the knee were relatively deep inside compared with the medial side. So the lateral condyle of the femur and tibia were not evaluated. Standardized sections of the knee are relatively easier to set in MRI than in ultrasound imaging. But MRI is time consuming for data acquisition, pricey and inaccessible in some clinical settings compared with ultrasound. All these factors make MRI not adaptive to be a routine method for BA evaluation.

Pearson's r between BA and the medial or lateral malleolus was low (with mean values of 0.75, 0.50 for boys and 0.78, 0.54 for girls respectively). No definite anatomic structures such as ligaments or tendons were selected to be a marker point for standardized scanning in this study. On the other hand, the epiphyses of the distal end of the malleolus sometimes appeared without a sharp outline. Both of these may magnify errors in measurement and cause the malleolus not to be good for evaluation of BA in this study.

Pearson's r between BA and the OR of the medial tibial condyle was 0.79 for boys and 0.81 for girls. We do not know why Pearson's r between BA and the OR of the tibia was much lower than that between BA and the OR of the femur (0.90 and 0.91 for boys and girls, respectively). Whether summed or not with the OR of the RUF, no obvious change in Pearson's r was observed (Table 1, 0.97 for girls and 0.96 for boys). Hence the medial tibial condyle was excluded from the final candidates used to evaluate BA.

Quantitative bone ultrasound, based on the principle of a different speed of sound and distance attenuation factor by bone and cartilage, has already been used to investigate bone status in the osteoporotic population (Camozzi et al. 2007; Malo et al. 2007) and to evaluate BA in children (Khan et al. 2009; Rachmiel et al. 2017). The overlying soft tissue, with a speed of sound different from that in bone, produces significant uncertainties, diminishing the reliability of the measurements (Malo et al. 2007; Khan et al. 2009). In this study, the influence of the different speeds of sound in soft tissue and bone, which make measurements of the diameters of the epiphysis and ossification center not accurate, may be compensated by using the OR parameter.

The limitation of this study is that only the ORs of bones from patients were used, and no clinically useful percentile values for healthy patients were obtained.

CONCLUSIONS

There are significant positive correlations between BA and the OR of the RUF measured by ultrasound imaging in patients from infants to teenagers (Pearson's $r = 0.97$ and 0.96 in boys and girls, respectively). The OR of the RUF obtained with ultrasound has the potential to assess BA quantitatively in an efficient (2.6 ± 0.6 min for data collection and calculation) and easy manner. Healthy volunteers will be recruited in our future work. The accuracy of the modality in evaluation of BA will also be assessed.

Conflict of interest disclosure—The authors declare no competing interests.

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