의학박사 학위논문

Early Prediction of the Need for Orthognathic Surgery in Patients with Repaired Unilateral Cleft Lip and Palate using Machine Learning and Longitudinal Lateral Cephalometric Analysis Data

기계학습과 두개안면계측촬영 영상데이터를 이용한 편측성 구순구개열 환자의 악교정 수술 필요성 여부의 조기 예측

2020 년 08 월

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의학과 성형외과학 전공

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Early Prediction of the Need for Orthognathic Surgery in Patients with Repaired Unilateral Cleft Lip and Palate using Machine Learning and Longitudinal Lateral Cephalometric Analysis Data

By

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A thesis submitted to the Department of Plastic and Reconstructive Surgery in partial fulfillment of the requirements for the Degree of Doctor of Philosophy in Medicine at Seoul National University College of Medicine

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논문초록

기계학습과 두개안면계측촬영 영상데이터를 이용한 편측성 구순구개열 환자의 악교정 수술 필요성 여부의 조기 예측

서론: 편측성 구순구개열 환아는 안면 뼈 성장이 끝난 후 부정교합 또는 악안면 외형적인 문제로 악교정 수술 혹은 신연골형성 수술 (DO) 필요한 경우가 흔히 있다 (약 12%~40%로 보고되고 있다). 본 연구의 목적은 machine learning을 이용하여 편측성 구순구개열 환아의 lateral cephalometric 계측치로 악안면 뼈 성장 예후 또는 악교정술 혹은 DO 수술의 필요성의 예측이 가능한지 조사하는 것이다.

방법: 동일한 성형외과의사 그리고 교정과의사의 같은 진료방침으로 치료를 받은 총 56명의 편측성 구순구개열 환아들을 대상으로 연구 하였다. 환아들의 교정/정형 치료받기 전 시기 T0 (평균연령 6.3세) 및 15세 이후 시기 T1 (평균연령 16.7세)의 lateral cephalogram을 수집 및 digitize하였다. 38개의 cephalometric 계측치들을 분석하였다. T1시기의 3개의 계측치 (ANB ≤ -3°; Wits appraisal ≤ -5 mm; Harvold unit difference ≥ 34 mm; 수술군)를 기준으로 환아들을 수술군 (n=10)과 비수술군 (n=46)으로 나누었다. Independent t test 통계분석을 실행 하였으며, Boruta 방법과 XGBoost algorithm을 사용하여 T0에서 악안면 뼈 성장을 예측 할 수 있는 계측치를 탐색하였다.

결과: T0 시기의 2개의 cephalometric 계측치 [ANB과 Facial convexity angle (FCA), 모두 $P < 0.05$] 결과에서 그룹간 유의한 통계 차이를 보였다. T1 시기의 18개의 계측치와 ΔT1-T0 (T0~T1 변화 값)의 14개의 계측치에서 유의한 차이가 관찰 되었다 (모두 $P < 0.05$). T0 시기 안면 뼈 성장 예후 예측이 가능한 계측치는 ANB, PP-FH, Combination factor, 그리고 Facial convexity angle로 확인되었다. 10-fold Cross-Validation 정확도는 87.4%이며 F1-score는 0.714로 확인되었다 (Sensitivity, 97.83%; Specificity, 90.00%).

결론: 편측성 구순구개열 환자 6세 시기에, 높은 정확도로 악안면 뼈 성장 예후 또는 뼈 성장 종료 후의 악교정 수술 혹은 신연골형성 수술 실행 여부 판단이 가능하다.

주요어: 장기적 측면 두개안면계측촬영 분석, 악교정수술, 편측성 구순구개열

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Abstract

Early Prediction of the Need for Orthognathic Surgery in Patients with Repaired Unilateral Cleft Lip and Palate using Machine Learning and Longitudinal Lateral Cephalometric Analysis Data

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Background: Some patients with unilateral cleft lip and palate (UCLP) need orthognathic surgery or distraction osteogenesis (DO) to obtain a more balanced intermaxillary relationship and improved esthetic outcome. This study was conducted to determine the cephalometric parameters that can predict the future need for orthognathic surgery or DO in Korean patients with repaired UCLP by using machine learning and longitudinal lateral cephalometric analysis.

Method: We included 56 Korean patients with UCLP (31 males and 25 females), who were treated by a single surgeon and a single orthodontist with the same treatment protocol. Lateral cephalograms were obtained before the commencement of orthodontic/orthopedic treatment (T0; mean age, 6.3 years) and at at least 15 years of age (T1; mean age, 16.7 years), and 38 cephalometric variables were measured. At the T1 stage, 3 cephalometric criteria were used to classify the participants into the surgery and non-surgery groups (ANB $\leq -3°$; Wits appraisal ≤ -5 mm; Harvold unit difference ≥ 34 mm for the surgical group). They were divided into the surgical group (n=10, 17.9%) and the non-surgical group (n=46, 82.1%). The one-way analysis of variance, Fisher's exact test, and independent *t*-test were used for statistical analyses. The Boruta method and XGBoost algorithm were used to determine the cephalometric variables at the T0 stage for the development of a prediction model.

Results: At the T0 stage, only 2 variables (ANB and Facial convexity angle, all P<0.05) exhibited a significant intergroup difference. At the T1 stage, 18 cephalometric variables showed a significant intergroup difference (A-N perp, SNB, ODI, articular angle, mandibular body length, IMPA, bisecting Occ plane to FH plane angle, occlusal plane to SN plane angle, and upper gonial angle, all *P*<0.05; Pog-N Perp, Co-Gn, and AB-MP, all *P*<0.01; and ANB, Wits appraisal, APDI, Harvold unit difference, facial convexity angle, and AB to occlusal plane angle, all *P*<0.001). For the quantification of change from T0 to T1, 14 variables exhibited a significant intergroup difference (ΔSNB, ΔPog-N Perp, ΔCo-Gn, ΔHarvold unit difference, ΔSN-MP, ΔWits appraisal, ΔBjork Sum, ΔMandibular body length, and ΔBody to anterior cranial base ratio, all *P*<0.05; ΔANB, ΔAB-MP, ΔFacial convexity, and ΔAB to occlusal plane angle, all *P*<0.01; ΔAPDI, *P*<0.001). At the T0 stage, the ANB, PP-FH, CF, and facial convexity angle were selected as predictive parameters, and had a 10-fold cross-validation accuracy of 87.4% with an F1-score of 0.714.

Conclusion: The 4 cephalometric variables identified in this study might be considered effective predictors, at approximately age 6 years, of the future need for orthognathic surgery to correct sagittal skeletal discrepancies in Korean patients with UCLP.

Keywords:

Longitudinal lateral cephalometric analysis, Orthognathic surgery, Unilateral cleft lip and palate

Student Number: 2017-36496

CONTENTS

INTRODUCTION

Skeletal Class III malocclusion with restricted maxillary growth is frequently observed in patients with unilateral cleft lip and palate (UCLP), and is related to the intrinsic factors and the scar tissue from surgical intervention.[1-3] A quarter to a half of patients with UCLP are known to need orthognathic surgery or distraction osteogenesis (DO) to obtain a normal intermaxillary relationship and an improved facial esthetics.[4-8]

Although the orthopedic treatment for maxillary protraction using face mask (FM) with bone-anchored mini-plates[9-10] might not fully correct Class III intermaxillary relationship, it would reduce the amount of maxillary advancement in orthognathic surgery or DO. Thus, the postoperative stability of the maxilla can be improved.[11-12] However, orthopedic treatment is usually conducted only when UCLP patients developed moderate sagittal skeletal discrepancy at around 10 years of age.[13-16] Clinicians and parents of cleft patients want to know the future need for the surgical correction of the sagittal skeletal discrepancy. Therefore, early prediction of the maxillofacial growth would be meaningful in determining to start orthopedic treatment or wait for the completion of growth.

Park et al.[17] used the feature wrapping method, a kind of machine learning, to determine the cephalometric predictors of the future need for orthognathic surgery to correct the sagittal skeletal discrepancy in Korean male patients with clefts. At the mean age of 9.3, a total of 10 cephalometric variables (APDI, ODI, Harvold unit difference, Wits appraisal, AB to mandibular plane angle, gonial angle, ANB, overjet, A to N perp, and IMPA) were selected as predictors, with a weighted classification accuracy of 77.3%. The study also reported that the frequency of surgical intervention increased with cleft severity from cleft lip and alveolus (CLA) group, UCLP group, to bilateral cleft lip and palate (BCLP) group (8.5%, 21.4%, and 30.0%).[17]

Among the diverse machine learning methods to find the relevant features, several previous studies have used the Boruta method due to its best performance.[18-21] The method is based on a random forest approach that can identify the most important features with high feature-selection stability.[22,23] The XGBoost algorithm[24] is an extendable, cutting-edge application for gradient-boosting machines, and has been proven to push the limits of computing power for boosted tree algorithms. Boosting is an ensemble technique whereby new models are appended to adjust the errors by preexisting models. Gradient boosting is an algorithm whereby new models are created to cover the residuals of prior models and then added together to obtain better predictions.[25] Therefore, this study used the Boruta method and the XGBoost algorithm to investigate the cephalometric predictors of the future need for orthognathic surgery or DO in patients with repaired UCLP.

METHODS

Patients

The samples consisted of 56 Korean patients with non-syndromic UCLP (31 males and 25 females), who were treated at the Department of Plastic Surgery, Seoul National University Children's Hospital (SNUCH) and the Department of Orthodontics, Seoul National University Dental Hospitals (SNUDH), Seoul, Republic of Korea. This retrospective study was reviewed and approved by the institutional review board of the SNUDH (ERI20014).

Treatment protocol

The treatment protocol used in SNUCH and SNUDH is summarized as below: (1) primary cheiloplasty (rotation and advancement flap) was performed between 3 and 5 months of age; (2) palatoplasty (Furlow double opposing Z-plasty) and late primary gingivoperiosteoplasty were performed between 12 and 18 months of age; (3) if needed, maxillary arch was expanded before secondary alveolar bone grafting (SABG); (4) SABG with cancellous bone from the iliac bone was conducted during the mixed dentition stage; (5) if needed, facemask with bone-anchored mini-plates was used for orthopedic maxillary protraction during the pubertal growth period; (6) fixed orthodontic treatment was performed during the permanent dentition stage; and (7) if needed, orthognathic surgery or DO were performed after completion of growth.

Inclusion criteria

Participants were enrolled on the basis of the following inclusion criteria : (1) patients who were born before 2002 and whose charts, radiographs, and clinical photographs were available for longitudinal follow-up; (2) patients who were treated with the same protocol by a single surgeon (SWK) and a single orthodontist (SHB) to eliminate the influences of different surgical and orthodontic treatments; (3) patients whose initial lateral cephalogram was obtained between 5 and 7 years of age (T0 stage) and who did not undergo orthodontic/orthopedic treatment and alveolar bone grafting to avoid the effects on the skeletodental growth; and (4) patients whose final lateral cephalogram was obrained at or above 15 years of age (T1 stage) to judge the need for orthognathic surgery or DO. Syndromic patients were excluded.

Grouping

A total of 56 patients with UCLP were recruited. At the T1 stage, patients (1) who had undergone orthognathic surgery or DO, (2) who were under presurgical orthodontic treatment, or (3) who met the cephalometric criteria for orthognathic surgery (ANB ≤ -3 degrees, Wits appraisal ≤ -5 mm, and Harvold unit difference ≥ 34 mm), were classified into the surgery group (n = 10, 17.9%).[17] The remaining patients were allocated into the non-surgery group (n = 46, 82.1%).

Cephalometric analysis

The Figure 1 and appendix-1 lists the definition of cephalometric landmarks and cephalometric variables included in the cephalometric analysis. The cephalometric analysis for all patients at the T0 and T1 stages was assessed twice by a single researcher (GL) by using the V-CEPH (Version 8.4;

CyberMed, Seoul, Korea) program. As there was no significant difference between the first and second measurements, the first measurement set was used for further statistical analysis.

Statistical analysis

The independent *t*-test was used to investigate the intergroup differences on the cephalometric variables at the T0 and T1 stages, and the amount of change (ΔT1-T0). The SPSS (version 12.0; SPSS, Chicago, Ill, USA) software package was used for statistical analysis. *P*-value less than 0.05 was set as an indicator of statistical significance.

Feature selection (Appendix-2)

The Boruta method was used to determine the cephalometric predictors at the T0 stage. The XGBoost algorithm was used to generate the machine learning model that classifies the need for surgical correction for each patient, and 10-fold cross-validation accuracy with F1-score were obtained. The prediction model was testified with the confusion matrix without normalization

RESULTS

Intergroup differences at each stage

The final analysis dataset included 56 patients (T0 stage; mean age, 6.3 years and T1 stage; mean age, 16.7 years). At the T0 stage, only 2 variables exhibited a significant intergroup difference [ANB and FCA, all $P < 0.05$; Table 1). At the T1 stage, 18 cephalometric variables showed a significant difference between the two groups (A-N perp, SNB, ODI, articular angle, mandibular body length, IMPA, bisecting occlusal plane to FH plane angle, occlusal plane to SN plane angle, and upper gonial angle, all $P < 0.05$; Pog-N perp, Co-Gn, and AB-MP, all $P < 0.01$; ANB, Wits appraisal, APDI, Harvold unit difference, FCA, and AB to occlusal plane angle, all $P < 0.001$; Table 1). For ΔT1-T0, 14 variables (ΔSNB, ΔPog-N perp, ΔCo-Gn, ΔHarvold unit difference, ΔSN-MP, ΔWits appraisal, ΔBjork Sum, Δmandibular body length, and Δbody to anterior cranial base ratio, all $P < 0.05$; ΔANB, ΔAB-MP, ΔFCA, and ΔAB to occlusal plane angle, all $P < 0.01$; ΔAPDI, $P < 0.001$; Table 1) exhibited a significant intergroup difference.

Prediction of the future need for orthognathic surgery or DO

Four cephalometric parameters of the T0 stage including ANB (intermaxillary relationship between the maxilla and mandible; degree of relative protrusion of B point in relation to A point), PP-FH (inclination of the palatal plane in relation to the FH plane), combination factor (CF; sum of ODI and APDI, which means the skeletal size of the maxilla and mandible) and FCA (intermaxillary relationship between the maxilla and mandible; degree of relative protrusion of Pogonion point in relation to A point) were selected as predictors of the future need for orthognathic surgery or DO (Table 2, Figure 2 and Figure 3). The feature importance of the ANB, PP-FH, CF and FCA were 0.2430162, 0.23951529, 0.24303272 and 0.27443576, respectively (Table 2).

The prediction model has a 10-fold cross-validation accuracy of 87.4% with F1-score of 0.714 (Figure 4). The sensitivity (the proportion of actual non-surgery patients that was correctly predicted as non-surgery patients) and specificity (the proportion of actual surgery patients that was correctly predicted as surgery patients) of the prediction model were 97.83% and 90.00%, respectively (Figure 4). This model is uploaded on the following Web site (http://147.47.41.53:8890). The prognosis prediction results for surgery and no surgery are generated when the values of 4 variables (ANB, PP-FH, CF, and FCA) are inserted.

DISCUSSION

Patients with cleft usually require a long-term multidisciplinary care in order to obtain good facial esthetics and functional occlusion.[26] In this retrospective longitudinal study, 17.9% of the UCLP patients needed orthognathic surgery or DO, which was similar to the results of previous studies (12%–40%).[17,27-30]

Statistics are widely used for inference about the relationships between variables, or to create a model that is able to predict future values. The way a statistical model is evaluated will involve evaluating the significance and robustness of the model parameters, which require adequate data size. Given the relatively small data size of the study subjects in this study, machine learning was used. Machine learning can be classified into supervised, unsupervised and reinforcement learnings. The unsupervised learning which is commonly used to discover the association between patient characteristics and disease prevalence, was applied in this study with Boruta method to select the predictive features. This method iteratively removes the features which are shown by a statistical test to prove to be less relevant than random probes.[19] Compared to the feature wrapping method used in Park et al.'s study[17], the random forest classification-based Boruta algorithm is relatively quick run without fine tuning of parameters, and gives a numerical estimate of the feature importance.[22] Instead of selecting features according to the predicting accuracy of each feature, the machine learning in this study was processed by assessing every combination of the features. Therefore, the respective classification accuracies were not calculated, and the prediction model is meaningful only when the four features (ANB, PP-FH, CF and FCA) come together.

At the T1 stage, 18 cephalometric parameters exhibited significant differences between the surgery and non-surgery groups (Table 1), while at the T0 stage, only 2 variables showed significant intergroup difference (ANB and FCA; Table 1). These results suggest that most of the unfavorable skeletodental features developed during growth (from age 6.3 to 16.7 years), which was confirmed by the significant intergroup differences of 14 variables in ΔT1-T0 between the 2 groups (Table 1).

When compared to Park et al.'s study,[17] this study showed four main differences in the composition of subjects; mean age at the T0 stage, number of cephalometric predictors, and weighted classification accuracy (CLA, UCLP and BCLP vs. UCLP only; 9.3 year-old vs. 6.3 year-old; 10 predictors vs. 4 predictors; 77.3% vs. 87.4%; Table 2 and Fig. 1). This finding suggests that it is possible to predict the skeletodental growth of UCLP patients using less number of cephalometric variables at earlier age compared to Park et al.'s study.[17]

Difference in the number of cephalometric predictors was most likely due to the age difference of the subjects between Park et al.[17] and this study because the skeletodental growth in 9.3 years of age might be relatively more actively appeared than those in 6.3 years of age.[31-33]

The implications of the 4 cephalometric predictors are enumerated as follows: First, as previously reported in several studies,[17,27,34] the ANB was confirmed as an effective factor to predict the skeletodental growth of UCLP patients in this study (Table 2, Figure 2). After the evaluation of the lateral cephalograms in UCLP patients at 5 and 10 years of age, Meazzini et al.[34] divided their patients into the orthognathic surgery and the non-orthognathic surgery group at the completion of growth. They reported significant differences in the SNA, SN-ANS and ANB between the 2 groups at both 5 and 10 years of age.[34] The present study suggested similar results in terms of the ANB and facial convexity angle (the degree of relative protrusion of the mandible by using B point and Pogonion point in relation to the maxilla, Table 2). Although Meazzini et al.[34] investigated participants with different ethnic backgrounds and surgical protocols than in this study, a similar pattern of sagittal skeletal discrepancy (ANB) was observed in the present study. Therefore, it can be stated that the difference in the maxillofacial growth pattern between Asian and Caucasian UCLP patients might be minor.

Second, the finding that PP-FH and CF were selected as predictors (Table 2, Figure 2) concurs with

Park et al.'s study.[17] The PP-FH is a common component in both APDI [sum of PP-FH angle, facial plane (N-Pog) to FH plane angle, and AB to facial plane angle; Appendix-1, Figure 2] and ODI (sum of PP-FH angle and AB to mandibular plane angle; Appendix-1, Figure 2), which represent the sagittal and vertical growth patterns, respectively. Similarly, as the CF is a sum of the APDI and ODI (Appendix-1, Figure 2), it indicates the skeletal size of the maxilla and mandible in the sagittal and vertical aspects.

Third, the FCA (the angle between the N-A plane and A-Pog plane; Appendix-1, Figure 2) would be a supplementary factor to ANB, which indicates the degree of relative protrusion of the Pogonion point in relation to the A point.

Although Park et al.[17] reported that the Wits appraisal and the Harvold unit difference were the crucial cephalometric predictors, these variables were not selected in the present study despite existence of significant difference in the values between the two groups at the T1 stage (Wits appraisal and Harvold unit difference, all $P < 0.001$; Table 1) and their amount of change (ΔWits appraisal and ΔHarvold unit difference, all $P < 0.001$; Table 1). The reason for this might be that the eruption of the permanent maxillary incisors is not completed and the growth of the mandible is not prominent at the T0 stage.[35-37] Moreover, the AB to mandibular plane angle, gonial angle, A to N perp, overjet, and IMPA were not selected as cephalometric predictors in the present study. It was also speculated due to the insufficient growth of the maxilla and mandible and eruption of the teeth at the T0 stage.

Compared to previous studies,[17,27-30] the present study used the lateral cephalometric data obtained at a younger age (6.3 years) to avoid the effect of orthodontic and orthopedic treatment and alveolar bone grafting on the skeletodental growth, and adopted strict inclusion criteria such as single ethnicity, UCLP patients only, the same treatment protocol with a single surgeon and a single orthodontist to reduce the bias for selection of the subjects. Although, by using machine learning, this study showed a good accuracy in the prediction of the future need for surgery to correct the intermaxillary discrepancy in the patients with UCLP.

The relatively small sample size would be the major limitation of the present study. The sample size could not be neglected either in traditional statistical analysis or in the machine learning. However, the machine learning, as a data-driven method, has been widely applied in current studies to select relevant features despite small sample size. In a study by Liu et al.,[38] a classification model for congestive heart failure (CHF) was presented by machine learning; and the number of the study subjects involved was 47 (17 CHF patients and 30 normal subjects). The other articles which used machine learning method with relatively small sample size and came out with somehow appreciable outcomes, could be found in the literature.[39-42] Besides, machine learning models provide various degrees of interpretability, from the lasso regression to neural networks, but they generally lack interpretability for predictive power. Thus, the external validation would be processed in further study in order to better clarify the reliability of the prediction model.

Early prediction of the future need for orthognathic surgery or DO can help clinicians to setup the proper treatment plan and to adjust the timing and duration of orthodontic/orthopedic treatment for maxillary protraction in cleft patients. Therefore, it is necessary to conduct well-designed case-control studies for the evaluation of the effects of orthodontic/orthopedic treatment for the correction of the maxillary hypoplasia with regard to reducing the frequency of orthognathic surgery or DO, or the amount of maxillary advancement in patients with cleft lip and palate.

CONCULSION

At age of 6 years it was possible to predict the future need for surgery to correct their sagittal skeletal discrepancy in patients with UCLP using cephalometric predictors with a good accuracy.

Disclosure

The authors have no potential conflicts of interest to disclose.

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FIGURE LEGEND

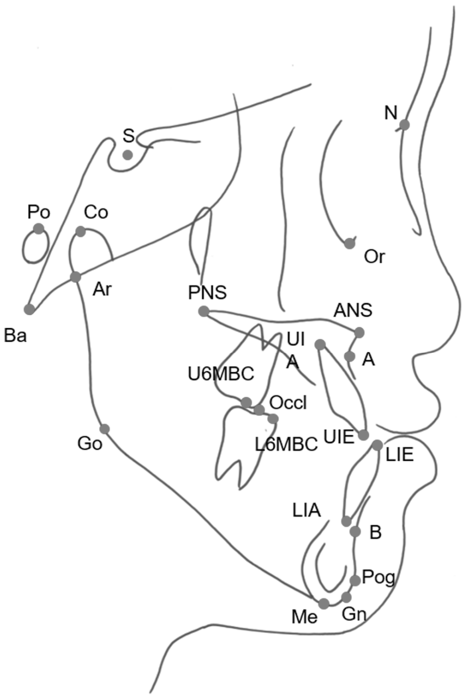

Figure 1. Cephalometric landmarks used in this study

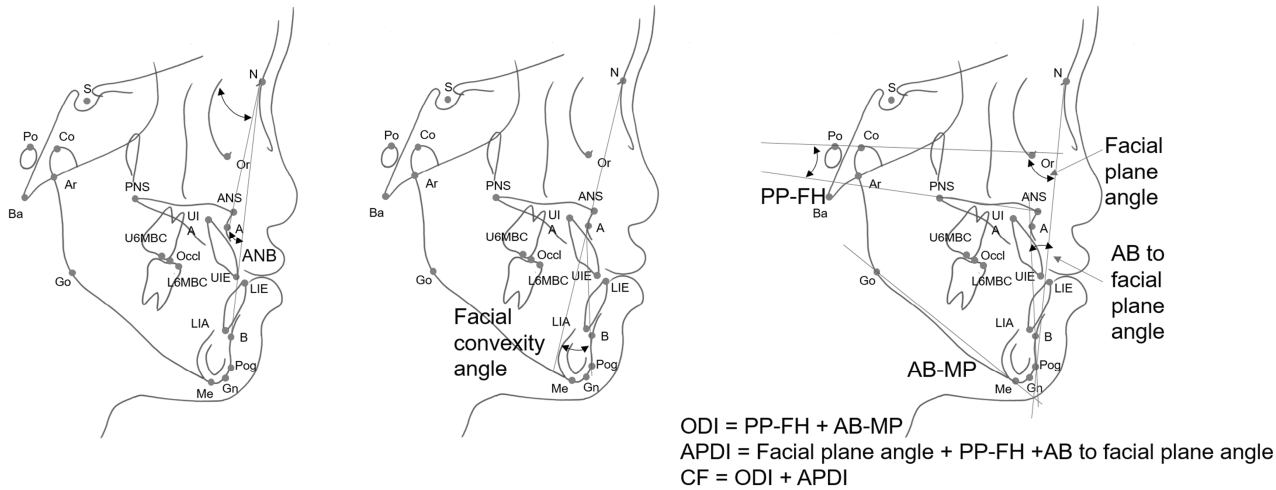

Figure 2. Four cephalometric parameters of the initial lateral cephalogram obtained between 5 and 7 years of age (T0 stage). ANB (degree of relative protrusion of B point in relation to A point), intermaxillary relationship between the maxilla and mandible; PP-FH, inclination of the palatal plane (ANS-PNS) in relation to the FH plane; combination factor (CF), sum of overbite depth indicator (ODI) and anteroposterior dysplasia indicator (APDI), which means the skeletal size of the maxilla and mandible; and Facial convexity angle (FCA, degree of relative protrusion of Pogonion point in relation to A point), intermaxillary relationship between the maxilla and mandible.

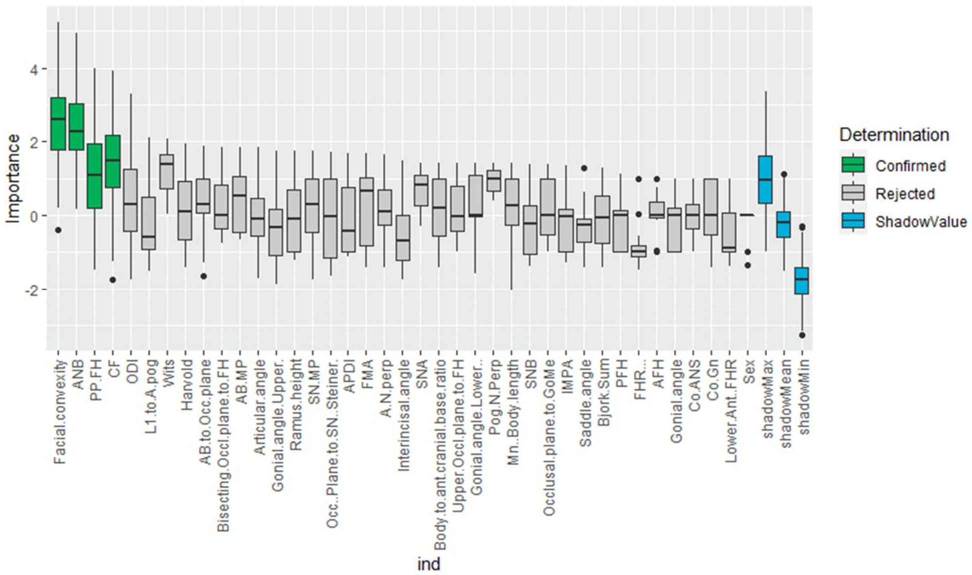

Figure 3. Feature importance

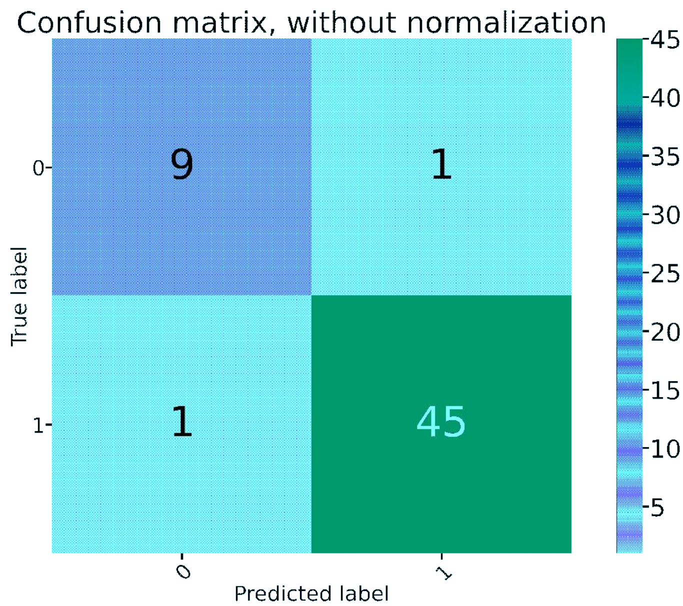

Figure 4. The quality of the prediction model. The confusion matrix without normalization was used. 0, surgery patient; 1, non-surgery patient; Sensitivity (the proportion of actual non-surgery patients that was correctly predicted as non-surgery patients), 97.83%; Specificity (the proportion of actual surgery patients that was correctly predicted as surgery patients), 90.00%. 10-fold cross-validation accuracy, 87.4%; F1-score, 0.714.

Table 1. Comparison of the cephalometric parameters at T0, T1 and Amount of change (from T0 to T1) between the surgery and non-surgery groups

	T0					T1					Amount of change				
	Surgery (n=10)		Non-Surgery (n=46)		*P*-value	Surgery (n=10)		Non-Surgery (n=46)		*P*-value	Surgery (n=10)		Non-Surgery (n=46)		*P*-value
	Mean	SD	Mean	SD		Mean	SD	Mean	SD		Mean	SD	Mean	SD	
SNA (°)	76.68	3.94	79.21	3.77	0.0612	73.85	4.62	75.89	3.65	0.2752	-2.84	3.84	-3.32	2.96	0.7645
A-N perpendicular (mm)	-1.63	4.38	0.86	4.82	0.1548	-6.53	3.67	-3.29	4.45	0.0291*	-4.91	3.85	-4.15	4.47	0.4540
SNB (°)	75.10	2.46	75.05	3.20	0.9148	78.19	4.65	74.54	3.32	0.0276*	3.09	4.18	-0.52	3.37	0.0152*
Pog-N perpendicular (mm)	-6.79	5.38	-9.35	7.65	0.2524	1.58	7.55	-8.28	8.01	0.0026**	8.37	7.29	1.07	9.18	0.0116*
ANB (°)	1.59	3.38	4.16	2.51	0.0209*	-4.34	2.76	1.35	2.16	0.0000***	-5.93	3.47	-2.81	2.75	0.0046**
Wits appraisal (mm)	-4.52	6.86	-2.19	4.03	0.2659	-9.54	3.93	-2.60	3.46	0.0000***	-5.02	7.19	-0.41	4.24	0.0131*
APDI (°)	83.22	6.16	81.18	5.71	0.2945	96.45	4.75	84.58	5.63	0.0000***	13.24	4.28	3.40	6.49	0.0000***
Co-Gn (mm)	124.82	25.78	127.61	25.47	0.6379	140.55	5.79	131.66	9.35	0.0015**	15.74	23.19	4.05	24.46	0.0276*
Co-ANS (mm)	97.97	17.08	102.30	20.45	0.5210	97.50	6.08	97.03	7.55	0.8641	-0.48	18.77	-5.27	20.13	0.3357
Harvold unit difference (mm)	26.84	11.23	25.31	6.76	0.7891	43.06	7.05	34.63	5.16	0.0006***	16.21	6.78	9.31	6.53	0.0123*
FMA (°)	26.28	3.75	28.18	4.61	0.3045	24.27	4.28	28.21	6.33	0.0598	-2.01	2.08	0.03	4.07	0.1343
SN-MP (°)	38.11	4.72	39.59	4.52	0.4412	35.32	6.90	39.76	6.42	0.0723	-2.79	3.69	0.16	4.48	0.0443*
ODI (°)	68.59	8.51	71.88	6.19	0.2480	60.97	8.61	68.13	6.92	0.0197*	-7.62	11.43	-3.75	6.45	0.0995
PP-FH (°)	-0.96	3.30	0.62	3.22	0.0952	0.85	4.19	0.46	4.62	0.5563	1.80	5.41	-0.16	4.15	0.3465
AB-MP (°)	69.54	7.93	71.26	5.76	0.6151	60.12	6.50	67.67	5.14	0.0015**	-9.42	7.05	-3.59	4.11	0.0018**
Saddle angle (°)	126.93	5.63	124.09	5.13	0.1134	126.07	7.35	124.73	5.62	0.5350	-0.86	3.89	0.64	3.79	0.2436
Articular angle (°)	143.03	9.22	147.72	5.73	0.1399	145.60	7.92	151.81	7.61	0.0276*	2.58	4.32	4.09	6.54	0.6766
Gonial angle (°)	128.15	5.58	127.79	7.35	0.8894	123.65	5.95	123.22	7.42	0.7161	-4.51	4.39	-4.57	4.94	0.8306
Bjork Sum (°)	398.11	4.72	399.59	4.52	0.4412	395.32	6.90	399.76	6.42	0.0723	-2.79	3.69	0.16	4.48	0.0443*
Anterior facial height (mm)	135.88	26.24	143.76	30.83	0.1993	149.71	9.37	150.80	10.04	0.9148	13.83	23.15	7.04	28.15	0.4286
Posterior facial height (mm)	82.67	14.15	87.49	17.52	0.3466	97.20	6.45	95.21	8.15	0.5141	14.53	15.94	7.72	18.21	0.1086
Facial height ratio (%)	61.12	3.84	61.09	3.46	0.7646	65.08	4.84	63.21	4.66	0.3357	3.96	3.09	2.12	3.37	0.1235
Lower Anterior facial height (mm)	55.03	2.95	54.29	2.33	0.3746	55.73	3.02	54.75	2.22	0.1847	0.70	3.22	0.45	2.05	0.4476
Combination factor (°)	151.80	5.99	153.06	7.04	0.2227	157.42	8.15	152.71	10.04	0.1518	5.62	11.19	-0.36	8.64	0.1288
Facial convexity angle (°)	3.90	7.35	9.36	5.59	0.0291*	-11.87	5.89	1.50	5.58	0.0000***	-15.77	6.10	-7.86	6.19	0.0012**
Ramus height (mm)	49.16	9.43	49.62	10.20	0.8810	58.80	4.50	55.29	6.52	0.0706	9.64	10.55	5.67	11.32	0.1993
Mandibular body length (mm)	80.58	15.86	82.46	17.07	0.7483	91.12	6.13	84.84	7.02	0.0147*	10.54	12.88	2.38	16.51	0.0342*
Body to anterior cranial base ratio	0.98	0.09	0.99	0.07	0.3913	1.11	0.09	1.07	0.08	0.2299	0.13	0.07	0.08	0.06	0.0397*
IMPA (°)	84.78	9.00	85.72	8.88	0.7002	83.31	8.57	88.70	6.25	0.0276*	-1.47	6.24	2.97	7.80	0.0910
L1 to A-pog (mm)	2.42	3.63	2.60	2.94	0.8641	6.05	5.55	4.87	2.95	0.3804	3.63	3.84	2.28	3.31	0.4349
Interincisal angle (°)	147.22	14.67	145.31	10.89	0.6076	134.38	13.01	129.13	8.34	0.1847	-12.84	14.64	-16.18	12.08	0.5492
Maxillary Occlusal plane to FH angle	11.13	3.42	12.55	4.36	0.4224	7.41	4.47	8.87	4.28	0.2309	-3.73	6.90	-3.68	4.84	0.7321
Bisecting Occlusal plane to FH angle	10.77	3.95	11.98	3.70	0.3746	5.49	4.34	8.88	4.32	0.0443*	-5.28	6.06	-3.09	4.22	0.1343
Occlusal Plane to SN angle (°)	22.57	4.22	23.36	3.49	0.4162	16.52	6.44	20.40	4.61	0.0421*	-6.05	6.37	-2.95	4.45	0.0658
AB to Occlusal plane angle (°)	95.31	8.69	93.12	5.35	0.3746	103.02	4.77	92.99	4.35	0.0000***	7.71	9.64	-0.12	6.34	0.0091**
Upper gonial angle (°)	52.91	5.05	50.46	4.40	0.1777	47.69	4.67	44.19	4.00	0.0490*	-5.22	3.12	-6.27	3.58	0.4286
Lower gonial angle (°)	75.25	3.90	77.33	4.60	0.2753	75.97	5.75	79.03	6.13	0.1644	0.72	3.13	1.71	3.30	0.4540
Occlusal plane to GoMe angle (°)	12.12	4.54	13.38	4.99	0.4286	17.70	6.47	17.03	5.23	0.8473	5.58	5.95	3.65	6.18	0.5635

Independent t test was performed. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$

Table 2. Cephalometric predictors and the calculated feature importance values

Feature	Feature importance value
ANB	0.2430162
PP-FH	0.23951529
Combination factor	0.24303272
Facial convexity angle	0.27443576

Feature selection algorithm was documented in the appendix.

APPENDIX-1: Cephalometric variables

1. SNA (degree): Angle between the anterior cranial base (SN) and the NA line
2. A-N perp (mm): Perpendicular distance from the A to the N perpendicular line to the FH plane
3. SNB (degree): Angle between the anterior cranial base (SN) and the NB line
4. Pog-N perp (mm): Perpendicular distance from the Pog to the N perpendicular line to the FH plane
5. ANB (degree): Angle between the NA and NB lines
6. Wits appraisal (mm): Perpendicular distance from the A to the B perpendicular line to the occlusal plane (The value is positive when the A is positioned anteriorly to the B)
7. APDI (degree): Sum of the facial plane (N-Pog) to the FH plane angle, the AB to facial plane angle, and the palatal plane (ANS-PNS) to the FH plane angle
8. Co-Gn (mm): Distance from the condylion to the gnathion
9. Co-ANS (mm): Distance from the condylion to the ANS
10. Harvold unit difference (mm): Difference between the distance of Co-Gn and the distance of Co-ANS
11. FMA (FH-Mandibular plane angle, degree): Angle between the FH plane and the mandibular plane
12. SN-MP (degree): Angle between the SN plane and the mandibular plane
13. PP-FH (degree): Angle between the palatal plane (ANS-PNS) and the FH plane
14. AB-MP (degree): Angle between the AB plane and the mandibular plane (Go-Me)
15. ODI (degree): Sum of AB-MP and PP-FH
16. Saddle angle (degree): Angle constructed by the SN plane and the S-Ar line
17. Articular angle (degree): Angle constructed by the S-Ar and Ar-Go lines
18. Gonial angle (degree): Angle constructed by the Me-Go and Ar-Go lines

19. Bjork Sum (degree): Sum of the saddle, articular, and gonial angles
20. Anterior facial height (AFH, mm): Length from N to Me
21. Posterior facial height (PHF, mm): Length from S to Go
22. Facial height ratio (FHR, %): (PFH/AFH) ×100
23. Lower Anterior Facial Height Ratio (%): (ANS-Me/AFH) ×100
24. CF (Combination factor, degree): Sum of the ODI and the APDI
25. Facial convexity angle (degree): Angle constructed by the A-N and the Pog-A
26. Ramus height (mm): Length from Go to Ar
27. Mandibular body length (mm): Length from Me to Go
28. Body to anterior cranial base ratio (ratio): Mandibular body length/Anterior cranial base
29. IMPA (degree): Angle between the mandibular central incisor axis line and the mandibular plane
30. L1 to A-Pog (mm): Perpendicular distance from the mandibular central incisor crown to the A-Pog plane
31. Interincisal angle (degree): Angle between the maxillary incisor axis line and the mandibular incisor axis line
32. Maxillary occlusal plane to FH plane angle (degree): Angle between the maxillary occlusal plane and the FH plane
33. Bisecting occlusal plane to FH plane angle (degree): Angle between the bisecting occlusal plane and the FH plane
34. Occlusal plane to SN plane angle (degree): Angle between the occlusal plane and the SN plane
35. AB to occlusal plane angle (degree): Angle between the AB plane and the occlusal plane
36. Upper gonial angle (degree): Angle constructed by the N-Go and Go-Ar lines
37. Lower gonial angle (degree): Angle constructed by the N-Go and Go-Me lines
38. Occlusal plane to Go-Me angle (degree): Angle between the occlusal plane and the Go-Me

APPENDIX-2: Feature selection algorithm

- The feature selection method of this study was Boruta method which was based on random forest classifier. The used libraries were "Random Forest Classifier" module in sklearn library and "BorutaPy" module in Boruta library. In Boruta feature selection method, default parameters were used.

- In model learning, XGBoost classifier was used. The library for XGBoost was "xgboost". The parameters for XGBoost model were as followed:

- learning_rate : from 1e-2 to 1e2
- gamma : from 1e-2 to 1e0
- max_depth : from 2 to 8
- colsample_bytree : from 0.3 to 1
- subsample: from 0.3 to 0.9
- reg_alpha : from 0 to 0.5
- reg_lambda: from 1 to 3
- min_child_weight: from 1 to 7
- n_estimators: 800, 3200
- early_stopping_rounds : 1, 7

의학박사 학위논문

Early Prediction of the Need for Orthognathic Surgery in Patients with Repaired Unilateral Cleft Lip and Palate using Machine Learning and Longitudinal Lateral Cephalometric Analysis Data

기계학습과 두개안면계측촬영 영상데이터를 이용한 편측성 구순구개열 환자의 악교정 수술 필요성 여부의 조기 예측

2020 년 08 월

서울대학교 대학원

의학과 성형외과학 전공

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지도교수 김석화

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Early Prediction of the Need for Orthognathic Surgery in Patients with Repaired Unilateral Cleft Lip and Palate using Machine Learning and Longitudinal Lateral Cephalometric Analysis Data

By

LIN GUANG

A thesis submitted to the Department of Plastic and Reconstructive Surgery in partial fulfillment of the requirements for the Degree of Doctor of Philosophy in Medicine at Seoul National University College of Medicine

July 2020

Approved by Thesis Commottee

Professor ________________ **Chairman**

Professor ________________ **Vice chairman**

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Professor ________________

논문초록

기계학습과 두개안면계측촬영 영상데이터를 이용한 편측성 구순구개열 환자의 악교정 수술 필요성 여부의 조기 예측

서론: 편측성 구순구개열 환아는 안면 뼈 성장이 끝난 후 부정교합 또는 악안면 외형적인 문제로 악교정 수술 혹은 신연골형성 수술 (DO) 필요한 경우가 흔히 있다 (약 12%~40%로 보고되고 있다). 본 연구의 목적은 machine learning을 이용하여 편측성 구순구개열 환아의 lateral cephalometric 계측치로 악안면 뼈 성장 예후 또는 악교정술 혹은 DO 수술의 필요성의 예측이 가능한지 조사하는 것이다.

방법: 동일한 성형외과의사 그리고 교정과의사의 같은 진료방침으로 치료를 받은 총 56명의 편측성 구순구개열 환아들을 대상으로 연구 하였다. 환아들의 교정/정형 치료받기 전 시기 T0 (평균연령 6.3세) 및 15세 이후 시기 T1 (평균연령 16.7세)의 lateral cephalogram을 수집 및 digitize하였다. 38개의 cephalometric 계측치들을 분석하였다. T1시기의 3개의 계측치 (ANB ≤ -3°; Wits appraisal ≤ -5 mm; Harvold unit difference ≥ 34 mm; 수술군)를 기준으로 환아들을 수술군 (n=10)과 비수술군 (n=46)으로 나누었다. Independent t test 통계분석을 실행 하였으며, Boruta 방법과 XGBoost algorithm을 사용하여 T0에서 악안면 뼈 성장을 예측 할 수 있는 계측치를 탐색하였다.

결과: T0 시기의 2개의 cephalometric 계측치 [ANB과 Facial convexity angle (FCA), 모두 $P < 0.05$] 결과에서 그룹간 유의한 통계 차이를 보였다. T1 시기의 18개의 계측치와 ΔT1-T0 (T0~T1 변화 값)의 14개의 계측치에서 유의한 차이가 관찰 되었다 (모두 $P < 0.05$). T0 시기 안면 뼈 성장 예후 예측이 가능한 계측치는 ANB, PP-FH, Combination factor, 그리고 Facial convexity angle로 확인되었다. 10-fold Cross-Validation 정확도는 87.4%이며 F1-score는 0.714로 확인되었다 (Sensitivity, 97.83%; Specificity, 90.00%).

결론: 편측성 구순구개열 환자 6세 시기에, 높은 정확도로 악안면 뼈 성장 예후 또는 뼈 성장 종료 후의 악교정 수술 혹은 신연골형성 수술 실행 여부 판단이 가능하다.

주요어: 장기적 측면 두개안면계측촬영 분석, 악교정수술, 편측성 구순구개열

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Abstract

Early Prediction of the Need for Orthognathic Surgery in Patients with Repaired Unilateral Cleft Lip and Palate using Machine Learning and Longitudinal Lateral Cephalometric Analysis Data

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Background: Some patients with unilateral cleft lip and palate (UCLP) need orthognathic surgery or distraction osteogenesis (DO) to obtain a more balanced intermaxillary relationship and improved esthetic outcome. This study was conducted to determine the cephalometric parameters that can predict the future need for orthognathic surgery or DO in Korean patients with repaired UCLP by using machine learning and longitudinal lateral cephalometric analysis.

Method: We included 56 Korean patients with UCLP (31 males and 25 females), who were treated by a single surgeon and a single orthodontist with the same treatment protocol. Lateral cephalograms were obtained before the commencement of orthodontic/orthopedic treatment (T0; mean age, 6.3 years) and at at least 15 years of age (T1; mean age, 16.7 years), and 38 cephalometric variables were measured. At the T1 stage, 3 cephalometric criteria were used to classify the participants into the surgery and non-surgery groups (ANB $\leq -3°$; Wits appraisal ≤ -5 mm; Harvold unit difference ≥ 34 mm for the surgical group). They were divided into the surgical group (n=10, 17.9%) and the non-surgical group (n=46, 82.1%). The one-way analysis of variance, Fisher’s exact test, and independent *t*-test were used for statistical analyses. The Boruta method and XGBoost algorithm were used to determine the cephalometric variables at the T0 stage for the development of a prediction model.

Results: At the T0 stage, only 2 variables (ANB and Facial convexity angle, all P<0.05) exhibited a significant intergroup difference. At the T1 stage, 18 cephalometric variables showed a significant intergroup difference (A-N perp, SNB, ODI, articular angle, mandibular body length, IMPA, bisecting Occ plane to FH plane angle, occlusal plane to SN plane angle, and upper gonial angle, all *P*<0.05; Pog-N Perp, Co-Gn, and AB-MP, all *P*<0.01; and ANB, Wits appraisal, APDI, Harvold unit difference, facial convexity angle, and AB to occlusal plane angle, all *P*<0.001). For the quantification of change from T0 to T1, 14 variables exhibited a significant intergroup difference (ΔSNB, ΔPog-N Perp, ΔCo-Gn, ΔHarvold unit difference, ΔSN-MP, ΔWits appraisal, ΔBjork Sum, ΔMandibular body length, and ΔBody to anterior cranial base ratio, all *P*<0.05; ΔANB, ΔAB-MP, ΔFacial convexity, and ΔAB to occlusal plane angle, all *P*<0.01; ΔAPDI, *P*<0.001). At the T0 stage, the ANB, PP-FH, CF, and facial convexity angle were selected as predictive parameters, and had a 10-fold cross-validation accuracy of 87.4% with an F1-score of 0.714.

Conclusion: The 4 cephalometric variables identified in this study might be considered effective predictors, at approximately age 6 years, of the future need for orthognathic surgery to correct sagittal skeletal discrepancies in Korean patients with UCLP.

Keywords:

Longitudinal lateral cephalometric analysis, Orthognathic surgery, Unilateral cleft lip and palate

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CONTENTS

INTRODUCTION

Skeletal Class III malocclusion with restricted maxillary growth is frequently observed in patients with unilateral cleft lip and palate (UCLP), and is related to the intrinsic factors and the scar tissue from surgical intervention.[1-3] A quarter to a half of patients with UCLP are known to need orthognathic surgery or distraction osteogenesis (DO) to obtain a normal intermaxillary relationship and an improved facial esthetics.[4-8]

Although the orthopedic treatment for maxillary protraction using face mask (FM) with bone-anchored mini-plates[9-10] might not fully correct Class III intermaxillary relationship, it would reduce the amount of maxillary advancement in orthognathic surgery or DO. Thus, the postoperative stability of the maxilla can be improved.[11-12] However, orthopedic treatment is usually conducted only when UCLP patients developed moderate sagittal skeletal discrepancy at around 10 years of age.[13-16] Clinicians and parents of cleft patients want to know the future need for the surgical correction of the sagittal skeletal discrepancy. Therefore, early prediction of the maxillofacial growth would be meaningful in determining to start orthopedic treatment or wait for the completion of growth.

Park et al.[17] used the feature wrapping method, a kind of machine learning, to determine the cephalometric predictors of the future need for orthognathic surgery to correct the sagittal skeletal discrepancy in Korean male patients with clefts. At the mean age of 9.3, a total of 10 cephalometric variables (APDI, ODI, Harvold unit difference, Wits appraisal, AB to mandibular plane angle, gonial angle, ANB, overjet, A to N perp, and IMPA) were selected as predictors, with a weighted classification accuracy of 77.3%. The study also reported that the frequency of surgical intervention increased with cleft severity from cleft lip and alveolus (CLA) group, UCLP group, to bilateral cleft lip and palate (BCLP) group (8.5%, 21.4%, and 30.0%).[17]

Among the diverse machine learning methods to find the relevant features, several previous studies have used the Boruta method due to its best performance.[18-21] The method is based on a random forest approach that can identify the most important features with high feature-selection stability.[22,23] The XGBoost algorithm[24] is an extendable, cutting-edge application for gradient-boosting machines, and has been proven to push the limits of computing power for boosted tree algorithms. Boosting is an ensemble technique whereby new models are appended to adjust the errors by preexisting models. Gradient boosting is an algorithm whereby new models are created to cover the residuals of prior models and then added together to obtain better predictions.[25] Therefore, this study used the Boruta method and the XGBoost algorithm to investigate the cephalometric predictors of the future need for orthognathic surgery or DO in patients with repaired UCLP.

METHODS

Patients

The samples consisted of 56 Korean patients with non-syndromic UCLP (31 males and 25 females), who were treated at the Department of Plastic Surgery, Seoul National University Children's Hospital (SNUCH) and the Department of Orthodontics, Seoul National University Dental Hospitals (SNUDH), Seoul, Republic of Korea. This retrospective study was reviewed and approved by the institutional review board of the SNUDH (ERI20014).

Treatment protocol

The treatment protocol used in SNUCH and SNUDH is summarized as below: (1) primary cheiloplasty (rotation and advancement flap) was performed between 3 and 5 months of age; (2) palatoplasty (Furlow double opposing Z-plasty) and late primary gingivoperiosteoplasty were performed between 12 and 18 months of age; (3) if needed, maxillary arch was expanded before secondary alveolar bone grafting (SABG); (4) SABG with cancellous bone from the iliac bone was conducted during the mixed dentition stage; (5) if needed, facemask with bone-anchored mini-plates was used for orthopedic maxillary protraction during the pubertal growth period; (6) fixed orthodontic treatment was performed during the permanent dentition stage; and (7) if needed, orthognathic surgery or DO were performed after completion of growth.

Inclusion criteria

Participants were enrolled on the basis of the following inclusion criteria : (1) patients who were born before 2002 and whose charts, radiographs, and clinical photographs were available for longitudinal follow-up; (2) patients who were treated with the same protocol by a single surgeon (SWK) and a single orthodontist (SHB) to eliminate the influences of different surgical and orthodontic treatments; (3) patients whose initial lateral cephalogram was obtained between 5 and 7 years of age (T0 stage) and who did not undergo orthodontic/orthopedic treatment and alveolar bone grafting to avoid the effects on the skeletodental growth; and (4) patients whose final lateral cephalogram was obrained at or above 15 years of age (T1 stage) to judge the need for orthognathic surgery or DO. Syndromic patients were excluded.

Grouping

A total of 56 patients with UCLP were recruited. At the T1 stage, patients (1) who had undergone orthognathic surgery or DO, (2) who were under presurgical orthodontic treatment, or (3) who met the cephalometric criteria for orthognathic surgery (ANB ≤ −3 degrees, Wits appraisal ≤ −5 mm, and Harvold unit difference ≥ 34 mm), were classified into the surgery group (n = 10, 17.9%).[17] The remaining patients were allocated into the non-surgery group (n = 46, 82.1%).

Cephalometric analysis

The Figure 1 and appendix-1 lists the definition of cephalometric landmarks and cephalometric variables included in the cephalometric analysis. The cephalometric analysis for all patients at the T0 and T1 stages was assessed twice by a single researcher (GL) by using the V-CEPH (Version 8.4;

CyberMed, Seoul, Korea) program. As there was no significant difference between the first and second measurements, the first measurement set was used for further statistical analysis.

Statistical analysis

The independent *t*-test was used to investigate the intergroup differences on the cephalometric variables at the T0 and T1 stages, and the amount of change (ΔT1-T0). The SPSS (version 12.0; SPSS, Chicago, Ill, USA) software package was used for statistical analysis. *P*-value less than 0.05 was set as an indicator of statistical significance.

Feature selection (Appendix-2)

The Boruta method was used to determine the cephalometric predictors at the T0 stage. The XGBoost algorithm was used to generate the machine learning model that classifies the need for surgical correction for each patient, and 10-fold cross-validation accuracy with F1-score were obtained. The prediction model was testified with the confusion matrix without normalization

RESULTS

Intergroup differences at each stage

The final analysis dataset included 56 patients (T0 stage; mean age, 6.3 years and T1 stage; mean age, 16.7 years). At the T0 stage, only 2 variables exhibited a significant intergroup difference [ANB and FCA, all $P < 0.05$; Table 1). At the T1 stage, 18 cephalometric variables showed a significant difference between the two groups (A-N perp, SNB, ODI, articular angle, mandibular body length, IMPA, bisecting occlusal plane to FH plane angle, occlusal plane to SN plane angle, and upper gonial angle, all $P < 0.05$; Pog-N perp, Co-Gn, and AB-MP, all $P < 0.01$; ANB, Wits appraisal, APDI, Harvold unit difference, FCA, and AB to occlusal plane angle, all $P < 0.001$; Table 1). For ΔT1-T0, 14 variables (ΔSNB, ΔPog-N perp, ΔCo-Gn, ΔHarvold unit difference, ΔSN-MP, ΔWits appraisal, ΔBjork Sum, Δmandibular body length, and Δbody to anterior cranial base ratio, all $P < 0.05$; ΔANB, ΔAB-MP, ΔFCA, and ΔAB to occlusal plane angle, all $P < 0.01$; ΔAPDI, $P < 0.001$; Table 1) exhibited a significant intergroup difference.

Prediction of the future need for orthognathic surgery or DO

Four cephalometric parameters of the T0 stage including ANB (intermaxillary relationship between the maxilla and mandible; degree of relative protrusion of B point in relation to A point), PP-FH (inclination of the palatal plane in relation to the FH plane), combination factor (CF; sum of ODI and APDI, which means the skeletal size of the maxilla and mandible) and FCA (intermaxillary relationship between the maxilla and mandible; degree of relative protrusion of Pogonion point in relation to A point) were selected as predictors of the future need for orthognathic surgery or DO (Table 2, Figure 2 and Figure 3). The feature importance of the ANB, PP-FH, CF and FCA were 0.2430162, 0.23951529, 0.24303272 and 0.27443576, respectively (Table 2).

The prediction model has a 10-fold cross-validation accuracy of 87.4% with F1-score of 0.714 (Figure 4). The sensitivity (the proportion of actual non-surgery patients that was correctly predicted as non-surgery patients) and specificity (the proportion of actual surgery patients that was correctly predicted as surgery patients) of the prediction model were 97.83% and 90.00%, respectively (Figure 4). This model is uploaded on the following Web site (http://147.47.41.53:8890). The prognosis prediction results for surgery and no surgery are generated when the values of 4 variables (ANB, PP-FH, CF, and FCA) are inserted.

DISCUSSION

Patients with cleft usually require a long-term multidisciplinary care in order to obtain good facial esthetics and functional occlusion.[26] In this retrospective longitudinal study, 17.9% of the UCLP patients needed orthognathic surgery or DO, which was similar to the results of previous studies (12%–40%).[17,27-30]

Statistics are widely used for inference about the relationships between variables, or to create a model that is able to predict future values. The way a statistical model is evaluated will involve evaluating the significance and robustness of the model parameters, which require adequate data size. Given the relatively small data size of the study subjects in this study, machine learning was used. Machine learning can be classified into supervised, unsupervised and reinforcement learnings. The unsupervised learning which is commonly used to discover the association between patient characteristics and disease prevalence, was applied in this study with Boruta method to select the predictive features. This method iteratively removes the features which are shown by a statistical test to prove to be less relevant than random probes.[19] Compared to the feature wrapping method used in Park et al.'s study[17], the random forest classification-based Boruta algorithm is relatively quick run without fine tuning of parameters, and gives a numerical estimate of the feature importance.[22] Instead of selecting features according to the predicting accuracy of each feature, the machine learning in this study was processed by assessing every combination of the features. Therefore, the respective classification accuracies were not calculated, and the prediction model is meaningful only when the four features (ANB, PP-FH, CF and FCA) come together.

At the T1 stage, 18 cephalometric parameters exhibited significant differences between the surgery and non-surgery groups (Table 1), while at the T0 stage, only 2 variables showed significant intergroup difference (ANB and FCA; Table 1). These results suggest that most of the unfavorable skeletodental features developed during growth (from age 6.3 to 16.7 years), which was confirmed by the significant intergroup differences of 14 variables in ΔT1-T0 between the 2 groups (Table 1).

When compared to Park et al.'s study,[17] this study showed four main differences in the composition of subjects; mean age at the T0 stage, number of cephalometric predictors, and weighted classification accuracy (CLA, UCLP and BCLP vs. UCLP only; 9.3 year-old vs. 6.3 year-old; 10 predictors vs. 4 predictors; 77.3% vs. 87.4%; Table 2 and Fig. 1). This finding suggests that it is possible to predict the skeletodental growth of UCLP patients using less number of cephalometric variables at earlier age compared to Park et al.'s study.[17]

Difference in the number of cephalometric predictors was most likely due to the age difference of the subjects between Park et al.[17] and this study because the skeletodental growth in 9.3 years of age might be relatively more actively appeared than those in 6.3 years of age.[31-33]

The implications of the 4 cephalometric predictors are enumerated as follows: First, as previously reported in several studies,[17,27,34] the ANB was confirmed as an effective factor to predict the skeletodental growth of UCLP patients in this study (Table 2, Figure 2). After the evaluation of the lateral cephalograms in UCLP patients at 5 and 10 years of age, Meazzini et al.[34] divided their patients into the orthognathic surgery and the non-orthognathic surgery group at the completion of growth. They reported significant differences in the SNA, SN-ANS and ANB between the 2 groups at both 5 and 10 years of age.[34] The present study suggested similar results in terms of the ANB and facial convexity angle (the degree of relative protrusion of the mandible by using B point and Pogonion point in relation to the maxilla, Table 2). Although Meazzini et al.[34] investigated participants with different ethnic backgrounds and surgical protocols than in this study, a similar pattern of sagittal skeletal discrepancy (ANB) was observed in the present study. Therefore, it can be stated that the difference in the maxillofacial growth pattern between Asian and Caucasian UCLP patients might be minor.

Second, the finding that PP-FH and CF were selected as predictors (Table 2, Figure 2) concurs with

Park et al.'s study.[17] The PP-FH is a common component in both APDI [sum of PP-FH angle, facial plane (N-Pog) to FH plane angle, and AB to facial plane angle; Appendix-1, Figure 2] and ODI (sum of PP-FH angle and AB to mandibular plane angle; Appendix-1, Figure 2), which represent the sagittal and vertical growth patterns, respectively. Similarly, as the CF is a sum of the APDI and ODI (Appendix-1, Figure 2), it indicates the skeletal size of the maxilla and mandible in the sagittal and vertical aspects.

Third, the FCA (the angle between the N-A plane and A-Pog plane; Appendix-1, Figure 2) would be a supplementary factor to ANB, which indicates the degree of relative protrusion of the Pogonion point in relation to the A point.

Although Park et al.[17] reported that the Wits appraisal and the Harvold unit difference were the crucial cephalometric predictors, these variables were not selected in the present study despite existence of significant difference in the values between the two groups at the T1 stage (Wits appraisal and Harvold unit difference, all $P < 0.001$; Table 1) and their amount of change (ΔWits appraisal and ΔHarvold unit difference, all $P < 0.001$; Table 1). The reason for this might be that the eruption of the permanent maxillary incisors is not completed and the growth of the mandible is not prominent at the T0 stage.[35-37] Moreover, the AB to mandibular plane angle, gonial angle, A to N perp, overjet, and IMPA were not selected as cephalometric predictors in the present study. It was also speculated due to the insufficient growth of the maxilla and mandible and eruption of the teeth at the T0 stage.

Compared to previous studies,[17,27-30] the present study used the lateral cephalometric data obtained at a younger age (6.3 years) to avoid the effect of orthodontic and orthopedic treatment and alveolar bone grafting on the skeletodental growth, and adopted strict inclusion criteria such as single ethnicity, UCLP patients only, the same treatment protocol with a single surgeon and a single orthodontist to reduce the bias for selection of the subjects. Although, by using machine learning, this study showed a good accuracy in the prediction of the future need for surgery to correct the intermaxillary discrepancy in the patients with UCLP.

The relatively small sample size would be the major limitation of the present study. The sample size could not be neglected either in traditional statistical analysis or in the machine learning. However, the machine learning, as a data-driven method, has been widely applied in current studies to select relevant features despite small sample size. In a study by Liu et al.,[38] a classification model for congestive heart failure (CHF) was presented by machine learning; and the number of the study subjects involved was 47 (17 CHF patients and 30 normal subjects). The other articles which used machine learning method with relatively small sample size and came out with somehow appreciable outcomes, could be found in the literature.[39-42] Besides, machine learning models provide various degrees of interpretability, from the lasso regression to neural networks, but they generally lack interpretability for predictive power. Thus, the external validation would be processed in further study in order to better clarify the reliability of the prediction model.

Early prediction of the future need for orthognathic surgery or DO can help clinicians to setup the proper treatment plan and to adjust the timing and duration of orthodontic/orthopedic treatment for maxillary protraction in cleft patients. Therefore, it is necessary to conduct well-designed case-control studies for the evaluation of the effects of orthodontic/orthopedic treatment for the correction of the maxillary hypoplasia with regard to reducing the frequency of orthognathic surgery or DO, or the amount of maxillary advancement in patients with cleft lip and palate.

CONCULSION

At age of 6 years it was possible to predict the future need for surgery to correct their sagittal skeletal discrepancy in patients with UCLP using cephalometric predictors with a good accuracy.

Disclosure

The authors have no potential conflicts of interest to disclose.

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FIGURE LEGEND

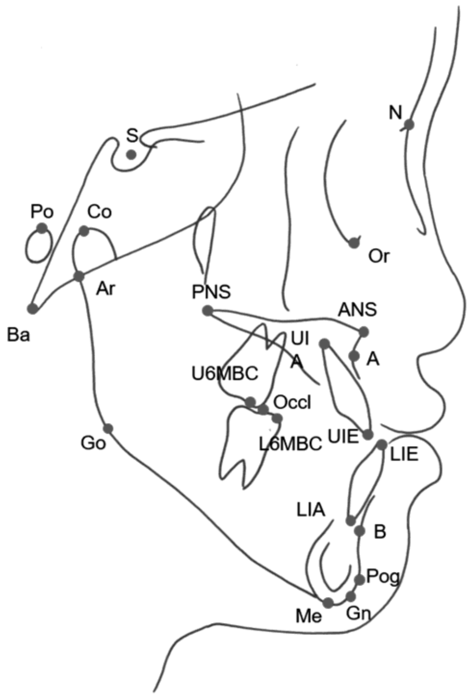

Figure 1. Cephalometric landmarks used in this study

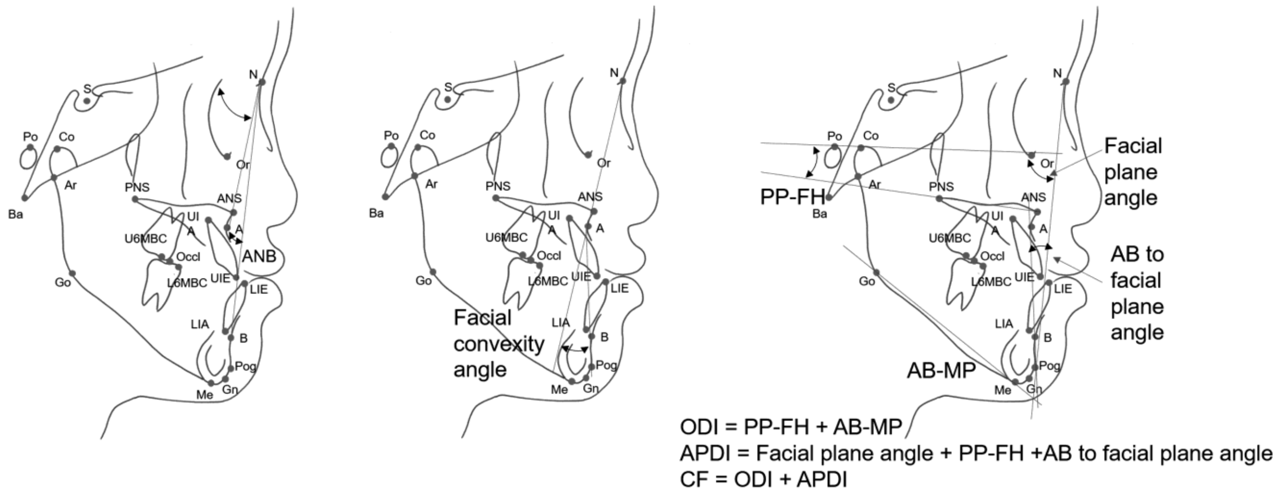

Figure 2. Four cephalometric parameters of the initial lateral cephalogram obtained between 5 and 7 years of age (T0 stage). ANB (degree of relative protrusion of B point in relation to A point), intermaxillary relationship between the maxilla and mandible; PP-FH, inclination of the palatal plane (ANS-PNS) in relation to the FH plane; combination factor (CF), sum of overbite depth indicator (ODI) and anteroposterior dysplasia indicator (APDI), which means the skeletal size of the maxilla and mandible; and Facial convexity angle (FCA, degree of relative protrusion of Pogonion point in relation to A point), intermaxillary relationship between the maxilla and mandible.

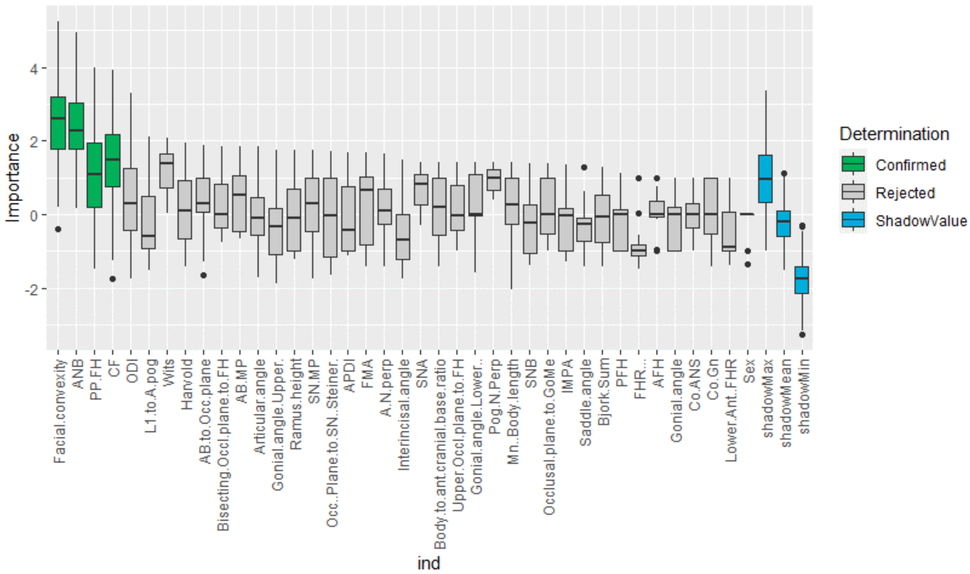

Figure 3. Feature importance

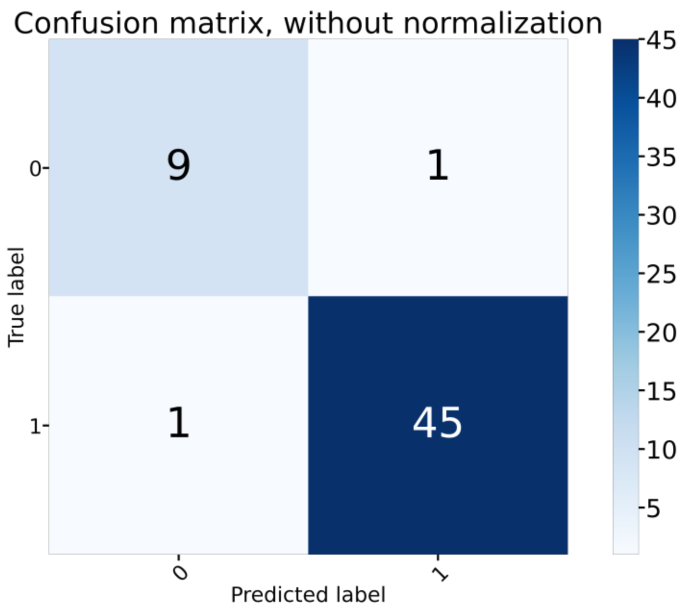

Figure 4. The quality of the prediction model. The confusion matrix without normalization was used. 0, surgery patient; 1, non-surgery patient; Sensitivity (the proportion of actual non-surgery patients that was correctly predicted as non-surgery patients), 97.83%; Specificity (the proportion of actual surgery patients that was correctly predicted as surgery patients), 90.00%. 10-fold cross-validation accuracy, 87.4%; F1-score, 0.714.

Table 1. Comparison of the cephalometric parameters at T0, T1 and Amount of change (from T0 to T1) between the surgery and non-surgery groups

	T0					T1					Amount of change				
	Surgery (n=10)		Non-Surgery (n=46)		*P*-value	Surgery (n=10)		Non-Surgery (n=46)		*P*-value	Surgery (n=10)		Non-Surgery (n=46)		*P*-value
	Mean	SD	Mean	SD		Mean	SD	Mean	SD		Mean	SD	Mean	SD	
SNA (°)	76.68	3.94	79.21	3.77	0.0612	73.85	4.62	75.89	3.65	0.2752	-2.84	3.84	-3.32	2.96	0.7645
A-N perpendicular (mm)	-1.63	4.38	0.86	4.82	0.1548	-6.53	3.67	-3.29	4.45	0.0291*	-4.91	3.85	-4.15	4.47	0.4540
SNB (°)	75.10	2.46	75.05	3.20	0.9148	78.19	4.65	74.54	3.32	0.0276*	3.09	4.18	-0.52	3.37	0.0152*
Pog-N perpendicular (mm)	-6.79	5.38	-9.35	7.65	0.2524	1.58	7.55	-8.28	8.01	0.0026**	8.37	7.29	1.07	9.18	0.0116*
ANB (°)	1.59	3.38	4.16	2.51	0.0209*	-4.34	2.76	1.35	2.16	0.0000***	-5.93	3.47	-2.81	2.75	0.0046**
Wits appraisal (mm)	-4.52	6.86	-2.19	4.03	0.2659	-9.54	3.93	-2.60	3.46	0.0000***	-5.02	7.19	-0.41	4.24	0.0131*
APDI (°)	83.22	6.16	81.18	5.71	0.2945	96.45	4.75	84.58	5.63	0.0000***	13.24	4.28	3.40	6.49	0.0000***
Co-Gn (mm)	124.82	25.78	127.61	25.47	0.6379	140.55	5.79	131.66	9.35	0.0015**	15.74	23.19	4.05	24.46	0.0276*
Co-ANS (mm)	97.97	17.08	102.30	20.45	0.5210	97.50	6.08	97.03	7.55	0.8641	-0.48	18.77	-5.27	20.13	0.3357
Harvold unit difference (mm)	26.84	11.23	25.31	6.76	0.7891	43.06	7.05	34.63	5.16	0.0006***	16.21	6.78	9.31	6.53	0.0123*
FMA (°)	26.28	3.75	28.18	4.61	0.3045	24.27	4.28	28.21	6.33	0.0598	-2.01	2.08	0.03	4.07	0.1343
SN-MP (°)	38.11	4.72	39.59	4.52	0.4412	35.32	6.90	39.76	6.42	0.0723	-2.79	3.69	0.16	4.48	0.0443*
ODI (°)	68.59	8.51	71.88	6.19	0.2480	60.97	8.61	68.13	6.92	0.0197*	-7.62	11.43	-3.75	6.45	0.0995
PP-FH (°)	-0.96	3.30	0.62	3.22	0.0952	0.85	4.19	0.46	4.62	0.5563	1.80	5.41	-0.16	4.15	0.3465
AB-MP (°)	69.54	7.93	71.26	5.76	0.6151	60.12	6.50	67.67	5.14	0.0015**	-9.42	7.05	-3.59	4.11	0.0018**
Saddle angle (°)	126.93	5.63	124.09	5.13	0.1134	126.07	7.35	124.73	5.62	0.5350	-0.86	3.89	0.64	3.79	0.2436
Articular angle (°)	143.03	9.22	147.72	5.73	0.1399	145.60	7.92	151.81	7.61	0.0276*	2.58	4.32	4.09	6.54	0.6766
Gonial angle (°)	128.15	5.58	127.79	7.35	0.8894	123.65	5.95	123.22	7.42	0.7161	-4.51	4.39	-4.57	4.94	0.8306
Bjork Sum (°)	398.11	4.72	399.59	4.52	0.4412	395.32	6.90	399.76	6.42	0.0723	-2.79	3.69	0.16	4.48	0.0443*
Anterior facial height (mm)	135.88	26.24	143.76	30.83	0.1993	149.71	9.37	150.80	10.04	0.9148	13.83	23.15	7.04	28.15	0.4286
Posterior facial height (mm)	82.67	14.15	87.49	17.52	0.3466	97.20	6.45	95.21	8.15	0.5141	14.53	15.94	7.72	18.21	0.1086
Facial height ratio (%)	61.12	3.84	61.09	3.46	0.7646	65.08	4.84	63.21	4.66	0.3357	3.96	3.09	2.12	3.37	0.1235
Lower Anterior facial height (mm)	55.03	2.95	54.29	2.33	0.3746	55.73	3.02	54.75	2.22	0.1847	0.70	3.22	0.45	2.05	0.4476
Combination factor (°)	151.80	5.99	153.06	7.04	0.2227	157.42	8.15	152.71	10.04	0.1518	5.62	11.19	-0.36	8.64	0.1288
Facial convexity angle (°)	3.90	7.35	9.36	5.59	0.0291*	-11.87	5.89	1.50	5.58	0.0000***	-15.77	6.10	-7.86	6.19	0.0012**
Ramus height (mm)	49.16	9.43	49.62	10.20	0.8810	58.80	4.50	55.29	6.52	0.0706	9.64	10.55	5.67	11.32	0.1993
Mandibular body length (mm)	80.58	15.86	82.46	17.07	0.7483	91.12	6.13	84.84	7.02	0.0147*	10.54	12.88	2.38	16.51	0.0342*
Body to anterior cranial base ratio	0.98	0.09	0.99	0.07	0.3913	1.11	0.09	1.07	0.08	0.2299	0.13	0.07	0.08	0.06	0.0397*
IMPA (°)	84.78	9.00	85.72	8.88	0.7002	83.31	8.57	88.70	6.25	0.0276*	-1.47	6.24	2.97	7.80	0.0910
L1 to A-pog (mm)	2.42	3.63	2.60	2.94	0.8641	6.05	5.55	4.87	2.95	0.3804	3.63	3.84	2.28	3.31	0.4349
Interincisal angle (°)	147.22	14.67	145.31	10.89	0.6076	134.38	13.01	129.13	8.34	0.1847	-12.84	14.64	-16.18	12.08	0.5492
Maxillary Occlusal plane to FH angle	11.13	3.42	12.55	4.36	0.4224	7.41	4.47	8.87	4.28	0.2309	-3.73	6.90	-3.68	4.84	0.7321
Bisecting Occlusal plane to FH angle	10.77	3.95	11.98	3.70	0.3746	5.49	4.34	8.88	4.32	0.0443*	-5.28	6.06	-3.09	4.22	0.1343
Occlusal Plane to SN angle (°)	22.57	4.22	23.36	3.49	0.4162	16.52	6.44	20.40	4.61	0.0421*	-6.05	6.37	-2.95	4.45	0.0658
AB to Occlusal plane angle (°)	95.31	8.69	93.12	5.35	0.3746	103.02	4.77	92.99	4.35	0.0000***	7.71	9.64	-0.12	6.34	0.0091**
Upper gonial angle (°)	52.91	5.05	50.46	4.40	0.1777	47.69	4.67	44.19	4.00	0.0490*	-5.22	3.12	-6.27	3.58	0.4286
Lower gonial angle (°)	75.25	3.90	77.33	4.60	0.2753	75.97	5.75	79.03	6.13	0.1644	0.72	3.13	1.71	3.30	0.4540
Occlusal plane to GoMe angle (°)	12.12	4.54	13.38	4.99	0.4286	17.70	6.47	17.03	5.23	0.8473	5.58	5.95	3.65	6.18	0.5635

Independent t test was performed. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$

Table 2. Cephalometric predictors and the calculated feature importance values

Feature	Feature importance value
ANB	0.2430162
PP-FH	0.23951529
Combination factor	0.24303272
Facial convexity angle	0.27443576

Feature selection algorithm was documented in the appendix.

APPENDIX-1: Cephalometric variables

1. SNA (degree): Angle between the anterior cranial base (SN) and the NA line
2. A-N perp (mm): Perpendicular distance from the A to the N perpendicular line to the FH plane
3. SNB (degree): Angle between the anterior cranial base (SN) and the NB line
4. Pog-N perp (mm): Perpendicular distance from the Pog to the N perpendicular line to the FH plane
5. ANB (degree): Angle between the NA and NB lines
6. Wits appraisal (mm): Perpendicular distance from the A to the B perpendicular line to the occlusal plane (The value is positive when the A is positioned anteriorly to the B)
7. APDI (degree): Sum of the facial plane (N-Pog) to the FH plane angle, the AB to facial plane angle, and the palatal plane (ANS-PNS) to the FH plane angle
8. Co-Gn (mm): Distance from the condylion to the gnathion
9. Co-ANS (mm): Distance from the condylion to the ANS
10. Harvold unit difference (mm): Difference between the distance of Co-Gn and the distance of Co-ANS
11. FMA (FH-Mandibular plane angle, degree): Angle between the FH plane and the mandibular plane
12. SN-MP (degree): Angle between the SN plane and the mandibular plane
13. PP-FH (degree): Angle between the palatal plane (ANS-PNS) and the FH plane
14. AB-MP (degree): Angle between the AB plane and the mandibular plane (Go-Me)
15. ODI (degree): Sum of AB-MP and PP-FH
16. Saddle angle (degree): Angle constructed by the SN plane and the S-Ar line
17. Articular angle (degree): Angle constructed by the S-Ar and Ar-Go lines
18. Gonial angle (degree): Angle constructed by the Me-Go and Ar-Go lines

19. Bjork Sum (degree): Sum of the saddle, articular, and gonial angles
20. Anterior facial height (AFH, mm): Length from N to Me
21. Posterior facial height (PHF, mm): Length from S to Go
22. Facial height ratio (FHR, %): (PFH/AFH) ×100
23. Lower Anterior Facial Height Ratio (%): (ANS-Me/AFH) ×100
24. CF (Combination factor, degree): Sum of the ODI and the APDI
25. Facial convexity angle (degree): Angle constructed by the A-N and the Pog-A
26. Ramus height (mm): Length from Go to Ar
27. Mandibular body length (mm): Length from Me to Go
28. Body to anterior cranial base ratio (ratio): Mandibular body length/Anterior cranial base
29. IMPA (degree): Angle between the mandibular central incisor axis line and the mandibular plane
30. L1 to A-Pog (mm): Perpendicular distance from the mandibular central incisor crown to the A-Pog plane
31. Interincisal angle (degree): Angle between the maxillary incisor axis line and the mandibular incisor axis line
32. Maxillary occlusal plane to FH plane angle (degree): Angle between the maxillary occlusal plane and the FH plane
33. Bisecting occlusal plane to FH plane angle (degree): Angle between the bisecting occlusal plane and the FH plane
34. Occlusal plane to SN plane angle (degree): Angle between the occlusal plane and the SN plane
35. AB to occlusal plane angle (degree): Angle between the AB plane and the occlusal plane
36. Upper gonial angle (degree): Angle constructed by the N-Go and Go-Ar lines
37. Lower gonial angle (degree): Angle constructed by the N-Go and Go-Me lines
38. Occlusal plane to Go-Me angle (degree): Angle between the occlusal plane and the Go-Me

APPENDIX-2: Feature selection algorithm

- The feature selection method of this study was Boruta method which was based on random forest classifier. The used libraries were “Random Forest Classifier” module in sklearn library and “BorutaPy” module in Boruta library. In Boruta feature selection method, default parameters were used.

- In model learning, XGBoost classifier was used. The library for XGBoost was “xgboost”. The parameters for XGBoost model were as followed:

- learning_rate : from 1e-2 to 1e2
- gamma : from 1e-2 to 1e0
- max_depth : from 2 to 8
- colsample_bytree : from 0.3 to 1
- subsample: from 0.3 to 0.9
- reg_alpha : from 0 to 0.5
- reg_lambda: from 1 to 3
- min_child_weight: from 1 to 7
- n_estimators: 800, 3200
- early_stopping_rounds : 1, 7