Pesquisa Brasileira em Odontopediatria e Clínica Integrada 2019, 19:e4642
DOI: http://doi.org/10.4034/PBOCI.2019.191.45
ISSN 1519-0501

ORIGINAL ARTICLE

Clinical Investigation of Congenital Factor Affecting Craniofacial Morphology of Unilateral Cleft Lip and Palate in Japanese Patients

Mohammad Khursheed Alam[1], Takashi S. Kajii[2], Yoshiaki Sato[3], Junichiro Iida[4]

[1]Orthodontic Department, College of Dentistry, Jouf University, Sakaka, Saudi Arabia. 0000-0001-7131-1752
[2]Section of Orthodontics, Department of Oral Growth and Development, Fukuoka Dental College, Fukuoka, Japan. 0000-0002-3500-5878
[3]Department of Orthodontics, Division of Oral Functional Science, Graduate School of Dental Medicine, Hokkaido University, Sapporo, Japan. 0000-0002-6070-2085
[4]Department of Orthodontics, Division of Oral Functional Science, Graduate School of Dental Medicine, Hokkaido University, Sapporo, Japan. 0000-0001-5554-0483

Author to whom correspondence should be addressed: Associate Professor Dr. Mohammad Khursheed Alam, Orthodontic Department, College of Dentistry, Jouf University, Sakaka, Saudi Arabia. Phone: +96 6535602339. E-mail: dralam@gmail.com.

Academic Editors: Alessandro Leite Cavalcanti and Wilton Wilney Nascimento Padilha

Received: 05 January 2019 / Accepted: 06 February 2019 / Published: 11 February 2019

Abstract

Objective: To evaluate the craniofacial morphology of Japanese patients with unilateral cleft lip and palate and to evaluate the multiple congenital factors that affects craniofacial morphology in unilateral cleft lip and palate patients. **Material and Methods:** Lateral cephalograms of 140 subjects with unilateral cleft lip and palate were taken before any orthodontic treatment and alveolar bone graft. Subjects mean age was 6.85 ±1.56 years. Primary surgeries performed by surgeons from Hokkaido University Hospital. The craniofacial morphology of the 140 subjects was assessed by angular and linear cephalometric measurements. Gender, side of cleft, complete/incomplete type of cleft, presence/absence of lateral incisor in the affected side, family history of cleft and family history of skeletal Class III was chosen as congenital factors. To compare the assessments using congenital factors affecting craniofacial morphology in the unilateral cleft lip and palate subjects, angular and linear cephalometric measured values from each individual subject (control group) were converted into Z scores in relation to the means and standard deviation of the two parameters. **Results:** Twelve out of 13 craniofacial morphology outcomes were insignificant in 5 out of 6 dependent variables. Only 1 dependent variable showed 3/13 significant differences. **Conclusion:** Current study revealed the evidence that there were almost no significant differences in the craniofacial morphology outcome among various congenital factors. This will provide base line information and help determine the effectiveness of such factors.

Keywords: Congenital Abnormalities; Mouth Abnormalities; Cleft Palate; Cleft Lip.

CC BY

Introduction

Cleft deformities are included as global burden of disease, recognized by World Health Organization (WHO). Overall worldwide prevalence of cleft deformities is 1/600 new born babies. Foregoing studies assumed that both environmental and genetic factors are responsible for cleft lip and palate (CLP) [1,2]. In children with cleft lip and palate, dental anomalies are common than in the general population [3]. Treatment of CLP involves a multidisciplinary approach for a successful treatment outcome.

In our previous study, we explored multiple postnatal factors that affect craniofacial morphology (CM) in Japanese patients with unilateral cleft lip and palate (UCLP). We conclude that, in subjects treated by a modified Millard type of cheiloplasty, a two-stage palatoplasty, and a Hotz plate there were fewer adverse effects on craniofacial morphology [4,5].

Several studies and considerations on the impact of the primary operation, such as the type of cheiloplasty [6-15] and the type of palatoplasty [6-17] have been reported. The effect of preoperative orthopaedic plate was used or not have been reported too [5,7,16,18,19]. However, the cause of maxillary retrusion in UCLP patient is still debatable.

Many reports have been assessed the multiple congenital and postnatal factors that affect treatment outcome based of dental arch relationship of patients with UCLP [6-15]. As well as, several researches have been published about CM in patients with clefts [4,20,21], however, we know of no clinical research with large enough samples to take account of all congenital factors.

We have retrospectively assessed the CM of Japanese patients with UCLP and investigated the various congenital factors that affect craniofacial morphology in these patients. We hypothesize that there is no differences in the CM outcome of UCLP patient among various congenital factors.

Material and Methods

Study Design

In this retrospective study a chart review was carried out to ascertain the subjects with UCLP visited at the Hokkaido University Hospital Orthodontic Clinic, Japan.

Sampling

Initially 450 CLP (UCLP, bilateral CLP, cleft lip, and alveolus and isolated cleft palate) subjects were selected from the record archive. Of these, 165 subjects were non-syndromic UCLP. Following strict inclusion and exclusion criteria, finally 140 UCLP subjects were included in this study.

Appropriate sample size calculation was done using PS software. Prior data indicate that the difference in the response of matched pairs is normally distributed with standard deviation 0.84. If the true difference in the mean response of matched pairs is 0.2, we will need to study 140 pairs of subjects to be able to reject the null hypothesis that this response disparities is zero with probability (power) 0.8. The Type I error probability related with this test of this null hypothesis is 0.05.

Hundred forty (140) lateral cephalogram of UCLP children and 382 lateral cephalogram of subjects with Angle Class I were used for the clinical investigation.

Data Collection

Subjects had undergone cheiloplasty and palatoplasty at the Hokkaido university hospital under the highly skilled specialist surgeon. Table 1 show the details about cheiloplasty and palatoplasty that used in this study [4]. Table 2 show the demographic data, selection criteria, congenital factors, details of control group and armamentarium. Figure 1 show the details of the measurements of CM outcome using lateral cephalogram.

Table 1. Particulars of cheiloplasty and palatoplasty.

Type of Surgery	N	Time of Surgery - Mean (SD)	Outcome
Modified Millard	60	5 (2) months	Favorable
Modified Millard with Vomer Flap	80	5 (2) months	Unfavorable
Pushback Alone	44	20 (3.1) months	Unfavorable
Pushback with Buccal Flap	83	18 (3.5) months	Unfavorable
Two-Stage Palatoplasty	13	20 (3.5) and 56 (10.7) months	Favorable

Table 2. Demographic data, selection criteria and armamentarium.

Information	Criteria	
Selection Guideline	Non-syndromic UCLP and had lip and palatoplasty repaired with no alveolar bone graft and no previous orthodontic treatment at Hokkaido University Hospital.	
Study Design	Retrospective study	
Sample Selection	450 Japanese cleft lip and palate patients were assessed for eligibility. 165 patients were assessed eligible as nonsyndromic UCLP. 25 patients were excluded due to incomplete records. Finally, 140 nonsyndromic UCLP patient were selected.	
Gestation Period (Mean)	274 days	
Weight at Birth (Mean)	3012 Gram	
	Congenital Factors	
Gender	Male = 76	Female = 64
UCLP Affected Side	Right = 38	Left = 102
UCLP Types	Complete = 97	Incomplete = 43
Upper Lateral Incisor on the Cleft Side	Missing = 65	Present = 75
Family History of Cleft	Positive = 20	Negative = 120
Family History of Skeletal Class III	Positive = 24	Negative = 116
Age (Mean and SD)	6.85 ±1.56	
Control Group	382 subjects with Angle Class I	
Armamentarium	1) Lateral cephalograms; 2) Panoramic radiographs; 3) Dental (periapical) radiographs; 4) Logitec Digitizer Mypad-A3 Model K- 510 (Kanto Denshi Corporation, Tokyo, Japan); 5) Statistical Package for the Social Sciences, v. 22 (IBM Corp., Armonk, NY, USA).	

Single calibrated investigator traced the Cephalograms and all landmarks were marked on tracing paper for digital analysis (Logitec Digitizer Mypad-A3 Model K-510, Kanto Denshi Corporation, Tokyo, Japan). Twenty randomly selected cephalograms were traced and digitized at 1 month's intervals for the error measurements.

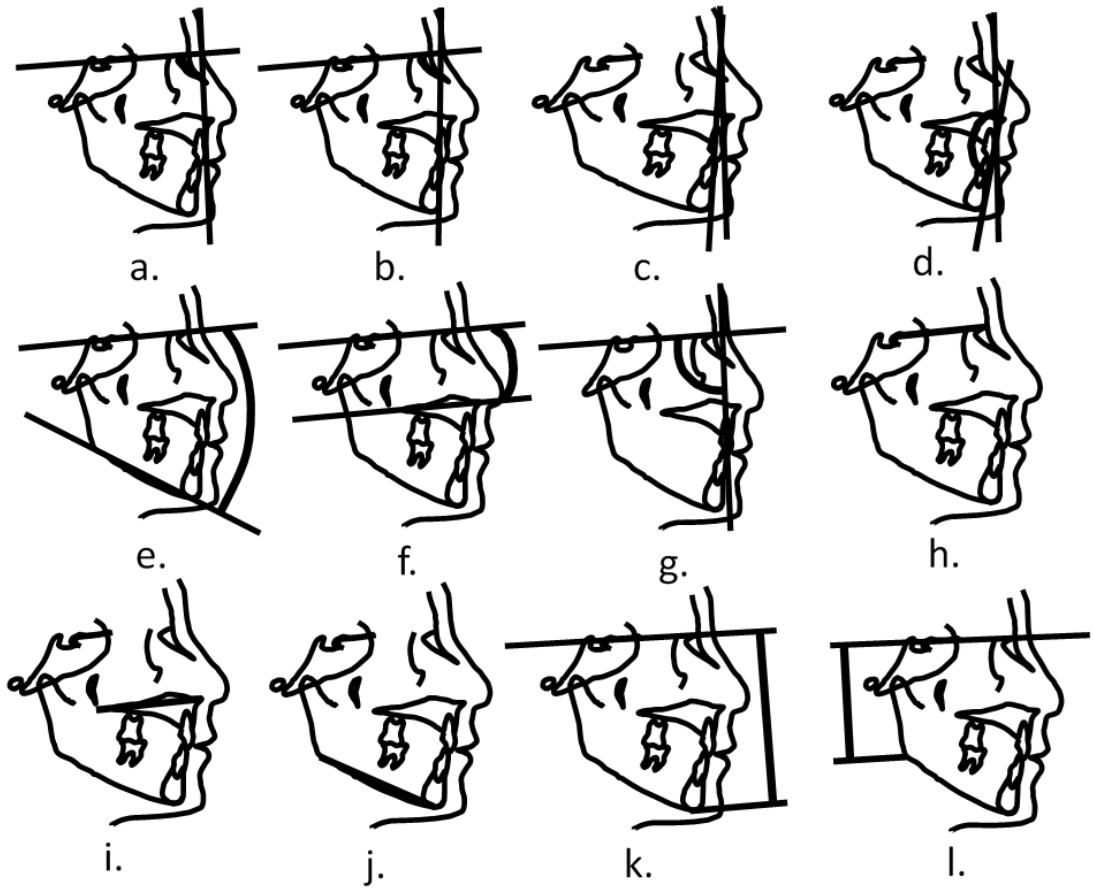

Figure 1. Cephalometric angular and linear measurements: a) SNA: Sella-Nasion-Point A; b) SNB: Sella-Nasion-Point B; c) ANB: Nasion-Point A/Nasion-Point B; d) N-A-Pog: Nasion-Point A-Pogonion; e) SN-MP: Sella-Nasion/Gonion-Menton; f) SN-NF: Sella-Nasion/ANS-PNS; g) U1-SN: Upper Incisor/Sella-Nasion; h) S-N: Sella-Nasion; i) ANS-PNS: Anterior Nasal Spine-Posterior Nasal Spine; j) Go-Pog: Gonion-Pogonion; k) ANT. HT: Me perpendicular to Sella-Nasion; l) POST. HT: Go perpendicular to Sella-Nasion.

Data Analysis

To compare the assessments using congenital factors in the UCLP subjects, all measured values for a subject were converted into Z scores in relation to the means and standard deviations of the two parameters in the Angle Class I subjects. The values of cephalometric measurements depended on the age and sex of the subjects in the 382 Angle Class I subjects. The Z score was calculated with the following formula: Z score (X) = (X - **X**) / SD

Where X is the measured value of UCLP subject, and **X** and SD are the mean and standard deviation of the Class I subjects. Using Z scores, the allocation in the congenital factors were compared for the UCLP subjects.

For error measurements, Dalhberg's formula, ME = $\sqrt{\Sigma}$(x1-x2)2/2n was used to establish the disparity between 2 measurements made at least a month apart. In which x1 was the first measurement, x2 was the second measurement, and n the number of repeated records.

Unpaired t test was used for comparison. All analyses were carried out using IBM SPSS Statistics for Windows Software, version 22 (IBM Corp., Armonk, NY, USA), with a 0.05 probability level considered statistically significant.

Ethical Aspects

Permission was obtained from Institutional Ethics and Research Advisory Committee, Hokkaido University Hospital. Informed consent was obtained from all the subjects.

Results

Congenital factors affecting CM of 140 Japanese patients with UCLP were assessed at Hokkaido University and compared the assessments using congenital factors in the UCLP subjects. 0.13 degrees to 0.83 degrees of combined error for the angular measurements, and from 0.10 mm to 0.35 mm for the linear measurements were found.

Male vs Female UCLP Patient

Figure 2 shows the mean and standard deviation of the Z score of the angular and linear measurements for the male and female patient. Significantly better facial convexity (NA-POG, p=0.003) was found in the male patient.

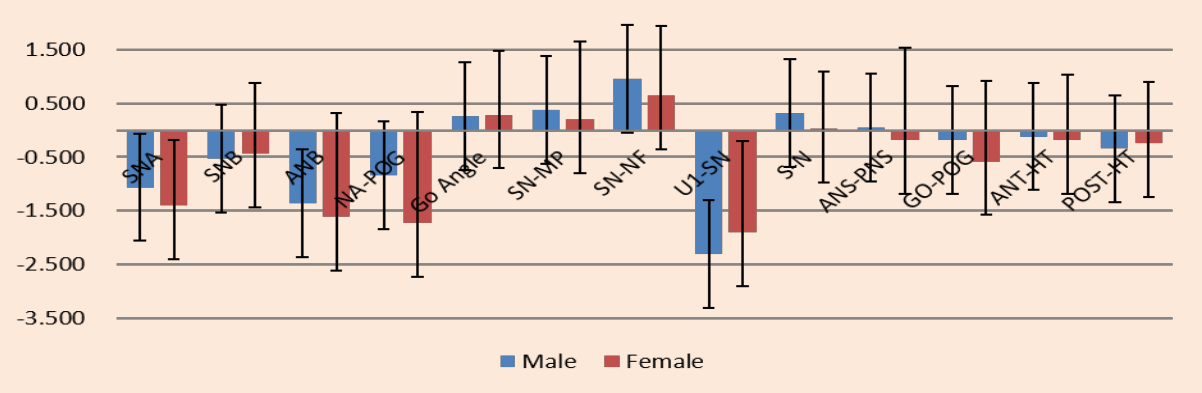

Figure 2. Comparison of Z score and SD values of male vs female patient.

Right vs Left Side of the UCLP Patient

Figure 3 shows the mean and standard deviation of the Z score of the angular and linear measurements for the right and left sided UCLP patient. Significantly better maxilla-mandibular relation (ANB, p=0.048) was found in the left sided UCLP patient.

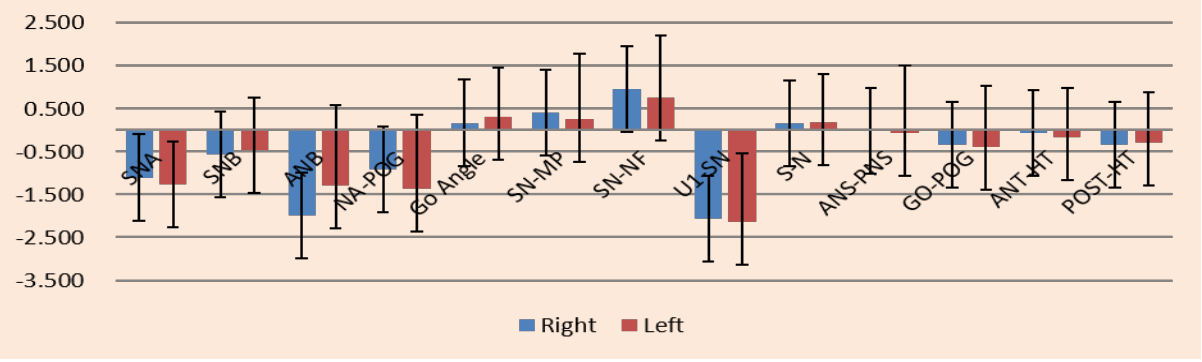

Figure 3. Comparison of Z score and SD values of right vs left side of the patient.

Complete vs Incomplete Type of UCLP Patient

Figure 4 shows the mean and standard deviation of the Z score of the angular and linear measurements for the complete and incomplete type UCLP patient. Significantly less inclined palatal plane (SN-NF, p=0.013) were found in the complete type UCLP patient.

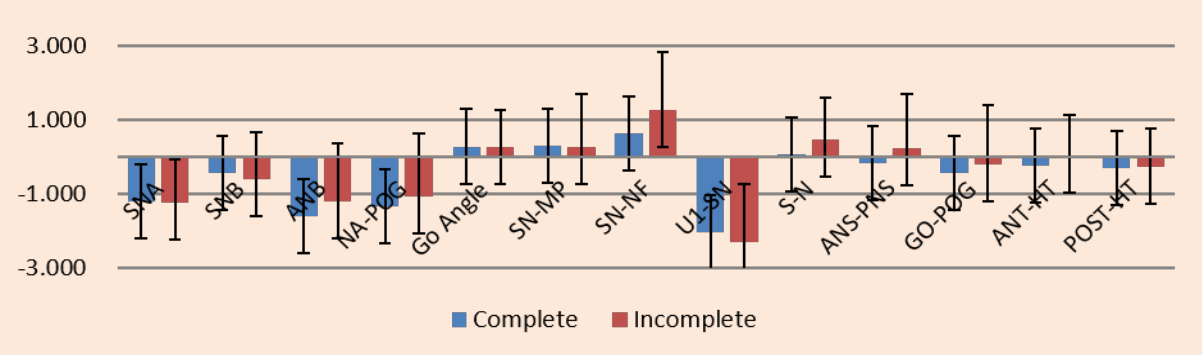

Figure 4. Comparison of Z score and SD values of complete vs incomplete UCLP.

Missing vs Presence of Lateral Incisor in the Affected Side of UCLP Patient

Figure 5 shows the mean and standard deviation of the Z score of the angular and linear measurements for the missing and presence of lateral incisor in the affected side of UCLP patient. Significantly better mandibular body length (Go-POG, p=0.044) was found in the presence of lateral incisor group of UCLP patient.

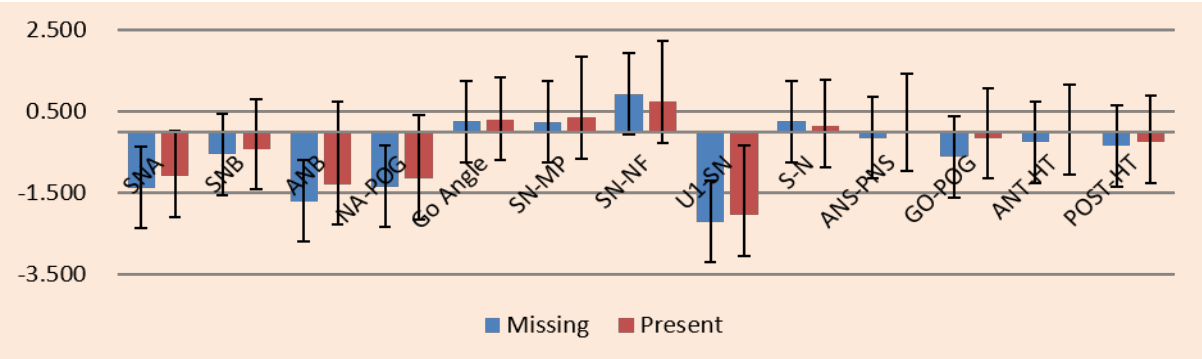

Figure 5. Comparison of Z score and SD values of missing vs presence of lateral incisor in the affected side of UCLP.

Family History of Cleft, Positive vs Negative Type of UCLP Patient

Figure 6 shows the mean and standard deviation of the Z score of the angular and linear measurements for the family history positive and negative type of UCLP patient. Significantly better mandibular relation (SNB, p=0.040) and posterior facial height (POSTHT, p=0.033) and significantly less facial convexity (NA-POG, p=0.039) were found in the negative family history of UCLP patient.

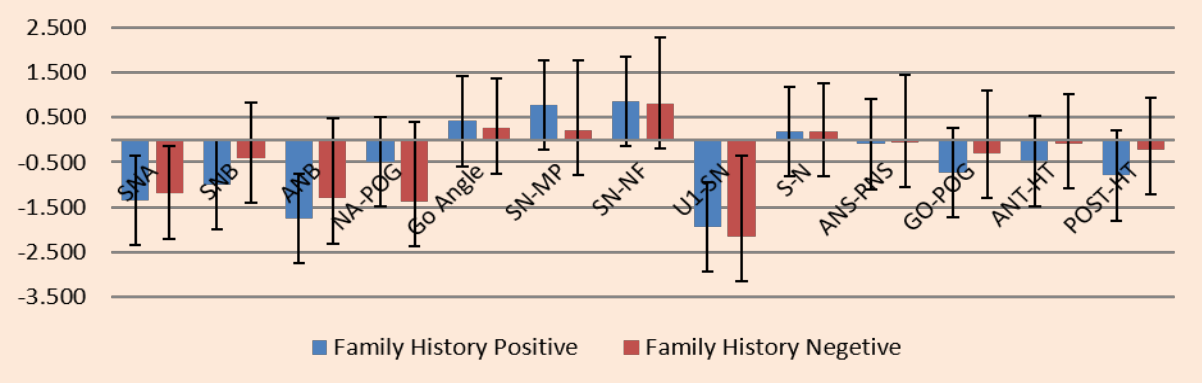

Figure 6. Comparison of Z score and SD values of family history of cleft, positive vs negative.

Family History of Class III, Positive vs Negative Type of UCLP Patient

Figure 7 shows the mean and standard deviation of the Z score of the angular and linear measurements for the family history of Class III, positive and negative type of UCLP patient. Significantly better mandibular relation (SNB, p=0.035) was found in the positive family history of Class III UCLP patient.

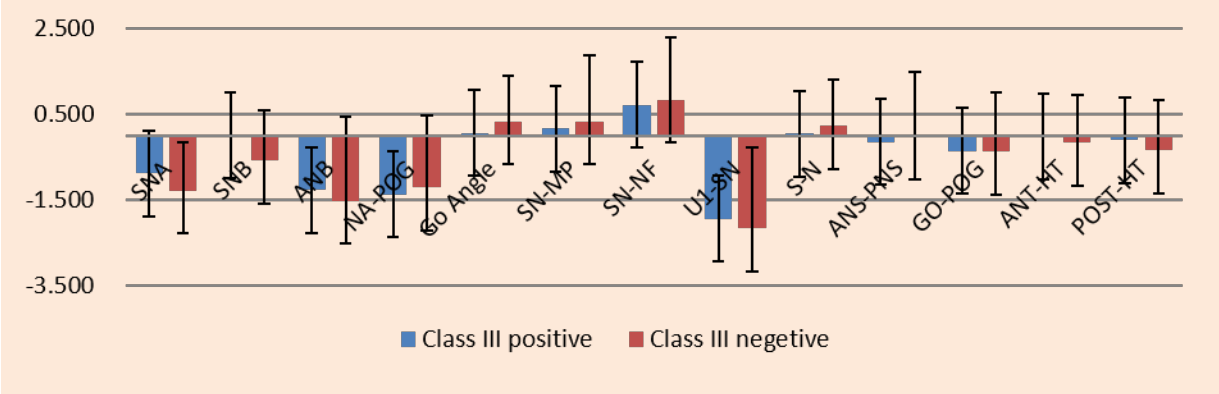

Figure 7. Comparison of Z score and SD values of family history of Class III, positive vs negative.

Discussion

According to literature, CLP has been extensively documented as one of the most commonly occurring hereditary orofacial birth defects [22]. Regarding the general birth defects world widely, it has been documented as the 2nd most common [23]. Contemporarily, it has also been deemed as the most common non-syndromic craniofacial defect [24]. An overall incidence ratio of approximately 1.30:1000 among Asian population has been published [25]. Regarding non-syndromic clefts 1.41:1000 in Japanese, 1.21:1000 in Chinese and 1.25:1000 in other Asian populations have been documented [25]. However, significant heterogeneity among different ethnicities has been computed [26].

Novelty of this research, we realize of no clinical researches with large enough samples to take account of all these congenital factors and the CM of UCLP children till to date. The great epidemiological benefit of our UCLP children is that all their cheiloplasty and palatoplasty were done at the same university hospital, not several hospitals, by surgeons with similar skill who were

using the same practice for each surgery. We cannot say whether analogous findings might be attained from other patients with UCLP. It might be useful to carry out such study in groups from other hospitals. As, this field of research remains unexhausted and ever growing towards improvement of patient care and quality of life. Despite of being one of the most common orofacial birth defects, even a single study has not been conducted on any population to assess the CM outcome in relation to congenital factors that are under practice. That led us to the comparison of established outcome with the surveys of treatment outcome based on dental arch relationship [5,7-15,27] and postnatal treatment factors [4] in other geographical locations.

Z score results of Figures 2 to 7 showed, compared with the control subjects, maxilla, mandible, maxilla-mandibular relation and upper incisor inclination are lesser in UCLP children. However, vertical analysis (Go-Pog, SN-MP and SN-NF) showed greater value compare to the control group. Other values were comparable with the control group.

In our previous study, we assessed the postnatal treatment factors affecting CM in Japanese UCLP subjects [4]. The results revealed, modified Millard cheiloplasty had significantly better maxillary growth in relation to the cranial base ($p = 0.004$), better jaw relations ($p = 0.005$), better facial convexity ($p = 0.002$), and better proclination of maxillary incisors ($p = 0.015$) compared to the subjects treated by modified Millard cheiloplasty with anterior hard palate closure with a vomer flap [4]. The results also revealed, subjects who had a two-stage palatoplasty had better maxillary growth and proclination of maxillary incisors and gave reliably better CM than other type of palatoplasty [4].

In the current study, our results showed, almost all CM outcomes have insignificant differences assessed by various congenital factors. However, male UCLP children had significantly better mandibular growth in relation to the facial plane (NA-Pog, $p = 0.003$) compared to female. This difference may be due to females have a comparatively higher rate of unfavourable growth, which has been previously reported in a study on Chinese population [28]. In another study, gender and growth outcome showed significant difference ($p=0.002$) in complete UCLP children. Females had 3.59 times higher odds of producing unfavourable growth outcome than male subjects [11].

Right-sided UCLP children had significantly smaller ANB value ($p = 0.048$) suggesting Class III/mandibular prognathism compared to left sided UCLP. Previous authors found patients who have right- sided UCLP were slightly correlated with favorable dental arch relationship, however, the association was not significant [5,13]. It is noteworthy to note that subjects who have a right-sided UCLP had favorable dental arch relationship. Future researches in a similar set-up from other hospital are needed to establish the cause [5,13].

Incomplete type UCLP children had significantly greater palatal inclination (SN-NF, $p = 0.013$) compared to complete type UCLP. Previous studies showed that complete type UCLP seemed to be correlate with unfavorable dental arch relationship [9,13]. Usually the treatment of the complete UCLP is more complex than the incomplete UCLP [9]. As both hard tissue and soft tissue structures of the soft palate, hard palate, alveolus, lip, and floor of the nostril are involved in

complete UCLP whereas an incomplete UCLP does not involve the floor of the nostril. Missing lateral incisor in the affected side of UCLP children had insignificant differences in 12/13 CM outcome. However, significantly lesser mandibular length (Go-Pog, p = 0.044) compared to presence of lateral incisor in the affected side of UCLP children was found. Foregoing studies also found no significant differences [5,7-15]. UCLP children with positive family history of cleft had significantly lesser mandibular growth (SNB, p = 0.040) and posterior facial height (p = 0.033) and greater mandibular growth in relation to the facial plane (NA-Pog, p = 0.039). Previous studies [5,7-15] evaluated treatment outcome based on dental arch relationship found no significant difference in relation to family history of cleft. These variations are may be due inequality in sample size.

UCLP children with positive family history of Class III had significantly better mandibular growth in relation to the cranial base (SNB, p = 0.040). Others authors also found subjects who had significant association with family history of skeletal Class III and unfavorable dental arch relationship [5,7,9,13]. These results revealed that cleft patients tend to develop Class III malocclusion not only as an effect of postnatal treatment factors but also due to the genetic influence of family history [5,7,9,13].

The design of present study limits the discussion to a specific cross-section of time. There is a need for longitudinal assessment of CLP from infancy to adulthood. The protocols should also include in-depth documentation and long-term follow-ups of the patients. To monitor the effects of treatments in relation to the initial set of complications and to assess the effects in the patterns of growth from young age to adulthood multiple additional factors are needed to be considered.

Conclusion

This study postulated evidence that there were almost no significant differences in the craniofacial morphology outcome among various congenital factors. Moreover, these differences are not related to the maxilla. Thus, null hypothesis is not rejected, as almost no significant differences of all dependent variables (gender, side of cleft, type of cleft, presence or missing lateral incisor in affected side, family history of cleft lip and palate and family history of Class III) with the craniofacial morphology outcome were detected.

Financial Support: None.

Conflict of Interest: The authors declare no conflicts of interest.

References

[1] Berkowitz S. Cleft Lip and Palate. 2nd. ed. Berlin: Springer-Verlag, 2006. p. 285-99, 395-404.

[2] Haque S, Alam MK, Basri R. Gene involvement in cleft lip and palate (CLP) patients. Bangladesh J Med Sci 2015; 14(1):113-6. https://doi.org/10.3329/bjms.v14i1.20928

[3] Haque S, Alam MK. Common dental anomalies in cleft lip and palate patients. Malays J Med Sci 2015; 22(2):55-60.

[4] Alam MK, Iida J, Sato Y, Kajii TS. Postnatal treatment factors affecting craniofacial morphology of unilateral cleft lip and palate (UCLP) patients in a Japanese population. Br J Oral Maxillofac Surg 2013; 51(8):e205-10. https://doi.org/10.1016/j.bjoms.2012.10.001

[5] Alam MK, Kajii TS, Koshikawa-Matsuno M, Yuki Sugawara-Kato, Yoshiaki Sato Y, Iida J. Multivariate analysis of factors affecting dental arch relationships in Japanese unilateral cleft lip and palate patients at Hokkaido University Hospital. Orthod Waves 2008; 67(2):45-53. https://doi.org/10.1016/j.odw.2007.12.001

[6] Haque S, Alam MK. Spectrum of cheiloplasty has detrimental effect on maxillary growth: Myth or fact? Bangladesh J Med Sci 2014; 13(4):473-6. https://doi.org/10.3329/bjms.v13i4.20653

[7] Kajii TS, Alam MK, Mikoya T, Oyama A, Koshikawa-Matsuno M, Sugawara-Kato Y, Yoshiaki Sato Y, Iida J. Congenital and postnatal factors inducing malocclusions in Japanese unilateral cleft lip and palate patients - determination using logistic regression analysis. Cleft Palate Craniofac J 2013; 50(4):466-72. https://doi.org/10.1597/11-150

[8] Yew CC, Alam MK, Rahman SA. Multivariate analysis on unilateral cleft lip and palate treatment outcome by EUROCRAN index: A retrospective study. Int J Ped Otorhinolaryngology 2016; 89:42-9. https://doi.org/10.1016/j.ijporl.2016.07.026

[9] Haque S, Alam MK, Khamis MF. Treatment outcome of Bangladeshi UCLP patients based on both phenotype and postnatal treatment factors using Modified Huddart Bodenham (mHB) Index. Cleft Palate Craniofac J 2016; 55(7):966-73. https://doi.org/10.1597/15-293

[10] Asif JA, Alam MK, Imanishi T, Mukai A, Yusa T, Haque S, Pohchi A. Treatment outcome and factors affecting dental arch relationship in Malay children with unilateral cleft lip and palate (UCLP). J Hard Tissue Biol 2016; 25(4):371-6. https://doi.org/10.2485/jhtb.25.371

[11] Arshad AI, Alam MK, Khamis MF. Assessment of complete unilateral cleft lip and palate patients: Determination of factors effecting dental arch relationships. Int J Pediatr Otorhinolaryngol 2017; 92:70-4. https://doi.org/10.1016/j.ijporl.2016.11.006

[12] Zin MNM, Alam MK, Haque S, Imanishi T, Toriya J, Osuga N, Razak NHA. The assessment of treatment outcome by evaluation of dental arch relationships in unilateral cleft lip and palate children using mHB scoring system. J Hard Tissue Biol 2017; 26(2):195-202. https://doi.org/10.2485/jhtb.26.195

[13] Haque S, Alam MK, Khamis MF. Factors responsible for unfavorable dental arch relationship in non syndromic unilateral cleft lip and palate children. J Clin Pediatr Dent 2017; 41(3):236-42. https://doi.org/10.17796/1053-4628-41.3.236

[14] Arshad AI, Alam MK, Khamis MF. Assessment of complete unilateral cleft lip and palate treatment outcome using EUROCRAN index and associated factors. Int J Pediatr Otorhinolaryngol 2017; 100:91-95. https://doi.org/10.1016/j.ijporl.2017.06.025

[15] Haque S, Alam MK, Khamis MF. The effect of various factors on the dental arch relationship in non-syndromic unilateral cleft lip and palate children assessed by new approach: A retrospective study. BMC Pediatr 2017; 17(1):119. https://doi.org/10.1186/s12887-017-0870-4

[16] Koshikawa-Matsuno M, Kajii TS, Alam MK, Sugawara-Kato Y, Iida J. The effects of palatoplasty and pre-surgical infant orthopedic treatment on occlusion in unilateral cleft lip and palate patients. Orthod Waves 2014; 73(4):114-20. https://doi.org/10.1016/j.odw.2014.06.006

[17] Haque S, Alam MK. Spectrum of palatoplasty has detrimental effect on maxillary growth: Myth or fact? Bangladesh J Med Sci 2015; 14(1):109-10. https://doi.org/10.3329/bjms.v14i1.20926

[18] Haque S, Alam MK. Pre-surgical orthopedic treatment using Hotz plate: An update. Int J Pharma Bio Sci 2015; 6(4):318-27.

[19] Bokhari S, Bokhari I, Qamaruddin I, Alam MK. Pre surgical nasoalveolar molding (PNAM) to reduce cleft severity in a nonsyndromic unilateral cleft lip and palate (UCLP) patient. Br J Med Med Res 2015; 8(12):1068-73. https://doi.org/10.9734/BJMMR/2015/18523

[20] Ross RB. Treatment variables affecting facial growth in complete unilateral cleft lip and palate. Cleft Palate J 1987; 24(1):5-77.

[21] Mølsted K, Asher-McDade C, Brattström V, Dahl E, Mars M, McWilliam J, et al. A six-center international study of treatment outcome in patients with clefts of the lip and palate. Part 2. Craniofacial form and soft tissue profile. Cleft Palate Craniofac J 1992; 29(5):398-404. https://doi.org/10.1597/1545-1569_1992_029_0398_asciso_2.3.co_2

[22] Murray JC. Face facts: Genes, environment, and clefts. Am J Hum Genet 1995; 57(2):227-32.
[23] Thong MK, Ho JJ, Khatijah NN. A population-based study of birth defects in Malaysia. Ann Hum Biol 2005; 32(2):180-7. https://doi.org/10.1080/03014460500075332
[24] Cardoso ML, Bezerra JF, Oliveira GH, Soares CD, Oliveira SR, de Souza KS, et al. MSX1 gene polymorphisms in non-syndromic cleft lip and/or palate. Oral Dis 2013; 19(5):507-12. https://doi.org/10.1111/odi.12033
[25] Cooper ME, Ratay JS, Marazita ML. Asian oral-facial cleft birth prevalence. Cleft Palate Craniofac J 2006; 43(5):580-9. https://doi.org/10.1597/05-167
[26] Schutte BC, Murray JC. The many faces and factors of orofacial clefts. Hum Mol Genet 1999; 8(10):1853-9.
[27] Haque S, Alam MK, Arshad AI. An overview of indices used to measure treatment effectiveness in patients with cleft lip and palate. Malays J Med Sci 2015; 22(1):4-11.
[28] Cooper ME, Stone RA, Liu YE, Hu DN, Melnick M, Marazita ML. Descriptive epidemiology of nonsyndromic cleft lip with or without cleft palate in Shanghai, China, from 1980 to 1989. Cleft Palate Craniofac J 2000; 37(3):274-80. https://doi.org/10.1597/1545-1569_2000_037_0274_deoncl_2.3.co_2