RESEARCH ARTICLE

The skeletal maturation status estimated by statistical shape analysis: axial images of Japanese cervical vertebra

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Objectives: To evaluate axial cervical vertebral (ACV) shape quantitatively and to build a prediction model for skeletal maturation level using statistical shape analysis for Japanese individuals.

Methods: The sample included 24 female and 19 male patients with hand–wrist radiographs and CBCT images. Through generalized Procrustes analysis and principal components (PCs) analysis, the meaningful PCs were extracted from each ACV shape and analysed for the estimation regression model.

Results: Each ACV shape had meaningful PCs, except for the second axial cervical vertebra. Based on these models, the smallest prediction intervals (PIs) were from the combination of the shape space PCs, age and gender. Overall, the PIs of the male group were smaller than those of the female group. There was no significant correlation between centroid size as a size factor and skeletal maturation level.

Conclusions: Our findings suggest that the ACV maturation method, which was applied by statistical shape analysis, could confirm information about skeletal maturation in Japanese individuals as an available quantifier of skeletal maturation and could be as useful a quantitative method as the skeletal maturation index.

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Introduction

In orthodontic treatment, methods for tracking the process of skeletal maturation are a pre-requisite for growing patients. Various skeletal maturation prediction methods have been introduced.^{1–5} Hand–wrist maturation, dental maturation and cervical vertebral maturation (CVM) have been applied by many researchers for the estimation of skeletal maturation.^{1,3–5}

Among the methods of skeletal maturation analysis, quantitative analysis was introduced to reduce examiner errors in the radiographic interpretation, such as the determination of developmental stages. Chatzigianni and Halazonetis⁶ applied statistical shape analysis to the lateral CVM method for skeletal maturation prediction. Statistical shape analysis is a morphometric analysis from a set of shapes in which the statistics are measured to describe geometric properties from similar shapes or different groups. Shape analysis has already been applied to mouse vertebral shapes, gorilla skulls and oncology.⁷ Recently, Yang et al⁸ also introduced this method for the estimation of skeletal maturation in Korean individuals. This application of statistical shape

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analysis to the skeletal maturation estimation could not only help orthodontists to determine treatment timing in growing patients but could also be used for the purposes of forensic science.

Conversely, gender and racial differences should also be considered for skeletal maturation. Gender differences in the velocity of growth and development, the timing of the adolescent growth spurt and the age of skeletal maturation are well known.^{9–12} Ethnic variations in the timing of skeletal maturation might be owing to genetic differences, environmental conditions, socioeconomic status, nutrition, hygiene conditions, and regional and climatic differences.^{11,13} By contrast, there have been several studies that reported that, in adolescence, no time difference in skeletal maturation exists between Caucasians and Africans.^{12,14} Despite several studies, the role of ethnic diversity in skeletal maturation remains unclear. However, under favourable environmental conditions, such as similar socioeconomic status, ethnic differences could be minimized.^{15–17} Among Asian populations, Korean and Japanese individuals have similar socioeconomic status. Differences in ethnicity between Koreans and Japanese might be expected to have a minimal effect on skeletal maturation. Unfortunately, there is limited information about the skeletal maturation of ethnic groups, including Koreans and Japanese.

Yang *et al*⁸ showed possible applications for axial cervical vertebral (ACV) images for the quantitative estimation of skeletal maturation in Korean individuals. In this study, investigators applied a new approach to the use of statistical shape analysis and ACV images that differed from previous studies with lateral cervical images in Japanese individuals.^{6,8,18} Therefore, the aims of this study were to investigate the application of a newly developed ACV maturation (ACVM) method in a Japanese population and to identify a regression model with a better prediction interval (PI). The specific aims of this study were to use statistical shape analysis to measure ACV shape, quantitatively and simultaneously, to build an estimation regression model for ossification levels in Japanese individuals and to compare the PIs with age and other variables.

Methods and materials

This was a retrospective study. The sample included 24 female and 19 male patients (ages, 6–18 years) with hand–wrist radiographs and CBCT images. Participants with a history of trauma, cleft lip and/or palate or other syndromes, and problems in growth and development were excluded. Hand–wrist radiograms were taken on a Rotanode DRX-3724HD (Toshiba Medical Systems, Tokyo, Japan) with exposure parameters of 42 kVp, 100 mA and 0.032 s. CBCT images were taken on a CB MercuRay (Hitachi Medical, Tokyo, Japan) with the following exposure parameters: 192.5-mm diameter spherical field of view, 0.376-mm voxel size, 100-kVp

tube voltage, 10-mA tube current and 9.6-s exposure time. The weighted CT dose index was 4.7 mGy. This study was reviewed and approved by the institutional review board of Pusan National University Dental Hospital (2013-011).

To assess the skeletal maturation stages from hand–wrist radiographic films, we used the maturity index used by Sempé [maturation index (MI) of Sempé, 0–999] and Fishman's 11-grade skeletal MI method.^{19,20} The CBCT data were processed by three-dimensional (3D) image software (OnDemand3D; Cybermed Co., Seoul, Republic of Korea). The axial CT images of the ACV shapes were produced with the same software. ACV images were obtained by the following steps:⁸

- (1) For the first cervical vertebrae (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 thickness of image layers was chosen for each cervical vertebra within the posterior arch, with neither the upper border of the band nor the lower border trespassing on either the upper or lower cortical lamina in the sagittal view.
- (2) For maximally distinguishable image acquisition in the second cervical vertebrae (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.
- (3) For the third and fourth cervical vertebrae (C3, 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 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, as indicated in [Figure 1](#). A single investigator obtained the *x,y* coordinates, which were scaled according to the true size. We considered four regions of interest (ROIs; C1, C2, C3 and C4) for statistical shape analysis, according to the previous studies.^{7,8} With the landmarks from these four ROIs, generalized Procrustes analysis (GPA) and principal components analysis (PCA) were carried out for shape and form, yielding principal component (PC) scores of each region of interest, with the centroid size (CS) as the size factor. These meaningful PC scores could then be used for multiple regression models of the Sempé's MI. Gender was treated as a dummy variable. It was included as a dummy variable where male was zero and female was one. Additionally, given the possibility of collinearity between and among the explanatory variables, we considered the stepwise variable selection method for accurate prediction.⁷

For landmark reliability, we repeatedly obtained the landmarks and Sempé's MI at 2-week intervals for 15 randomly selected samples. The language R (R development core team; R Foundation for Statistical

Figure 1 The landmarks for shape analysis on the regions of interest acquired from the axial cervical vertebral images. (a) The atlas (C1): the most anterior point (Point 1), the most posterior point (Point 2), the most lateral point, right and left (Point 3), the inflexion point located anteriorly and where the curvature of the articular surface begins, right and left (Point 4), the point farthest from the line joining Point 3 and Point 4 and located between Point 3 and Point 4, right and left (Point 5). (b) The axis (C2): the most posterior point in the vertebral foramen (Point 1), the most lateral point of the vertebral arch, right and left (Point 3), the most lateral point of the vertebral foramen, right and left (Point 4), the inflexion point on the line joining Point 4 and Point 6 located on the posterior lamina of the vertebral body, right and left (Point 5), the most posterior point of the vertebral body (Point 6), the point farthest from the line joining Point 1 and Point 4 and located between Point 1 and Point 4, right and left (Point 2). (c) Third and fourth cervical vertebrae (C3 and C4): the most posterior point of the vertebral body (Point 1), the most posterior point of the vertebral foramen (Point 2), the most lateral point of the vertebral foramen, right and left (Point 3), the inflexion point from the line joining Point 1 and Point 3 located on the posterior lamina of the vertebral body, right and left (Point 4), the most anterior point of the vertebral body (Point 5), the most lateral point of the vertebral body, right and left (Point 6).

Computing, Vienna, Austria) was used for statistical computation.

Results

For the reliability of the landmarks and skeletal maturation status, the intraclass correlation coefficient and kappa index confirmed the high reproducibility (average intraclass correlation coefficient: 0.978 for intraexaminer, 0.871 for interexaminer; average Kappa index: 0.815 and 0.726, respectively). For Sempé's MI as the alternative skeletal maturation index (SMI), Pearson's correlation coefficient showed it to be highly correlated with Fishman's SMI ($r = 0.956$; $p < 0.05$).

The scatter plot shows the correlation between age and Sempé's MI (Figure 2a). The correlation coefficient was 0.866. The correlation coefficient between the natural logarithm of Sempé's MI and age was slightly lower, but the dispersion of the points was represented more symmetrically ($r = 0.831$; Figure 2b). Actually, the box plot of the logarithm of Sempé's MI shows that

the dispersion was close to symmetrical (Figure 2d), while that of Sempé's MI was tilted down (Figure 2c). This log transformation is appropriate for the normality assumption of the multiple regression model. Additionally, Figure 2b shows that the skeletal maturation level was higher in females than in males.

By means of GPA and PCA, the corresponding indicator spaces (shape, size and form) and their PC scores were obtained (Table 1). Table 1 shows the meaningful PCs, which have >70% explanatory power of the total shape variation for each axial cervical vertebra, with the first three PCs in the vertebral foramen for the first axial cervical vertebra (ACV1), and the first two PCs in the vertebral body for the third and fourth axial cervical vertebrae (ACV3, ACV4), respectively. There was no meaningful PC in the second axial cervical vertebra (ACV2) (Table 1, Figure 3) nor was there significance in the CS as a size factor for skeletal maturation level. The CS also lacked gender differences ($p > 0.05$).

To compare the PIs by PC, gender and age, we built multiple regression models with stepwise variable

Figure 2 Dispersion of maturity index used by Sempé [Sempé's maturation index (MI)] and correlation between maturity index used by Sempé's MI and age. (a) Scatter plot of Sempé's MI and age. (b) Scatter plot of log(Sempé's MI) and age. (c) Box plot of Sempé's MI. (d) Box plot of log(Sempé's MI).

Table 1 Percent variance explained by the first four principal components (PCs) for each object studied in form space and shape space

PCs	ACV1		ACV3		ACV4	
	Form (%)	Shape (%)	Form (%)	Shape (%)	Form (%)	Shape (%)
PC1	41.1 ^a	40.9 ^a	51.4 ^a	51.0 ^a	54.1 ^a	53.6 ^a
PC2	20.2 ^a	20.2 ^a	25.3 ^a	25.1 ^a	24.4 ^a	24.3 ^a
PC3	11.0 ^a	11.0 ^a	13.3	13.3	16.6	16.4
PC4	6.7	6.7	9.8	9.8	4.6	4.6
Sum	79.0	78.8	99.8	99.2	99.7	98.9

ACV1, the first axial cervical vertebra; ACV3, the third axial cervical vertebra; ACV4, the fourth axial cervical vertebra.
^aPCs that were considered meaningful and were retained for further analysis.

selection methods, with the form and shape spaces for meaningful PCs of ACV1 and ACV4 (Table 2). Table 2 shows the R^2 of multiple regression models for each axial cervical vertebra and its width of 90% PI (w90% PI). The w90% PI for the regression of Sempé’s MI on age was 42.777 ($R^2 = 0.691$), and the w90% PI for the regression of Sempé’s MI on gender was 91.422 for females and 57.240 for males ($R^2 = 0.203$), respectively. For age and gender, w90% PI was 36.968 for females and 24.708 for males ($R^2 = 0.840$), respectively. No PC and gender from the axial cervical vertebrae had a PI smaller than those for age, and age and gender. When age was incorporated into the regression model, it had a decreased w90% PI. In Table 2, it can be seen that the shape space and form space had similar PIs. Even though the form space PCs had the size factor, their PI was not improved.

Overall, the male group showed smaller PIs than did the female group. The smallest PIs were from the combination of the shape space PCs, age and gender. There were approximately 20 fewer units than the w90% PI of age for males and 7 fewer units than age for females.

Discussion

Statistical shape analysis is a morphometric analysis for describing geometric properties from similar shapes or different groups. In biology, shape analysis could be

used for determining functionally, systematically, developmentally and generally important characteristics. Based on radiographic images, shape analysis can compare the shape of pathology with that of normal structures and classify it. And given that orthodontic treatment planning is usually based on two- or three-dimensional images such as lateral cephalograms or 3D images (CBCT or CT), statistical shape analysis can be flexibly employed, not only in radiographic image diagnosis but also in orthodontic treatment planning. Yang et al⁸ introduced the applicability of statistical shape analysis from the ACV image for the determination of skeletal maturation status. Among the SMIs, the ACVM method was the first to find the relation between the axial shape of cervical vertebrae and skeletal maturation status.

In this study, we evaluated the four ACV shapes (ACV1, ACV2, ACV3 and ACV4) to find the relationship between their shape information and skeletal maturation level. From GPA and PCA in the statistical shape analysis, regression models were built with the corresponding indicator spaces (shape and form). During the assessment of skeletal maturation status, the correlation analysis between age and Sempé’s MI showed that age and Sempé’s MI had a curve-linear distribution because skeletal maturation follows a somatic growth curve. Therefore, in this study, the log-transformed Sempé’s MI was used to build an improved regression model.

Figure 3 The mean shapes in axial cervical vertebrae. (a) First axial cervical vertebra. (b) Third axial cervical vertebra. (c) Fourth axial cervical vertebra.

Table 2 Coefficient of determination (squared adjusted multiple regression correlation coefficient: R^2) and width of 90% prediction interval (w90% PI) for multiple regression of maturity index used by Sempé (Sempé's maturation index) on the meaningful principal components (PCs) of the four objects, in form and shape spaces

	Form space						Shape space					
	PCs and gender			PCs, age and gender			PCs and gender			PCs, age and gender		
	w90% PI			W90% PI			w90% PI			w90% PI		
Axial cervical vertebrae	R^2	Male	Female	R^2	Male	Female	R^2	Male	Female	R^2	Male	Female
ACV1	0.299	55.969	83.339	0.856	23.348	35.892	0.299	55.959	83.356	0.856	23.348	35.892
ACV3	0.379	51.633	80.376	0.850	24.351	35.990	0.378	51.662	80.368	0.850	24.341	35.970
ACV4	0.328	55.807	79.951	0.840	24.708	36.968	0.328	55.823	79.925	0.840	24.708	36.968
ACV1 + ACV3	0.417	52.174	74.552	0.864	23.166	35.153	0.418	52.120	74.497	0.864	23.143	35.118

ACV1, the first axial cervical vertebra; ACV3, the third axial cervical vertebra; ACV4, the fourth axial cervical vertebra.

Gender dimorphism in skeletal maturation is well known.^{3,9,10,12,21} The present study also confirmed considerably the earlier steps in growth and development for females (Figure 1). Chatzigianni and Halazonetis,⁶ using lateral cephalograms, reported that gender dimorphism was found for both cervical vertebral size and shape. Hellsing²² and Stemper et al²³ also found gender differences in vertebral size. However, we found no gender differences in CS. From the lateral cephalogram study, the growth of the spinous process could be seen to follow the somatic growth curve.²⁴ The landmark on the spinous process was expected to influence shape variation. However, we found no significant landmarks in these ROIs. This might produce differences compared with previous studies.^{6,22–24}

Through GPA and PCA, we found meaningful PCs (Table 1); the first three PCs in the vertebral foramen for ACV1 and two PCs in the vertebral body for the ACV3 and ACV4. Figure 3 shows the mean shape. In this study, we found no statistically significant PC in the ACV2, which differed from the results of the study by Yang et al.⁸ During the process of obtaining axial images, we noted that the odontoid process and the body of C2 might overlap, and the odontoid process might influence the outline of the body and the vertebral foramen. This may represent a difference from other ACV images because other cervical vertebrae lacked the upwardly processed structure, such as the odontoid process.

In this study, we determined meaningful PCs that amounted to >70% coefficient of determination (Table 1). These PCs improved the explanatory power of the regression model compared with those with only the CS.⁸ The smallest PIs were from the combination of the shape space PCs, age and gender and showed approximately 20 fewer levels than did the 90% PI of age for males and 7 fewer levels for females. However, all w90% PIs for males had a smaller range than those of females. This was contrary to the results of other studies.^{6,25,26} Furthermore, we found no independent variables with a better estimating power than age. When age was incorporated into the regression model, it decreased w90% PI. This result was consistent with those of previous studies.^{6,8} No PCs and gender from

axial cervical vertebrae had smaller PIs than age, and age and gender. Even though we found no predictors with a smaller PI than age, this study showed that the shape variation of the axial cervical vertebra could be used for the estimation of skeletal maturation levels. Further study should be undertaken to find predictors with a PI better than age, such as a 3D approach to cervical vertebral shape.

From this study, we confirmed that ACV shape contained information about skeletal maturation and validated ACVM as one of the few available quantifiers of skeletal maturation. Compared with the previous study in Koreans,⁸ there were differences in sample distribution, log-transformed value of dependent variables and meaningful PCs. This produced different results for Japanese population. Therefore, this retrospective study had limitations in the evaluation of ethnic differences. Another, related limitation is the small sample size. All of the CBCT data on Japanese children were obtained for clinical use following the justification of practices. As such, it was difficult to collect a large sample. A further, large-sample study will be needed. Nevertheless, the study improved the estimating regression model using statistical shape analysis with ACV shapes. This ACVM method could also be used in specifying the residual growth of Japanese orthodontic and dentofacial orthopaedic patients. However, further study is needed to find gender and ethnic differences. 3D shape analysis could be applied for improving the best model to predict skeletal maturation based on the previous CVM and ACVM shape study.

The radiographic sample data were obtained for clinical use (indeed, CBCT data include a wealth of valuable information), not for the use of this study. Not every patient requires CBCT scanning for orthodontic or radiographic examination, even though effective CBCT doses are lower than those of conventional CT. In fact, the results of this study do not suggest that CBCT should be used to estimate skeletal maturation in orthodontic patients, but rather that when CBCT is used, additional hand–wrist images are unnecessary. Therefore, the use of CBCT should be considered on a risk/benefit basis in comparison with traditional radiography.

Conclusions

From this study, we confirmed that ACV shape contained information about skeletal maturation and validated ACVM as one of the few available quantifiers of skeletal maturation. However, this study had limitations in the evaluation of ethnic differences. Nevertheless, the

study improved the estimating regression model using statistical shape analysis with ACV shapes. This ACVM method could also be used in specifying the residual growth of Japanese orthodontic and dentofacial orthopaedic patients. 3D shape analysis could be applied for improving the best model to predict skeletal maturation based on the previous CVM and ACVM shape study.

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