RESEARCH ARTICLE

The estimation of skeletal maturity of patients with cleft lip and palate using statistical shape analysis: a preliminary study

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Objectives: To propose a skeletal maturity assessment method by developing a statistical regression analysis model through the integration of lateral and axial images of the cervical vertebrae of patients with cleft lip and palate obtained through CBCT.

Methods: 49 patients with cleft lip and palate (28 females, 21 males; age range, 4–16 years) underwent CBCT examination, and the hand-wrist radiographic data were selected. With coordinates of landmarks from lateral and axial images of the cervical vertebrae, Procrustes analysis and principal component (PC) analysis yielded PC scores of each cervical vertebra, with the centroid size as the size factor. The meaningful PC scores from these were used for multiple regression models.

Results: When both axial and lateral cervical vertebrae were used together, there was a 6.7% increase in the Sempé maturation level explanatory power for skeletal maturation estimation in females and an 11.4% increase in males compared with that when only the chronological age was used.

Conclusions: This study improved the estimating regression models using statistical shape analysis with lateral and axial cervical vertebral shapes. The obtained models had improved explanatory power for skeletal maturity estimation than previous studies with healthy people. *Dentomaxillofacial Radiology* (2017) **46**, 20160491. doi: 10.1259/dmfr.20160491

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Keywords: CBCT; cervical vertebrae; CLP; skeletal maturation; shape analysis

Introduction

Cleft lip and palate (CLP) is a common congenital deficiency syndrome with a birth prevalence rate of 1.46 per 1000 live births.¹ CLP appears in various

morphologies such as cleft lip, cleft lip and alveolus, cleft palate, unilateral cleft lip and palate (UCLP), bilateral cleft lip and palate (BCLP) and facial cleft.² Among these, UCLP and BCLP have high frequencies of occurrence.² Being able to evaluate the growth and skeletal maturity among patients with CLP is essential to establish an effective orthopaedic treatment plan because they have certain growth differences and a need to consider growth modification frequently.³ There are, however, various controversies on whether or not the physical development of patients with CLP is similar to

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that of normal people. Some studies^{4,5} state that defects, post-surgical scars and sociological stresses impede physical growth, whereas other studies^{6,7} state that these factors do not have an effect. Moreover, studies on the growth of patients with CLP are easily accessible, yet studies about skeletal maturity are rare, one of which was a recent study about skeletal maturity using the cervical vertebral maturation (CVM) method.^{8,9}

Skeletal maturity is essential for growth modification treatment in orthodontics. For this reason, many researchers have explored various indices to evaluate skeletal maturity.^{10,11} The assessment of hand-wrist maturation is one fairly accurate method,¹⁰ but it possesses the drawback of taking hand-wrist radiographs separately and using qualitative evaluation. The CVM is a method of skeletal maturity evaluation based on the morphological traits of cervical vertebrae.¹¹ However, the poor reproducibility of the CVM method has been noted, and judgmental errors may be prevalent.¹² In order to improve and overcome the limitations, other methods^{13–17} that apply shape analysis by measuring vertebral shapes of the lateral or axial planes of the first, second, third and fourth cervical vertebrae (C1–C4) have been devised. Because human development is three dimensional rather than two dimensional, the method of using both lateral cervical vertebrae (LCV) and axial cervical vertebrae (ACV) is expected to be a more accurate predictor of skeletal maturity than the existing method of using a single plane, yet there is no previous study on this subject matter. For a three-dimensional assessment, three-dimensional imaging is required, and it can be obtained through CBCT.

The purpose of this study was to propose a skeletal maturity assessment method by developing a statistical regression analysis model through the integration of lateral and axial images of cervical vertebrae of patients with CLP obtained through CBCT.

Methods and materials

Study design and samples

The samples of this retrospective study were 49 patients with BCLP or UCLP (age range, 4–16 years) who undertook CBCT and had the hand-wrist radiographic films assessed at the Department of Orthodontics in the School of Dentistry at Showa University. There were 28 female and 21 male patients (Table 1). CBCT data were taken for clinical purposes (*e.g.* bone graft, impacted tooth). The following are the exclusion criteria: any history of trauma or other developmental syndrome; 10

cases were excluded. This study was reviewed and approved by the institutional review board of Pusan National University Dental Hospital (PNUDH-2014-019).

CBCT images were taken on a CB MercuRay[®] (Hitachi Medical, Tokyo, Japan) with 9 × 9-inch field of view, 0.376 mm voxel size, 100 kVp tube voltage, 10 mA tube current and 9.6 s scan time. CBCT data were converted and saved as digital imaging and communications in medicine files.

Skeletal maturation status from hand-wrist assessment

To assess the skeletal maturational stages from the hand-wrist radiographic films, Sempé maturation level (SML) method²⁰ was used for the dependent variables. This method quantifies skeletal maturation level into an index ranging from 0 at birth to 999 at the stage when growth is completed as continuous scales. We used a free software (Skelema 1.1, Paris, France) for SML assessment.

CBCT-generated LCV and ACV images acquisition

Any head tilting of the patient in the CBCT image was corrected on the computer. That is, the CBCT scan was reoriented using the Frankfort horizontal plane-based method which sets four landmarks (nasion, left orbitale, right orbitale and right porion) in the multiplanar reformation mode of the OnDemand3D[™] program (Cybermed Inc., Seoul, Korea). Later, CBCT-generated LCV and ACV images were produced in the OnDemand3D program.

Obtaining CBCT-generated LCV images: The CBCT-generated LCV images were obtained by the following steps:¹⁵ the LCV images were constructed from the midsagittal reference plane, which consisted of the midpoint of the anterior lower border of the second cervical vertebral body and spinous process and the most superior point of the odontoid process. A total of 30 landmarks were obtained from the images of the second, third and fourth cervical vertebrae (Figure 1). The landmarks were positioned manually.

Obtaining CBCT-generated ACV images: The CBCT-generated ACV images were obtained by the following steps:¹⁶ for C1, the most anterior and posterior points were used to generate the anteroposterior axis. Once the anteroposterior axis was set, the vertical axis was adjusted to pass through the midpoint. Then, with the horizontal axis maintained, the image layer thickness was selected for each cervical vertebra within the posterior arch with neither the upper border of the band nor the lower border overlapping either the upper or lower cortical lamina in the sagittal view.

For maximally distinguishable image acquisition in C2, the same vertical axis as in C1 was used. The thickness of the image layer encompassed the entire posterior arch in the sagittal section. For C3 and C4, the vertical axis was constructed from the lowermost point of the posterior lamina of the C4 body to the uppermost point of the posterior lamina of the C3 body. The

Table 1 Descriptive statistics of subjects

Chronologic age (years)	4	5	6	7	8	9	10	11	12	13	14	15	16
Female (<i>n</i> = 28)	9	3	2	4	2	2	1	0	1	0	3	0	1
Male (<i>n</i> = 21)	8	3	1	0	2	0	1	2	1	1	1	1	0

Figure 1 Landmarks for determining the lateral cervical vertebral shape dens: uppermost (Point 1), most anterior-lower (Point 4), most posterior-lower (Point 6), inflection between Points 1 and 4 (Point 2), inflection between Points 4 and 6 (Point 5), inflection between Points 1 and 6 (Point 3); C2: most anterior-upper (Point 7), most anterior-lower (Point 12), most posterior-upper (Point 9), most posterior-lower (Point 14), inflection between Points 7 and 12 (Point 10), inflection between Points 12 and 14 (Point 13), inflection between Points 9 and 14 (Point 11), inflection between Points 7 and 9 (Point 8); C3: most anterior-upper (Point 15), most anterior-lower (Point 20), most posterior-upper (Point 17), most posterior-lower (Point 22), inflection between Points 15 and 20 (Point 18), inflection between Points 20 and 22 (Point 21), inflection between Points 17 and 22 (Point 19), inflection between Points 15 and 17 (Point 16); C4 : most anterior-upper (Point 23), most anterior-lower (Point 28), most posterior-upper (Point 25), most posterior-lower (Point 30), inflection between Points 23 and 28 (Point 26), inflection between Points 28 and 30 (Point 29), inflection between Points 25 and 30 (Point 27) and inflection between Points 23 and 25 (Point 24).

Figure 2 Landmarks for determining the axial cervical vertebral shape (a) C1: most anterior (Point 1), most posterior (Point 5), most lateral, right and left (Point 4), inflection located anteriorly and where curvature of the articular surface begins, right and left (Point 2), farthest from the line joining Points 2 and 4 and located between Points 2 and 4, right and left (Point 3). (b) C2: most posterior in the vertebral foramen (Point 1), most lateral of the vertebral arch, right and left (Point 3), most lateral of the vertebral foramen, right and left (Point 4), most posterior of the body (Point 6), inflection on the line joining Points 4 and 6 located on the posterior lamina of the body, right and left (Point 5), farthest from the line joining Points 1 and 4 and located between Points 1 and 4, right and left (Point 2). (c) C3 and C4: most posterior of the vertebral body (Point 4), most posterior of the vertebral foramen (Point 1), most lateral of the vertebral foramen, right and left (Point 2), inflection from the line joining Points 2 and 4 located on the posterior lamina of the body, right and left (Point 3), most anterior of the body (Point 6) and most lateral of the body, right and left (Point 5).

thickness of the image layer was made from the upper and lower borders of the cervical vertebral body. In total, 36 landmarks were positioned on the obtained ACV images (Figure 2). We considered four regions of interest (ROIs): C1, C2, C3 and C4, for shape analysis based on the previous studies.^{15–17}

Procrustes analysis and principal component analysis

Full generalized Procrustes analysis (GPA) was performed to analyze the shape of the ROIs, and partial GPA was used to determine the form of the ROIs. In full GPA, the configurations of ROIs, which are recognized by the statistical program when their x - y coordinates are provided, are translated, rescaled and rotated relative to one other. This is carried out to minimize the generalized Procrustes sum of squares, a measure of the sum of pairwise differences of each corresponding landmark. In the course of full GPA, information on the size of each object is extracted as a centroid size (CS). Meanwhile, in partial GPA of each ROI, sets of landmarks from the corresponding ROI are translated and rotated but not rescaled, thus generating information on the form of the ROI.

With the landmarks, GPA and principal component analysis (PCA) were carried out to determine the shape and form, yielding principal component (PC) scores of each ROI with the CS as the size factor. These meaningful PC scores could then be used for multiple regression models.

Multivariable regression models

The SML was used as a dependent variable, whereas gender, age, PC scores, centroid sizes of each shape and form space were used as predictor variables. For landmark reliability, we repeatedly obtained the landmarks and SML of 15 randomly selected samples at 2-week intervals. The intra- and interexaminer agreements were

evaluated using the intraclass correlation coefficient and Cohen's kappa statistic. The intra- and interexaminer reliabilities of the linear measurements were very high according to the intraclass correlation coefficient (mean of 0.953 and 0.920, respectively), and the Cohen's kappa index for SML also showed substantial agreement (mean of 0.821 and 0.753, respectively). The language R (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical computation.

Results

Centroid size comparison by gender

There was a positive correlation between the CS and skeletal maturity. The correlation coefficients of the CS and skeletal maturity (female/male) at the second, third and fourth ACV were, respectively, 0.6458 (0.8287/0.6374), 0.5695 (0.7582/0.8001) and 0.5291 (0.6176/0.7623). In addition, the correlation coefficients of the CS and skeletal maturity (female/male) at the second, third and fourth LCV were 0.8583 (0.9093/0.8340), 0.8910 (0.9287/0.8922) and 0.8906 (0.9043/0.9132). It can also be inferred that CS can be a predictive indicator for multivariate regression models.

Principal components analysis

By means of GPA and PCA, the corresponding indicator spaces (shape, form and centroid size) and their PC scores were obtained. Table 2 shows the meaningful PCs with explanatory power of >70%.

Multivariate regression models for skeletal maturity estimation

The age and PC scores were used to construct multiple regression models for the estimation of skeletal maturity. The gender was the dummy variable in this case.

Table 2 Meaningful principal components (PCs) from the PCs analysis (second, third and fourth cervical vertebrae)

	Second cervical vertebra												Third cervical vertebra												Fourth cervical vertebra												
	Form space						Shape space						Form space						Shape space						Form space						Shape space						
	Female			Male			Female			Male			Female			Male			Female			Male			Female			Male			Female			Male			
	L	A	Overall	L	A	Overall	L	A	Overall	L	A	Overall	L	A	Overall	L	A	Overall	L	A	Overall	L	A	Overall	L	A	Overall	L	A	Overall	L	A	Overall				
%	36.8	63.1	24.7	89.3	28.0	72.0	36.1	62.8	24.6	89.1	27.4	71.7	73.3	19.9	55.5	28.9	65.7	21.5	72.1	19.9	54.8	28.8	64.7	21.5	63.9	21	48.5	28.8	58.3	18.5	63.0	20.9	47.8	28.5	57.5	18.3	
PC1	36.8	63.1	24.7	89.3	28.0	72.0	36.1	62.8	24.6	89.1	27.4	71.7	73.3	19.9	55.5	28.9	65.7	21.5	72.1	19.9	54.8	28.8	64.7	21.5	63.9	21	48.5	28.8	58.3	18.5	63.0	20.9	47.8	28.5	57.5	18.3	
PC2	13.3	36.8	19.2	14.4	14.4	14.4	13.3	36.8	19.2	14.4	14.4	14.4	17.8	17.7	19.8	8.8	17.0	17.7	14.7	19.8	8.8	17.0	17.0	10.5	16.5	15.0	21.3	9.3	16.3	16.5	15.1	21.3	9.4	16.3	16.3	16.3	
PC3	10.0	14.3	11.5	11.5	11.5	11.5	10.0	14.3	11.5	11.5	11.5	11.5	13.0	13.5	13.5	13.0	13.5	13.6	13.0	8.2	13.6	9.3	9.3	9.2	12.6	10.3	11.3	8.6	12.4	12.6	10.3	11.4	8.6	12.3	12.3	12.3	
PC4	8.5	11.3	9.1	11.3	9.1	9.1	8.5	11.3	9.1	11.3	9.1	9.1	11.9	9.3	9.3	11.9	9.3	9.2	11.9	9.0	11.9	9.0	9.0	8.4	10.9	10.5	10.9	8.9	10.5	10.5	10.9	9.0	10.5	10.5	10.5	10.5	
PC5	7.6	7.9	7.0	7.9	7.0	7.0	7.7	7.9	7.0	7.9	7.0	7.0	9.0	9.0	9.0	9.0	8.4	9.0	9.0	9.0	9.0	9.0	8.4	8.6	8.6	8.6	8.6	8.6	8.8	8.6	8.6	8.6	8.8	8.8	8.8	8.8	
PC6	7.6	7.9	7.0	7.9	7.0	7.0	7.6	7.9	7.0	7.9	7.0	7.0	9.0	9.0	9.0	9.0	8.4	9.0	9.0	9.0	9.0	9.0	8.4	8.6	8.6	8.6	8.6	8.6	8.8	8.6	8.6	8.6	8.8	8.8	8.8	8.8	
SUM	76.3	99.9	77.4	89.3	70.0	72.0	75.6	99.6	77.2	89.1	75.1	71.7	73.3	71.5	70.3	71.6	74.5	74.2	72.1	71.4	71.7	71.5	73.5	74.1	74.4	76.8	73.9	70.4	76.2	72.9	73.5	76.7	73.2	70.1	75.4	72.7	72.7

A, axial cervical vertebra; L, lateral cervical vertebra.

According to the analysis results, the regression analysis models obtained by the “step elimination” method are as follows:

- Model 1: gender + age
- Model 2-A: gender + age + CV1.PCs(A) + CV2.PCs(A) + CV3.PCs(A) + CV4.PCs(A)
- Model 2-L: gender + age + CV2.PCs(L) + CV3.PCs(L) + CV4.PCs(L)
- Model 3-A: gender + age + CV1.PCs(A) + CV2.PCs(A) + CV3.PCs(A) + CV4.PCs(A) + CSs(A)
- Model 3-L: gender + age + CV2.PCs(L) + CV3.PCs(L) + CV4.PCs(L) + CSs(L)
- Model 4: gender + age + CV1.PCs(A) + CV2.PCs(A) + CV3.PCs(A) + CV4.PCs(A) + CV2.PCs(L) + CV3.PCs(L) + CV4.PCs(L)
- Model 5: gender + age + CV1.PCs(A) + CV2.PCs(A) + CV3.PCs(A) + CV4.PCs(A) + CV2.PCs(L) + CV3.PCs(L) + CV4.PCs(L) + CSs(A) + CSs(L)

where (A) is axial, (L) is lateral, CS is the centroid size, PC is the principal component and CV is the cervical vertebra.

Model 1 is for comparison. For Model 2, only ACV or only LCV was applied. For Model 3, CS was added to Model 2. For Model 4, both ACV and LCV were applied and for Model 5, CS was added to Model 4.

The PCs and CSs used in the models are shown in Tables 3 and 4. There was no significant difference in model explanation and prediction interval between form space and shape space. The narrowest prediction interval was male Model 5 based on the shape space (Table 5). The models with CS (Models 3 and 5) presented higher explanatory power than the models without CS (Models 2 and 4). Models that included both ACV and LCV (Models 4 and 5) showed higher explanatory power but lower prediction intervals than the models that used only ACV or only LCV (Models 2 and 3). In addition, LCV had a higher explanatory power than ACV. For models with shape space in females, the explanatory power when only chronological age, only ACV or only LCV was used was 90.7%, 93.8% or 95.8%, respectively. On the other hand, the explanatory power when both ACV and LCV were used was 97.4%. For males, the explanatory powers were 87.4%, 90.2%, 98.5% and 98.8%, respectively. According to the results, when ACV and LCV were used together, there was a 6.7% increase in SML explanatory power for females and an 11.4% increase for males compared with that when only chronological age was used.

Discussion

Statistical shape analysis,¹³ which extracts the mean shape of the samples and compares morphological differences among samples, can be used in a variety of fields including orthodontics.¹⁷ This study tried to

Table 3 Multivariate regression models for skeletal maturation estimation: form space

Models	Female	Male	Overall
Model 1	$-18.11 + 7.19 \times \text{age}$	$-15.96 + 5.72 \times \text{age}$	$-13.29 - 8.59 \times \text{gender} + 6.53 \times \text{age}$
Model 2-A	$-11.34 + 6.26 \times \text{age} + 74.26 \times \text{CV1.PC1(A)}$	$-14.49 + 5.53 \times \text{age} - 85.54 \times \text{CV4.PC2(A)}$	$-9.74 - 7.07 \times \text{gender} + 5.95 \times \text{age} - 37.38 \times \text{CV1.PC1(A)} + 89.97 \times \text{CV3.PC6(A)} + 65.98 \times \text{CV4.PC2(A)} - 118.65 \times \text{CV4.PC6(A)}$
Model 2-L	$-12.97 + 6.48 \times \text{age} - 46.84 \times \text{CV2.PC1(L)} - 70.65 \times \text{CV2.PC2(L)} - 73.95 \times \text{CV2.PC3(L)}$	$-4.40 + 4.16 \times \text{age} - 104.45 \times \text{CV2.PC3(L)} + 76.47 \times \text{CV3.PC1(L)} - 47.15 \times \text{CV3.PC2(L)}$	$3.86 - 6.35 \times \text{gender} + 4.06 \times \text{age} + 73.43 \times \text{CV2.PC4(L)} + 66.25 \times \text{CV2.PC5(L)} - 74.73 \times \text{CV3.PC1(L)}$
Model 3-A	$-53.49 + 5.36 \times \text{age} + 71.90 \times \text{CV1.PC1(A)} + 1.33 \times \text{CS2(A)}$	$-14.49 + 5.53 \times \text{age} - 85.54 \times \text{CV4.PC2(A)}$	$-9.74 - 7.07 \times \text{gender} + 5.95 \times \text{age} - 37.38 \times \text{CV1.PC1(A)} + 89.97 \times \text{CV3.PC6(A)} + 65.98 \times \text{CV4.PC2(A)} - 118.65 \times \text{CV4.PC6(A)}$
Model 3-L	$-58.70 + 4.59 \times \text{age} - 56.74 \times \text{CV2.PC2(L)} - 64.96 \times \text{CV2.PC3(L)} + 1.52 \times \text{CV2(L)}$	$-36.44 + 2.42 \times \text{age} + 60.80 \times \text{CV2.PC1(L)} + 91.25 \times \text{CV3.PC1(L)} + 2.10 \times \text{CS3(L)}$	$-36.60 - 7.03 \times \text{gender} + 2.02 \times \text{age} - 40.88 \times \text{CV2.PC1(L)} - 71.48 \times \text{CV3.PC1(L)} + 2.62 \times \text{CS3(L)}$
Model 4	$-10.94 + 6.21 \times \text{age} + 66.69 \times \text{CV1.PC1(A)} - 34.53 \times \text{CV2.PC1(L)}$	$-4.40 + 4.16 \times \text{age} - 104.45 \times \text{CV2.PC3(L)} + 76.47 \times \text{CV3.PC1(L)} - 47.15 \times \text{CV3.PC2(L)}$	$1.02 - 5.60 \times \text{gender} + 4.40 \times \text{age} + 54.74 \times \text{CV4.PC2(A)} - 78.07 \times \text{CV4.PC6(A)} + 63.53 \times \text{CV2.PC5(L)} - 77.66 \times \text{CV3.PC1(L)}$
Model 5	$-66.49 + 4.56 \times \text{age} + 54.30 \times \text{CV1.PC1(A)} + 59.64 \times \text{CV3.PC3(A)} - 48.90 \times \text{CV3.PC1(L)} + 72.18 \times \text{CV4.PC1(L)} + 1.73 \times \text{CS2(L)}$	$-21.19 + 2.44 \times \text{age} + 98.30 \times \text{CV2.PC1(L)} + 93.89 \times \text{CV3.PC1(L)} - 1.14 \times \text{CS1(A)} + 0.93 \times \text{CS4(A)} + 2.01 \times \text{CS3(L)}$	$-40.16 - 6.58 \times \text{gender} + 2.45 \times \text{age} - 75.62 \times \text{CV4.PC6(A)} - 39.03 \times \text{CV2.PC1(L)} - 34.41 \times \text{CV2.PC2(L)} - 57.44 \times \text{CV3.PC1(L)} + 2.63 \times \text{CS3(L)}$

A, axial; L, lateral.

increase the explanatory power of skeletal maturity by statistical shape analysis, which uses LCV and ACV together, different from the existing method of using LCV or ACV alone. Likewise, it showed a 3.6% increase for females and an 8.6% increase for males compared with the results of when ACV was used alone. Previous methods using ACV or LCV alone take a two-dimensional approach, whereas the present study was designed to take more of a three-dimensional approach

by combining ACV and LCV. It was thus considered to possess a higher explanatory power due to the three-dimensional growth of the human body.

Furthermore, the models containing CS (Models 3 and 5) showed higher explanatory power than those not containing CS (Models 2 and 4), and the models using LCV had higher explanatory power than those using ACV. This difference occurs because the amount of vertical growth of the cervical vertebrae is three times

Table 4 Multivariate regression models for skeletal maturation estimation: shape space

Models	Female	Male	Overall
Model 1	$-18.11 + 7.19 \times \text{age}$	$-15.96 + 5.72 \times \text{age}$	$-13.29 - 8.59 \times \text{gender} + 6.53 \times \text{age}$
Model 2-A	$-11.33 + 6.26 \times \text{age} + 74.71 \times \text{CV1.PC1(A)}$	$-14.51 + 5.53 \times \text{age} - 84.93 \times \text{CV4.PC2(A)}$	$-9.77 - 7.09 \times \text{gender} + 5.96 \times \text{age} - 37.85 \times \text{CV1.PC1(A)} + 89.44 \times \text{CV3.PC6(A)} + 65.10 \times \text{CV4.PC2(A)} - 117.96 \times \text{CV4.PC6(A)}$
Model 2-L	$-12.99 + 6.49 \times \text{age} - 47.32 \times \text{CV2.PC1(L)} - 71.64 \times \text{CV2.PC2(L)} - 73.12 \times \text{CV2.PC3(L)}$	$-4.45 + 4.17 \times \text{age} - 104.07 \times \text{CV2.PC3(L)} + 76.83 \times \text{CV3.PC1(L)} - 47.78 \times \text{CV3.PC2(L)}$	$3.90 - 6.31 \times \text{gender} + 4.05 \times \text{age} + 72.33 \times \text{CV2.PC4(L)} + 67.61 \times \text{CV2.PC5(L)} - 76.04 \times \text{CV3.PC1(L)}$
Model 3-A	$-53.30 + 5.36 \times \text{age} + 72.23 \times \text{CV1.PC1(A)} + 1.32 \times \text{CS2(A)}$	$-14.51 + 5.53 \times \text{age} - 84.93 \times \text{CV4.PC2(A)}$	$-9.77 - 7.09 \times \text{gender} + 5.96 \times \text{age} - 37.85 \times \text{CV1.PC1(A)} + 89.44 \times \text{CV3.PC6(A)} + 65.10 \times \text{CV4.PC2(A)} - 117.96 \times \text{CV4.PC6(A)}$
Model 3-L	$-58.67 + 4.59 \times \text{age} - 57.49 \times \text{CV2.PC2(L)} - 64.22 \times \text{CV2.PC3(L)} + 1.52 \times \text{CS2(L)}$	$-39.53 + 2.01 \times \text{age} + 54.08 \times \text{CV2.PC1(L)} + 117.58 \times \text{CV3.PC1(L)} + 59.63 \times \text{CV3.PC3(L)} - 31.82 \times \text{CV4.PC1(L)} + 2.38 \times \text{CS3(L)}$	$-36.40 - 7.00 \times \text{gender} + 2.01 \times \text{age} - 41.08 \times \text{CV2.PC1(L)} - 72.78 \times \text{CV3.PC1(L)} + 2.61 \times \text{CS3(L)}$
Model 4	$-10.92 + 6.20 \times \text{age} + 67.10 \times \text{CV1.PC1(A)} - 34.83 \times \text{CV2.PC1(L)}$	$-4.45 + 4.17 \times \text{age} - 104.07 \times \text{CV2.PC3(L)} + 76.83 \times \text{CV3.PC1(L)} - 47.78 \times \text{CV3.PC2(L)}$	$1.09 - 5.61 \times \text{gender} + 4.40 \times \text{age} + 53.05 \times \text{CV4.PC2(A)} - 78.44 \times \text{CV4.PC6(A)} + 64.95 \times \text{CV2.PC5(L)} - 79.06 \times \text{CV3.PC1(L)}$
Model 5	$-66.74 + 4.56 \times \text{age} + 54.42 \times \text{CV1.PC1(A)} + 59.22 \times \text{CV3.PC3(A)} - 49.86 \times \text{CV3.PC1(L)} + 73.68 \times \text{CV4.PC1(L)} + 1.73 \times \text{CS2(L)}$	$-11.81 + 2.16 \times \text{age} + 44.19 \times \text{CV2.PC1(L)} + 105.17 \times \text{CV3.PC1(L)} + 62.59 \times \text{CV3.PC3(L)} - 0.76 \times \text{CS2(A)} + 2.42 \times \text{CS3(L)}$	$-40.05 - 6.55 \times \text{gender} + 2.44 \times \text{age} - 75.90 \times \text{CV4.PC6(A)} - 39.10 \times \text{CV2.PC1(L)} - 35.09 \times \text{CV2.PC2(L)} - 58.56 \times \text{CV3.PC1(L)} + 2.62 \times \text{CS3(L)}$

A, axial; L, lateral.

Table 5 Multivariate regression models for skeletal maturation estimation with explanatory power and prediction intervals

Models	Female				Male				Overall			
	R ²		w90%CI		R ²		w90%CI		R ²		w90%CI	
	Form	Shape	Form	Shape	Form	Shape	Form	Shape	Form	Shape	Form	Shape
Model 1	0.9068	0.9068	29.93	29.93	0.8737	0.8737	30.57	30.57	0.8870	0.8870	F: 30.64 M: 30.82	F: 30.64 M: 30.82
Model 2-A	0.9301	0.9302	26.46	26.45	0.9025	0.9020	27.67	27.74	0.9182	0.9178	F: 27.36 M: 27.53	F: 27.42 M: 27.59
Model 2-L	0.9444	0.9444	24.70	24.69	0.9682	0.9677	16.86	17.01	0.9308	0.9308	F: 24.85 M: 25.00	F: 24.85 M: 25.00
Model 3-A	0.9381	0.9381	25.47	25.47	0.9025	0.9020	27.67	27.74	0.9182	0.9178	F: 27.36 M: 27.53	F: 27.42 M: 27.59
Model 3-L	0.9578	0.9578	21.53	21.52	0.9760	0.9854	14.67	12.34	0.9555	0.9554	F: 19.92 M: 20.04	F: 19.95 M: 20.07
Model 4	0.9396	0.9396	25.16	25.16	0.9682	0.9677	16.86	17.01	0.9366	0.9365	F: 24.09 M: 24.24	F: 24.11 M: 24.26
Model 5	0.9735	0.9737	17.91	17.85	0.9863	0.9880	11.95	11.19	0.9623	0.9623	F: 18.81 M: 18.92	F: 18.81 M: 18.92

F, female; M, male; w90%CI, 90% confidence intervals.

greater than the amount of horizontal growth,^{18,19} which parallels the results from previous studies.¹⁷ It is also the reason that lateral images of the cervical vertebrae were frequently used for previous skeletal maturity analysis. On the other hand, the correlation between CS and skeletal maturity of the cervical vertebrae can be inferred from the increase in the size of the cervical vertebrae, which has a somatic growth pattern^{18,19} that steadily increases until an individual is 15–16 years old. It also agrees with the study by Rhee *et al*¹⁷ using only LCV, in which the CS was used as a predictive indicator of multivariable regression models.

Model 5 based on shape space showed the highest explanatory power for both males and females. Model 5 used both ACV and LCV, and it included CS as a predictive indicator.

Unfortunately, this study was limited by a small sample size because it was hard to collect data from patients with CLP. Confirmation of the validity of the present results will require a further, larger-scale study. Other limitations were having a single ethnicity sample group and a narrow age range. To increase the validity, a further study with a larger and more diverse sample

size is necessary. Also, the landmarks have to be positioned automatically in order to be applied on a daily routine. Finally, there still is a remaining controversy concerning whether CBCT imaging is required in every patient. Our result can be utilized in clinical applications with the use of pre-existing CBCT data.

Conclusions

Statistical shape analysis with the integrated lateral and axial images of the cervical vertebrae of patients with CLP obtained through CBCT could be applied to improve regression models that are used to estimate skeletal maturation. The obtained models had improved explanatory power in skeletal maturity estimation compared with previous studies with healthy individuals.

Disclosure of Conflict of Interest

We declare that there is no conflict of interest with regard to this study.

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