http:// ijp.mums.ac.ir
Original Article (Pages: 17737-15745)

Associated Congenital Heart Anomalies in Children with Cleft Lip and Palate: A Cross Sectional Study

Hassan Mottaghi Moghaddam Shahri[1], Mohsen Farzaneh[2], *Alireza Chamani[3], Arezoo Jahanbin[4]

[1] Pediatric department, Faculty of medicine, Mashhad University of medical sciences, Mashhad, Iran.

[2] Pediatric department, Faculty of medicine, Mashhad University of medical sciences, Mashhad, Iran.

[3] Department of Orthodontics, School of Dentistry, Zahedan University of Medical Sciences, Zahedan, Iran.

[4] Department of Orthodontics, School of Dentistry, Mashhad University of Medical Sciences, Mashhad, Iran.

Abstract

Background: Cleft lip and palate has a frequency of 1 per 700 live births, making it among the most prevalent orofacial congenital anomalies of the craniofacial region. Congenital heart disease is the most commonly associated disease with oral cleft. Hence, we have reviewed the association between heart disease and cleft lip and/or palate in the pediatric population.

Methods: In this cross-sectional study, the patients with oral clefts referring to the hospitals affiliated with the Mashhad University of Medical Sciences during 2015 to 2016 were evaluated. Demographic, clinical, and echocardiographic data were collected and analyzed statistically.

Results: One hundred twenty two patients with cleft lip and/or palate underwent echocardiography (49.2% males, 50.8% females). Based on Z-score outcomes, most of the patients with scores above zero had isolated cleft palate (63.6%). Patients with Z-scores of 0 to -1.3 and lower than -1.3 mostly had both cleft lip and palate (61.3%) or isolated cleft palate (55.5%), and these differences were significant (p=0.010). Furthermore, the frequency of the patients with Z-scores lower than zero was significantly higher in cleft lip and palate cases with congenital heart disease compared to non-congenital heart disease cases (43 vs. 19; p=0.002). The patients with pathologic symptoms in the physical examination were mainly diagnosed as abnormal based on their echocardiography (71.2%), and those without these symptoms were mainly diagnosed as normal based on their echocardiography (59.2%) with significant differences (p=0.001).

Conclusions: No significant difference was observed regarding the distribution of different types of congenital heart disease between the different types of cleft lip and/or palate.

Key Words: Cleft lip, Cleft palate, Congenital heart disease.

* Please cite this article as: Mottaghi Moghaddam Shahri H, Farzaneh M, Chamani A, Jahanbin A. Associated Congenital Heart Anomalies in Children with Cleft Lip and Palate: A Cross Sectional Study. Int J Pediatr 2022; 10 (4):15737-15745. DOI: **10.22038/ IJP.2021.60012.4666**

**** Corresponding Author:***

Alireza Chamani, Department of Orthodontics, School of Dentistry, Zahedan University of Medical Sciences, Zahedan, Iran. Email: Alireza.chamani72@yahoo.com

Received date: Sep.1,2021; Accepted date:Dec.27,2021

1- INTRODUCTION

Environmental, genetic, or idiopathic factors can lead to congenital abnormalities. Among the highly prevalent congenital disorders are orofacial anomalies including isolated cleft lip (CL), isolated cleft palate (CP), and cleft lip and palate (CLP) (1, 2). These orofacial anomalies are estimated to account for 1 out of every 500 to 1000 live births (3). Furthermore, Asian races are more prone to orofacial defects than other races and the least observed orofacial anomalies are among African races (4).

CL comprises 70% of all detected craniofacial anomalies and the incidence of CP and CLP without an association with another disease is lower than CL cases (5). Vallino-Napoli proposed that around 30% of orofacial anomalies occur coincidentally with other disorders (6). Around 300 syndromes have been found to present with a combination of an orofacial cleft and other congenital abnormalities (7). Beriaghi reported higher concomitant congenital malformations in CP than CLP (38.7% vs. 26.4%) (8). Natsume et al. reported the prevalence of coincident anomalies with CL, CLP, and CP to be 11.4%, 16.2%, and 20.7%, respectively (5). Sarkozi stated that 8 out of every 10 CP patients demonstrated no concomitant malformation (9).

Stoll et al. reported central nervous system anomalies to be the most commonly associated disorder with craniofacial disorder (10). However, Luijsterburg et al. found head and neck anomalies as the most commonly associated disorder with craniofacial disorders (11). Some studies reported musculoskeletal disorders to be the most commonly associated disorder in craniofacial defects (9, 12, 13). However, many other studies reported congenital heart disorders (CHDs) as the most commonly concomitant abnormality accompanying craniofacial defects (6, 14-17). The associated incidence of CHDs in orofacial clefts differs between various races. Shafi et al., in a study done on Pakistani children, found that around half of the children with orofacial defects suffered from CHDs (16), while Barbosa et al. reported this rate to be approximately 10% in Brazilian children (18). Another study in Taiwan reported a coincidence rate of 5.4% for craniofacial and cardiovascular anomalies (19) while Nancy et al. reported 6.7% (20).

As shown above, the literature has only reported the incidence rates, and we couldn't find any study comparing the different congenital abnormalities between the different types of orofacial clefts. Thus, in this study, we aimed to assess the distribution and coincidence of cardiac anomalies between different orofacial defects.

2- MATERIALS AND METHODS

In this cross-sectional study, we enrolled all isolated cleft lip, isolated cleft palate, and cleft lip and palate patients referring to hospitals affiliated with the Mashhad University of Medical Sciences between 2015 and 2016. The patients' records were extracted and the data was inserted into the researcher-made forms. The data comprised demographic features (age, gender, birth weight, and gestational age), type of orofacial cleft (isolated cleft lip, isolated cleft palate, or cleft lip and palate), presence or absence of auscultatory signs (e.g., murmurs or clicks) before echocardiography, presence or absence of congenital heart diseases, and the type of congenital heart disease.

The extracted data were entered into the software Statistical Package for Social Sciences (SPSS) version 20 for further analyses. After describing the quantitative statistics of frequencies and percentages, Chi-square test was used to compare the qualitative data. P-values under 0.05 were considered significant.

2-1. Ethical Considerations

All the patients' parents or guardians gave their written consent after the study method and goal were explained to them and their records were coded and kept confidential. All the stages of the study were based on the Helsinki Declaration. Furthermore, the Ethics Committee of the Mashhad University of Medical Sciences approved the protocol of the study (Research code: 931608).

3- RESULT

Totally, 122 cleft lip and/or palate patients were enrolled in the study. 49.2% of the patients were male and 49.2% were female. The mean age of the patients was 36.26 months. The most commonly found type of orofacial anomaly was isolated cleft palate (52.5%), and the least found was isolated cleft lip (8.2%). Most of the patients were in the age range of 0-12 months (73.8%) while the other patients were placed into the ≥73 month group (6.6%). Cardiac anomalies were found in 57.4% of the patients. **Table 1** shows the details of the above mentioned data. The patients also had a mean weight of 11.37 kg. According to the calculated Z-scores, the weight of 71 (58.2%) of the patients was more than the fiftieth percentile, 20 (16.4%) were between the tenth and the fiftieth percentiles, and 31 (25.4%) had a weigh less than the tenth percentile.

Table-1: The baseline frequencies of gender, type of orofacial cleft, age group, and cardiac anomalies

Variable		N (%)
Gender	Male	62 (50.8)
	Female	60 (49.2)
Type of cleft	Lip	10 (8.2)
	Palate	64 (52.5)
	Lip and palate	48 (39.3)
Age (months)	0-12	90 (73.8)
	13-24	9 (7.4)
	25-72	15 (12.3)
	≥73	8 (6.6)
Cardiac anomalies	Yes	70 (57.4)
	No	52 (42.6)

Seventy (57.4%) of the patients had cardiac anomalies. The most common type of cardiac anomaly was ventricular septal defect (VSD) comprising 25 cases. The least found anomaly was atrioventricular septal defect (AVSD) comprising only 3 cases. Furthermore, there was no significant difference regarding the type of cardiac anomalies between different orofacial clefts ($p>0.05$). **Table 2** shows the details of the comparison of cardiac anomalies between different craniofacial defects.

Table 3 shows the comparison of age, gender, and birth weight Z-score between the different types of orofacial clefts. No significant difference was found regarding the age between different types of clefts ($p=0.577$); however, the differences regarding the gender were significant ($p=0.019$). Most of the females had isolated cleft palate (61.3%) and most of the males had cleft lip and palate (51.7%). In addition, no significant difference was revealed regarding the birth weight Z-score between different orofacial defects (p-value=0.010). The highest frequency of

birth weight Z-score in the ≥0 group was found in the isolated cleft palate group (63.6%), in the 0 to -1.3 group the highest frequency was in the cleft lip and palate (61.3%), and in ≤ -1.3 the highest frequency was in the isolated cleft palate group (55.5%). **Table 3** shows the above mentioned comparisons.

Table-2: The comparison of cardiac anomalies between different craniofacial problems

Variable		CL* N (%)	CP* N (%)	CLP* N (%)	Total N (%)	P-value*
VSD	Yes	1 (4)	14 (56)	10 (40)	25 (20.5)	0.686
	No	9 (9.3)	50 (51.5)	38 (39.2)	97 (79.5)	
ASD	Yes	0	8 (52.3)	7 (46.7)	15 (12.3)	0.441
	No	10 (9.3)	56 (52.3)	41 (38.3)	107 (87.7)	
AS	Yes	1 (20)	3 (60)	1 (20)	5 (4.1)	0.487
	No	9 (7.7)	61 (52.1)	47 (40.2)	117 (95.9)	
TOF	Yes	1 (11.1)	5 (55.6)	3 (33.3)	9 (7.4)	0.901
	No	9 (8)	59 (52.2)	45 (39.8)	113 (92.6)	
PS	Yes	3 (15.8)	9 (47.4)	7 (36.8)	19 (15.6)	0.421
	No	7 (6.8)	55 (53.4)	41 (39.8)	103 (84.4)	
PDA	Yes	1 (5.9)	10 (58.8)	6 (35.3)	17 (13.9)	0.834
	No	9 (8.6)	54 (51.4)	42 (40)	105 (86.1)	
DORV	Yes	0	3 (100)	0	3 (2.5)	0.248
	No	10 (8.4)	61 (51.3)	48 (40.3)	119 (97.5)	
AVSD	Yes	0	1 (33.3)	2 (66.7)	3 (2.5)	0.592
	No	10 (8.4)	63 (52.9)	46 (38.7)	119 (97.5)	

Table-3: The comparison of age, gender, and birth weight Z-scores between different orofacial problems

Variable		CL N (%)	CP N (%)	CLP N (%)	P-value
Age group	0-12	9 (10)	44 (48.9)	37 (4.1)	0.577
	13-24	0	7 (77.8)	2 (22.2)	
	25-72	0	9 (60)	6 (40)	
	≥73	1 (12.5)	4 (50)	3 (37.5)	
Gender	Female	7 (11.3)	38 (61.3)	17 (27.4)	0.019
	Male	3 (5)	26 (43.3)	31 (51.7)	
Birth weight Z-score	≥0	3 (13.6)	14 (63.6)	5 (22.7)	0.010
	0 – -1.3	1 (3.2)	11 (35.5)	19 (61.3)	
	≤ -1.3	0	19 (55.5)	10 (34.5)	

The patients who had positive findings in their history and physical examination (71.2 %) also showed positive findings in their echocardiography. However, around 40% of the patients without notable findings in their history and physical examination, had positive findings in their echocardiography (**Table 4**).

The differences were significant ($p<0.001$). History and physical examination had a sensitivity of 72% and specificity of 58% in detecting cardiac anomalies. Significant differences did not

exist regarding the positive pathologic findings in the history and physical examination between different types of orofacial clefts (p=0.761). The parents of 45 patients with cardiac abnormalities had consanguinity, while 23 patients with these abnormalities had no consanguinity, and the differences were significant (p=0.023).

Table-4: Comparing different cardiac anomalies between the patients having or not having pathologic findings in their history and physical examination

Variable		Pathologic findings in history and physical examination		P-value*
		Yes N (%)	No N (%)	
VSD	Yes	22 (88)	3 (12)	0.001
	No	51 (52.6)	46 (47.4)	
ASD	Yes	11 (73.3)	4 (26.7)	0.255
	No	62 (57.9)	45 (42.1)	
AS	Yes	5 (100)	0	0.061
	No	68 (58.1)	49 (41.9)	
TOF	Yes	6 (66.7)	3 (33.3)	0.664
	No	67 (59.3)	46 (40.7)	
PS	Yes	16 (84.2)	3 (15.8)	0.018
	No	57 (55.3)	46 (44.7)	
PDA	Yes	10 (58.8)	7 (41.2)	0.927
	No	63 (60)	42 (40)	
DORV	Yes	3 (100)	0	0.151
	No	70 (58.8)	49 (41.2)	
AVSD	Yes	1 (33.3)	2 (66.7)	0.343
	No	72 (60.5)	47 (39.5)	

Although significant differences existed regarding having or not having pathologic findings in the history and physical examination for ventricular septal defect (VSD) and pulmonary stenosis (PS) (p=0.001 and 0.018. respectively), no significant difference was found in regard to the other anomalies. Also, no significant difference existed regarding consanguinity between the different types of clefts (p=0.559). Furthermore, no significant difference was found regarding the family history between different types of orofacial clefts (p=0.868).

Table 5 presents the comparison of the anomalies other than cardiac problems between different orofacial defects. The orthopedic problems had the highest frequency in the CLP group, and the isolated cleft palate group had the second position in showing high pathologic findings. However, none of these differences were significant (p>0.05).

4- DISCUSSION

Orofacial clefts are reported to be the most common congenital anomaly and in some cases accompany the congenital heart disease. However, the prevalence rate of this anomaly is not exactly known. Studies propose varying ranges from 1.5% to 63% for orofacial anomalies and CHDs coincidence (21, 22). Assessment of the prevalence of cardiac anomalies accompanied with orofacial clefts is important, since it can help in developing new protocols for screening and improving the existing ones.

We found that 57.4% (70.12) of cleft lip and/or palate patients had CHDs,

concurrently. Most of the patients with orofacial defects had isolated cleft palate while the most common cleft in males was cleft lip and palate. The most and the least common cardiac anomalies were VSD and AVSD, respectively. However, there was no notable statistical difference regarding the different cardiac anomalies between different orofacial clefts.

Table-5: Comparing the anomalies other than cardiac problems between different orofacial defects

Pathologic finding		CL N (%)	CP N (%)	CLP N (%)	P-value
Icterus	Yes	0	3 (100)	0	0.248
	No	10 (8.4)	61 (51.3)	48 (40.3)	
Seizure	Yes	0	0	2 (100)	0.209
	No	10 (38.3)	64 (53.3)	46 (38.3)	
Neurology	Yes	1 (25)	2 (50)	1 (25)	0.439
	No	9 (7.6)	62 (52.5)	47 (39.8)	
Orthopedics	Yes	1 (16.7)	2 (33.3)	3 (50)	0.556
	No	9 (7.8)	62 (53.4)	45 (38.8)	
ENT	Yes	0	7 (87.5)	1 (12.5)	0.118
	No	10 (8.8)	57 (50)	47 (41.2)	
Urogenital	Yes	1 (11.1)	4 (44.4)	4 (44.4)	0.868
	No	9 (8)	60 (53.1)	44 (38.9)	

Most of the patients with ≥0 Z-score had an isolated cleft palate. Patients with a Z-score between 0 and -1.3 had mainly cleft lip and palate, and those with a ≤ -1.3 Z-score were mostly cleft palate cases. No significant difference was found regarding the birth weight Z-score between different orofacial defects.

Similar to our results, Miri et al. reported the most common type of orofacial cleft to be the cleft palate (23). However, several other studies in Iran (24), Europe (25), Latin America (26), and India (27) proposed the cleft lip and palate to be the most frequent type. In our study, the cleft lip and palate was ranked second; and these differences may be due to different sample sizes in the studies. The importance of this epidemiologic finding is due to the fact that the isolated cleft lip and the cleft lip and palate can cause feeding problems. Thus, the high prevalence of these two problems is important.

Regarding the prevalence of CHD, different numbers have been reported. MO et al. reported a prevalence of 20% in 30 cases of isolated cleft lip and isolated cleft palate. Sun et al. reported a prevalence of 26% for orofacial cleft and CHD coincidence among 2180 studied cases (28). A study by Altunhan et al. in Turkey proposed a prevalence of 66% (29). Another study done on a US population reported a prevalence of 32.2% (8). The reported prevalence in Australia (6) was 33.3%, and in Taiwan (30) it was 56%.

Our study found VSD to be the most prevalent type of accompanying cardiac anomaly. However, many other studies proposed ASD to be the most common type of CHD accompanying orofacial problems (14, 28, 31-34). Two similar studies in France (35) and Japan (36) proposed VSD to be the most frequent type of cardiac anomaly in patients with orofacial clefts. However, we found no significant difference regarding the different types of cardiac anomalies

between CP, CL, and CLP patients. Furthermore, there were no significant differences in cases of other anomalies including neurology, orthopedic, ENT, and urogenital problems.

Most of the patients (71.2 %) who had positive findings in their history and physical examination also showed positive findings in their echocardiography. However, only around 40% of the patients without notable findings in their history and physical examination, had positive findings in their echocardiography. The specificity and sensitivity of echocardiography in detecting associated cardiac anomalies were 72% and 58%, respectively; hence, the reported specificity and sensitivity were not enough to detect cardiac problems.

In short, CHDs are common congenital problems associated with craniofacial anomalies and hence, it is advisable that the patients be screened for cardiac problems. However, echocardiography could not satisfactorily fulfill the criteria for being a great screening tool. History and physical examination also missed 20 out of 122 patients. Thus, it seems that developing superior screening methods is required.

4-1. Limitations of the study

Our study, similar to other studies, had some limitations. One of them was its retrospective manner. Furthermore, we only had access to the data of a few health centers, and the causes of accompanying cardiac diseases with orofacial clefts remained unknown.

5- CONCLUSION

The aim of this study was to define the prevalence of the association of CHDs with orofacial clefts. We found that around 1 out of 2 patients with cleft lip and/or palate had some type of CHD. However, no statistical difference regarding the type of CHDs between different orofacial clefts was found.

6- REFERENCES

1. Brent RL. Environmental causes of human congenital malformations: the pediatrician's role in dealing with these complex clinical problems caused by a multiplicity of environmental and genetic factors. Pediatrics-English Edition. 2004; 113(4):957-68.

2. Francine R, Pascale S, Aline1a H. Congenital anomalies: prevalence and risk factors. Universal Journal of Public Health. 2014; 2(2):58-63.

3. Cooper ME, Ratay JS, Marazita ML. Asian oral-facial cleft birth prevalence. The Cleft palate-craniofacial journal. 2006; 43(5):580-9.

4. Vanderas AP. Incidence of cleft lip, cleft palate, and cleft lip and palate among races: a review. Cleft palate J. 1987; 24(3):216-25.

5. Friedman MA, Miletta N, Roe C, Wang D, Morrow BE, Kates WR, et al. Cleft palate, retrognathia and congenital heart disease in velo-cardio-facial syndrome: A phenotype correlation study. International Journal of Pediatric Otorhinolaryngology. 2011; 75(9):1167-72.

6. Vallino-Napoli LD, Riley MM, Halliday JL. An Epidemiologic Study of Orofacial Clefts with Other Birth Defects in Victoria, Australia. The Cleft Palate-Craniofacial Journal. 2006; 43(5):571-6.

7. Tremlett M. Anaesthesia for cleft lip and palate surgery. Current Anaesthesia & Critical Care. 2004; 15(4):309-16.

8. Beriaghi S, Myers S, Jensen S, Kaimal S, Chan C, Schaefer GB. Cleft lip and palate: association with other congenital malformations. Journal of Clinical Pediatric Dentistry. 2009; 33(3):207-10.

9. Sárközi A, Wyszynski DF, Czeizel AE. Oral clefts with associated anomalies: findings in the Hungarian Congenital Abnormality Registry. BMC Oral Health. 2005; 5(1):4.

10. Stoll C, Alembik Y, Dott B, Roth MP. Associated Malformations in Cases with Oral Clefts. The Cleft Palate-Craniofacial Journal. 2000; 37(1):41-7.

11. Luijsterburg AJM, Vermeij-Keers C. Ten Years Recording Common Oral Clefts with a New Descriptive System. The Cleft Palate-Craniofacial Journal. 2011; 48(2):173-82.

12. Mueller AA, Sader R, Honigmann K, Zeilhofer HF, Schwenzer-Zimmerer K. Central nervous malformations in presence of clefts reflect developmental interplay. International Journal of Oral and Maxillofacial Surgery. 2007; 36(4): 289-95.

13. Hagberg C, Larson O, Milerad J. Incidence of Cleft Lip and Palate and Risks of Additional Malformations. The Cleft Palate-Craniofacial Journal. 1998; 35(1): 40-5.

14. Rawashdeh MaA, Jawdat Abu-Hawas B. Congenital Associated Malformations in a Sample of Jordanian Patients With Cleft Lip and Palate. Journal of Oral and Maxillofacial Surgery. 2008; 66(10):2035-41.

15. Milerad J, Larson O, Hagberg C, Ideberg M. Associated Malformations in Infants With Cleft Lip and Palate: A Prospective, Population-based Study. Pediatrics. 1997; 100(2):180.

16. Shafi T, Khan MR, Atiq M. Congenital heart disease and associated malformations in children with cleft lip and palate in Pakistan. British Journal of Plastic Surgery. 2003; 56(2):106-9.

17. Aqrabawi HE. Facial cleft and associated anomalies: incidence among infants at a Jordanian medical centre. East Mediterr Health J. 2008; 14(2):356-9.

18. Barbosa MM, Rocha CMG, Katina T, Caldas M, Codorniz A, Medeiros C. Prevalence of Congenital Heart Diseases in Oral Cleft Patients. Pediatric Cardiology. 2003; 24(4):369-74.

19. Munabi NC, Swanson J, Auslander A, Sanchez-Lara PA, Ward SLD, Magee III WP. The Prevalence of Congenital Heart Disease in Nonsyndromic Cleft Lip and/or Palate: A Systematic Review of the Literature. Annals of plastic surgery. 2017; 79(2):214-20.

20. Geis N, Seto B, Bartoshesky L, Lewis M, Pashayan H. The prevalence of congenital heart disease among the population of a metropolitan cleft lip and palate clinic. The Cleft palate journal. 1981; 18(1):19-23.

21. Yi N, Yeow V, Lee S. Epidemiology of cleft lip and palate in Singapore--a 10-year hospital-based study. Annals of the Academy of Medicine, Singapore. 1999; 28(5):655-9.

22. Shprintzen RJ, Siegel-Sadewitz VL, Amato J, Goldberg RB, Opitz JM, Reynolds JF. Anomalies associated with cleft lip, cleft palate, or both. American journal of medical genetics. 1985; 20(4):585-95.

23. MIRI S, Kiani A, Mehrabi V. Do Cleft Lip/And Or Palate Patients Need the Cardiologist Consultation before the Surgery? 2004.

24. Nahvi H, Mollaeian M, Kazemian F, Hoseinpoor M, Keiani A, Khatami F, et al. Congenital heart defects in children with oral clefts. Tehran University Medical Journal. 2007; 65(6):60-4.

25. Derijcke A, Eerens A, Carels C. The incidence of oral clefts: a review. British Journal of Oral and Maxillofacial Surgery. 1996; 34(6):488-94.

26. Menegotto BG, Salzano FM. Epidemiology of oral clefts in a large South American sample. The Cleft Palate-Craniofacial Journal. 1991; 28(4):373-7.

27. Eckstein DA, Wu RL, Akinbiyi T, Silver L, Taub PJ. Measuring quality of life in cleft lip and palate patients: currently available patient-reported outcomes measures. Plastic and reconstructive surgery. 2011; 128(5):518e-26e.

28. Sun T, Tian H, Wang C, Yin P, Zhu Y, Chen X, et al. A survey of congenital heart disease and other organic malformations associated with different types of orofacial clefts in Eastern China. PloS one. 2013; 8(1):e54726.

29. Altunhan H, Annagür A, Konak M, Ertuğrul S, Örs R, Koç H. The incidence of congenital anomalies associated with cleft palate/cleft lip and palate in neonates in the Konya region, Turkey. British Journal of Oral and Maxillofacial Surgery. 2012; 50(6):541-4.

30. Liang C-D, Huang S-C, Lai J-P. A survey of congenital heart disease in patients with oral clefts. Acta paediatrica Taiwanica= Taiwan er ke yi xue hui za zhi. 1999; 40(6):414-7.

31. Barbosa M, Rocha C, Katina T, Caldas M, Codorniz A, Medeiros C. Prevalence of congenital heart diseases in oral cleft patients. Pediatric cardiology. 2003; 24(4):369-74.

32. Lee CW, Hwang SM, Lee YS, Kim M-A, Seo K. Prevalence of orofacial clefts in Korean live births. Obstetrics & gynecology science. 2015; 58(3):196-202.

33. Wichajarn K, Panamonta O, Pradubwong S, Panamonta M, Weraarchakul W, Chowchuen B. Prevalence and type of associated syndromes in patients with cleft lip and cleft palate who received the treatment in Tawanchai Center until 4-5 years of age. J Med Assoc Thai. 2014; 97(Suppl 10):S105-9.

34. Liang CD, Huang SC, Lai JP. A survey of congenital heart disease in patients with oral clefts. Acta Paediatr Taiwan. 1999; 40(6):414-7.

35. Stoll C, Alembik Y, Dott B, Roth MP. Epidemiological and genetic study in 207 cases of oral clefts in Alsace, north-eastern France. Journal of Medical Genetics. 1991; 28(5):325.

36. Natsume N, Niimi T, Furukawa H, Kawai T, Ogi N, Suzuki Y, et al. Survey of congenital anomalies associated with cleft lip and/or palate in 701,181 Japanese people. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology. 2001; 91(2):157-61.