Original Article

Congenital Heart Diseases and Associated Malformations in Children with Cleft Lip and Palate: A Single-Center Study

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ABSTRACT

Background: Congenital heart disease (CHD) is the most common congenital anomaly worldwide, while cleft lip and/or palate (CLP) represents one of the most frequent craniofacial malformations. Several international studies have reported an increased frequency of CHD and other associated anomalies among children with CLP, suggesting shared genetic and environmental mechanisms. The objective of this study was to determine the frequency and pattern of congenital heart disease and associated malformations in children with cleft lip and/or palate compared with children without orofacial clefts.

Methods: This retrospective case-control study was conducted at a tertiary care cardiac center from September 2021 to September 2024. A total of 646 infants aged less than one year were included, comprising 323 children with CLP (study group) and 323 age- and sex-matched children without orofacial clefts (control group). All participants underwent echocardiographic evaluation. Congenital heart diseases were classified as cyanotic or non-cyanotic, while patent foramen ovale was recorded separately. Demographic variables, risk factors, and associated non-cardiac anomalies were analyzed using Chi-square and Fisher's exact tests.

Results: Congenital heart disease was significantly more frequent in children with CLP compared to controls (27% vs. 5%, p-value<0.001). Non-cyanotic CHDs, particularly septal defects, were the most common. Associated non-cardiac anomalies were observed in 36% of the study group versus 7% of controls (p-value <0.001). Parental consanguinity and maternal smoking were significantly associated with CLP and CHD.

Conclusion: Children with cleft lip and/or palate have a significantly increased risk of congenital heart disease and associated malformations. Early echocardiographic screening and comprehensive evaluation are recommended to improve clinical outcomes in this high-risk population.

Keywords: Cleft lip; Cleft palate; Heart defects; Congenital; Risk factors

INTRODUCTION

Congenital heart diseases (CHD) and orofacial clefts, particularly cleft lip and/or palate (CLP), are among the most frequently reported congenital anomalies worldwide. The global incidence of CHD is approximately 8 per 1,000 live births.[1] Orofacial clefts occur in nearly 1 in 700 live births and represent a major public health concern due to their functional, aesthetic, and psychosocial implications.[2,3] When present together, these anomalies significantly increase morbidity and complicate surgical and medical management.[4] In general, children with isolated cleft palate have fewer associated malformations, whereas those with cleft lip and palate exhibit a higher burden of systemic anomalies.[5]

Several international and regional studies have demonstrated a significantly increased prevalence of congenital heart defects in children with CLP, suggesting a shared genetic susceptibility and common environmental risk factors.[6] Septal defects, including atrial septal defect and ventricular septal defect, followed by patent ductus arteriosus and more complex lesions such as tetralogy of Fallot, are the most commonly reported cardiac anomalies in this population.[7] If these cardiac malformations remain undiagnosed in early infancy, they may delay corrective surgery for cleft repair and adversely affect long-term outcomes.

In Pakistan and other South Asian countries, the burden of congenital anomalies is expected to be higher due to the high prevalence of consanguineous marriages, limited prenatal screening, and suboptimal maternal healthcare services.[8] Locoregional studies have reported a notable association between CLP and CHD, yet compre-

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hensive comparative data remain scarce. Therefore, this study determined the frequency of congenital heart disease and associated anomalies in children with cleft lip and/or palate at a tertiary care hospital in Bahawalpur, Pakistan, and compared these findings with a control group of children without orofacial clefts to identify significant differences in risk factors and outcomes

PATIENTS AND METHODS

This retrospective case-control study was conducted at the Department of Pediatric Cardiology, Cardiac Centre, Bahawal Victoria Hospital, Bahawalpur, from September 2021 to September 2024. Victoria Hospital, Bahawalpur, is a tertiary care referral center serving the population of South Punjab. Before data collection, ethical approval (Ref. No. 2463/DME/QAMC/BWP, dated June 13, 2024) was obtained from the Institutional Review Board of Bahawal Victoria Hospital, Bahawalpur. Informed consent was obtained from the parents or the legal guardians of the participants.

Medical records of children aged less than one year were reviewed. The case group consisted of children diagnosed with cleft lip, cleft palate, or cleft lip with palate who were referred for cardiac evaluation during the study period. The control group included children without orofacial clefts who underwent echocardiographic evaluation during the same period for clinical indications such as cardiac murmur, poor weight gain, or preoperative assessment for non-cardiac surgery. Controls were frequency-matched to the study group on age and gender.

Children with surgically repaired clefts, incomplete medical records, missing echocardiographic data, or recognized genetic syndromes unrelated to clefting or congenital heart disease were excluded. The sample size for comparing two independent proportions was calculated using the formula described by Lemeshow et al. in the WHO manual "Adequacy of Sample Size in Health Studies." The calculation was based on an expected prevalence of congenital heart disease of 27% among children with cleft lip and/or palate and 5% among controls[9], with a two-sided alpha of 0.05 and power of 80%. The required minimum sample size per group was calculated. Our final analysed enrolled sample of 323 participants per group exceeded this requirement.

Data were collected using a structured data extraction proforma designed for this study. Recorded variables included demographic characteristics such as age and gender, type and severity of cleft anomaly, echocardiographic findings, classification of congenital heart disease, presence of pulmonary hypertension, associated non-cardiac anomalies, and potential risk factors including parental consanguinity, maternal smoking, and maternal age. Cleft anomalies were categorized based on clinical examination and surgical records into isolated cleft lip, isolated cleft palate, and cleft lip with palate. The severity of clefting was assessed clinically based on the laterality of lip involvement and the extent of palatal involvement.

All children underwent transthoracic echocardiography using a Vivid E95 echocardiography machine performed by a consultant pediatric cardiologist. Congenital heart diseases were classified according to clinical presentation into cyanotic and non-cyanotic types. Non-cyanotic congenital heart diseases included atrial septal defect, ventricular septal defect, patent ductus arteriosus, and pulmonary stenosis, while cyanotic congenital heart diseases included tetralogy of Fallot and double outlet right ventricle. Congenital heart diseases were also categorized according to developmental type into septal defects, outflow tract abnormalities, and complex cardiac malformations. Patent foramen ovale was recorded separately as an echocardiographic finding and was not considered a structural congenital heart disease for primary analysis.

Data were stratified according to the type and severity of cleft anomaly, cyanotic versus non-cyanotic congenital heart disease, and gender distribution to assess potential associations. In addition to cardiac anomalies, associated non-cardiac anomalies were documented on the basis of clinical examination, imaging studies, and specialist consultations. These included neurological manifestations such as seizures, musculoskeletal anomalies including limb and joint malformations, gastrointestinal and abdominal wall anomalies, urogenital anomalies, and the presence of multiple system involvement.

Statistical analysis was performed using SPSS version 26. Categorical variables were expressed as frequencies and percentages. Comparisons between the study and control groups were made using the Chi-square test or Fisher's exact test where appropriate. Associations between risk factors and congenital heart disease were assessed using Chi-square analysis, and a p-value of less than or equal to 0.05 was considered statistically significant.

RESULTS

A total of 646 children were included in the study, comprising 323 children with cleft lip and/or palate (study group) and 323 children without orofacial clefts (control group). The overall male predominance was observed in both groups, with males accounting for 185 (57.3%) and females for 138 (42.7%) children in the study group. The mean age of the study population was 4.3 ± 2.1 months in the study group and 4.5 ± 2.3 months in the control

Table 1: Demographic data and risk factors

Characteristics	Study Group (n = 323)	Control Group (n = 323)	p-value*
Age groups			
<3 months	129 (39.9%)	113 (35.0%)	0.045
3–6 months	97 (30.0%)	81 (25.1%)	0.023
>6 months	97 (30.0%)	129 (39.9%)	0.002
Gender			
Male	185 (57.3%)	168 (52.0%)	0.065
Female	138 (42.7%)	155 (48.0%)	0.065
Risk factors			
Parental consanguinity	110 (34.1%)	32 (9.9%)	<0.001
Maternal smoking	49 (15.2%)	16 (5.0%)	0.001
Maternal age >35 years	65 (20.1%)	48 (14.9%)	0.035

*p-values were calculated using the Chi-square test. Fisher's exact test was applied where expected cell counts were less than 5. A p-value of ≤0.05 was considered statistically significant.

group, with no statistically significant difference between groups. Demographic characteristics and risk factors of both groups are summarized in Table 1.

Parental consanguinity and maternal smoking were significantly more frequent in the study group, observed in 110 (34.1%) and 49 (15.2%) children, respectively, compared with 32 (9.9%) and 16 (5.0%) children in the control group. Maternal age above 35 years was also significantly higher in the study group. These factors demonstrated statistically significant associations with the presence of cleft lip and/or palate (Table 1).

Congenital heart disease, excluding isolated patent foramen ovale, was identified in 87 (26.9%) children in the study group compared with 16 (5.0%) children in the control group, indicating a significantly higher prevalence among children with cleft anomalies. Non-cyanotic congenital heart diseases were more common than cyanotic defects. The distribution of specific cardiac lesions differed significantly between the two groups and is summarized in Table 2. Septal defects constituted the majority of cardiac anomalies observed among children with cleft lip and/or palate.

Associated non-cardiac anomalies were detected in 116 (35.9%) children in the study group compared with 23 (7.1%) children in the control group. The most frequently observed non-cardiac anomalies included musculoskeletal malformations, gastrointestinal and abdominal wall anomalies, urogenital anomalies, and neurological manifestations such as seizures. Musculoskeletal and gastrointestinal anomalies showed the strongest associations with cleft lip and/or palate (Table 3).

The p-values were calculated using the Chi-square test. Fisher's exact test was applied where expected cell counts were less than 5. A p-value <0.05 was considered statistically significant. Stratified analysis demonstrated that children with combined cleft lip and palate had a higher frequency of both cardiac and non-cardiac anomalies compared with isolated cleft lip or isolated cleft palate. Male children exhibited a slightly higher prevalence of congenital heart disease; however, gender-wise differences were not statistically significant.

DISCUSSION

The present study demonstrates a significantly higher frequency of congenital heart disease among children with cleft lip and/or palate compared with children without orofacial clefts, which is consistent with previously published international and regional studies.[9-11] The strong association observed between orofacial clefts and congenital heart disease supports the hypothesis of

Table 2: Cardiac anomalies in children with cleft lip and/or palate

Cardiac lesion	Study group (n = 323)	Control group (n = 323)	p-value*
Patent foramen ovale	36 (11.1%)	3 (0.9%)	<0.001
Atrial septal defect	23 (7.1%)	6 (1.9%)	0.004
Ventricular septal defect	13 (4.0%)	3 (0.9%)	0.002
Patent ductus arteriosus	10 (3.1%)	3 (0.9%)	0.041
Pulmonary stenosis	6 (1.9%)	2 (0.6%)	0.034
Tetralogy of Fallot	6 (1.9%)	0 (0.0%)	0.008
Double outlet right ventricle	3 (0.9%)	0 (0.0%)	0.054
Pulmonary hypertension	13 (4.0%)	3 (0.9%)	0.014

*The p-values were calculated using the Chi-square test.
Fisher's exact test was applied where expected cell counts were less than 5.
A p-value of ≤0.05 was considered statistically significant.

Table 3: Non-cardiac anomalies in children with orofacial anomalies

Non-cardiac anomalies	Study group (n = 323)	Control group (n = 323)	p-value*
Neonatal icterus	16 (5.0%)	6 (1.9%)	0.023
Seizures	10 (3.1%)	3 (0.9%)	0.031
Joint and limb malformations	32 (9.9%)	10 (3.1%)	<0.001
Urogenital anomalies	13 (4.0%)	3 (0.9%)	0.003
Gastrointestinal/abdominal wall anomalies	23 (7.1%)	3 (0.9%)	0.001
Multiple anomalies	13 (4.0%)	3 (0.9%)	0.002

*The p-values were calculated using the Chi-square test. Fisher's exact test was applied where expected cell counts were less than 5. A p-value of ≤0.05 was considered statistically significant.

shared genetic susceptibility and common environmental risk factors contributing to both conditions.[12]

In the current study, non-cyanotic congenital heart diseases predominated, with septal defects representing the most frequent cardiac lesions observed among children with cleft anomalies. Similar patterns have been reported in prior studies, where atrial and ventricular septal defects were the most common cardiac abnormalities identified in children with cleft lip and/or palate.[13,14] A comparable prevalence of congenital heart disease in children with cleft anomalies has also been reported in population-based studies, further reinforcing the consistency of these findings across different geographic regions.[15]

Associated non-cardiac anomalies were identified in more than one-third of children with cleft lip and/or palate in this study, a significantly higher proportion than that observed in the control group. These findings are in agreement with earlier reports demonstrating that children with orofacial clefts frequently present with multisystem involvement, including musculoskeletal, gastrointestinal, and urogenital anomalies, particularly when congenital heart disease is also present.[16,17]

Parental consanguinity and maternal smoking were found to be significantly associated with the occurrence of cleft lip and/or palate and congenital heart disease in the present study. A previous study demonstrated a strong association between consanguinity, maternal teratogenic exposures, and congenital heart defects in children with orofacial clefts.[18] The identification of these modifiable and non-modifiable risk factors highlights the importance of targeted preventive strategies, particularly in regions with a high prevalence of consanguineous marriages.

Additionally, a higher frequency of dysmorphic features and syndromic diagnoses was observed among children with cleft anomalies in this study, reflecting the heterogeneity of these conditions. Similar observations have been reported, emphasizing that children with craniofacial anomalies, especially cleft lip and palate, are more likely to have syndromic diagnoses and associated cardiac defects.

CONCLUSION

The present study demonstrates a significant association between cleft lip and/or palate and congenital heart disease in children. Congenital heart diseases were markedly more frequent among children with orofacial clefts compared with controls, with non-cyanotic lesions, particularly septal defects, being the most commonly observed cardiac anomalies. In addition, children with cleft lip and/or palate showed a substantially higher prevalence of associated non-cardiac anomalies, highlighting the multisystem nature of these congenital conditions. Parental consanguinity and maternal smoking were identified as significant risk factors associated with the occurrence of both cleft lip and/or palate and congenital heart disease. These findings are consistent with previously published international studies reporting an increased burden of cardiac anomalies among children with orofacial clefts.

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