



ORIGINAL ARTICLE

The prevalence of non-syndromic orofacial clefts and associated congenital heart diseases of a tertiary hospital in Riyadh, Saudi Arabia



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Received 9 September 2019; revised 10 December 2019; accepted 11 December 2019

Available online 19 December 2019

KEYWORDS

Prevalence;
Non-syndromic;
Orofacial cleft;
Cleft lip and palate;
Congenital heart disease;
Saudi Arabia

Abstract *Background:* Orofacial clefts are considered one of the most common birth defects and are frequently associated with other malformations. Congenital heart disease is one of the most prevalent congenital malformation.

Objective: To investigate the prevalence of congenital heart diseases associated with non-syndromic orofacial clefts in the Saudi population.

Methods: Electronic files of non-syndromic orofacial cleft patients who visited the Oral and Maxillofacial Surgery Department in King Abdulaziz Medical City of Riyadh, Saudi Arabia from January 2015 to December 2018 were retrospectively reviewed. Data were recorded in an excel sheet and analyzed using SPSS via frequency tests.

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Peer review under responsibility of King Saud University.



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Results: In the cleft children identified, the prevalence of non-syndromic orofacial clefts was (77%). Orofacial clefts showed a male predominance (62%). The most common orofacial phenotype was unilateral cleft lip and palate (34%). The prevalence of associated congenital malformations with orofacial clefts was (41%). The most prevalent congenital malformation was congenital heart disease (35%), mainly found in unilateral cleft lip and palate patients (33%). The prevalence of associated congenital heart disease with orofacial clefts was (19%). The most frequent type of congenital heart disease was atrial septal defect (37%).

Conclusion: This study highlights the recognition of the associated congenital heart disease with non-syndromic orofacial cleft patients. Global screening protocols designed for newborns with non-syndromic orofacial cleft are needed to eliminate late diagnosis of critical congenital heart diseases which might present operative risks of anesthesia and/or surgical procedures.

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1. Introduction

Birth defects are the main cause of disability, morbidity and mortality in children (Noori et al., 2016). Orofacial clefts (OFCs) are considered the most common orofacial congenital anomaly among live births (Noori et al., 2016).

The etiology behind an OFC is multifactorial and heterogeneous. However, it can also be attributed to multiple genes and environmental risk factors, such as smoking, drinking alcohol and taking some oral medications during the pregnancy (DeRoo et al., 2016; Honein et al., 2014; Watkins et al., 2014). Familial aggregation increases the risk of OFCs, although the genetic etiological backgrounds remain unclear (Beaty et al., 2016).

OFCs include a range of congenital deformities, most commonly presenting as cleft lip (CL), cleft lip and palate (CLP) or isolated cleft palate (CP) (Shkoukani et al., 2013).

OFCs can present as syndromic or non-syndromic cases. The mean global prevalence of non-syndromic OFCs is 1.25/1000 live births (Mossey and Modell, 2012), which is marginally higher than that of Saudi Arabia (1.17/1000 live births) (Sabbagh et al., 2015). A recent study conducted in the southern province of Saudi Arabia resulted in an overall OFC prevalence of 0.65/1000 live births, where non-syndromic cases accounted for 43.75% (Alyami et al., 2019).

Furthermore, OFCs are commonly associated with other malformations, such as congenital heart disease (CHD) (Munabi et al., 2017; Panamonta et al., 2015). CHD presents in various forms and is considered the most common malformation associated with OFCs (Aljohar et al., 2008; Hadadi et al., 2017; Munabi et al., 2017). About 8% of non-syndromic OFCs present with CHD (Munabi et al., 2017). However, there are wide variations in the prevalence of CHD in patients with OFCs, but more importantly, it is reported as the principal cause of death among infants with an OFC (Panamonta et al., 2015).

A systematic review examined the demographics and severity of CHD in the non-syndromic OFC population concluded that atrial or ventricular septal defects are the most common forms of CHD associated with OFCs (Munabi et al., 2017). This study reported a prevalence of 7.42% (301/4055) in non-syndromic OFC patients with associated CHDs, and were significantly more common in cleft palates (Munabi et al., 2017).

In 2008, Aljohar et al. reported that out of 238 OFC cases associated with anomalies in Saudi Arabia, 91 had CHD (Aljohar et al., 2008). Many studies have described the

prevalence of non-syndromic OFCs in Saudi Arabia, yet no correlations to CHDs have been made (Alamoudi et al., 2014; Alyami et al., 2019; Hadadi et al., 2017; Sabbagh et al., 2015).

Global protocols to screen the associated anomalies in non-syndromic OFC patients seem to be lacking (Munabi et al., 2017). There is currently insufficient evidence available in literature to confirm how frequently associated anomalies, such as CHD, occur in patients with non-syndromic OFCs (Munabi et al., 2017). Moreover, the clinical significance and operative risks of CHD when associated with OFCs demand more investigation (Munabi et al., 2017).

Newborns with non-syndromic OFC are not usually subjected to detailed examination for subclinical congenital anomalies when they have not yet manifested clinical symptoms and are therefore discharged undiagnosed until the time of cleft repair surgery. According to Kumar et al., 30–50% of children with critical CHD are discharged from hospital without diagnosis of their cardiac lesions and may present for evaluation of cleft repair with an occult condition (Kumar, 2016).

Conventional surgical management of an OFC is usually postponed until 3 months of age, in order to lower the neurodevelopmental and cardiopulmonary risks of anesthesia (Zhang et al., 2015). While medical services internationally have progressed into initiating cleft repair operations at an earlier age, understanding the incidence and severity of CHD in non-syndromic OFC depends on the necessity and timing of the pre-operative evaluation, the evaluator's expertise and whether the operation could be performed safely (Munabi et al., 2017). Thus, knowledge of the prevalence of CHD in children with OFCs is even more important when it comes to critical cardiac diseases requiring operative intervention.

To the best of our knowledge, no study has reported the prevalence of non-syndromic OFCs associated with CHDs in Saudi Arabia. Therefore, the objective of the present study was to describe the prevalence and characteristics of CHD in patients with non-syndromic OFCs within the Saudi population who visited the Oral and Maxillofacial Surgery Department of King Abdulaziz Medical City, Riyadh.

2. Methodology

2.1. Study design and settings

The current study was an observational cross-sectional study. Data were accessed via the BestCare electronic system from

the Oral and Maxillofacial Surgery Department, King Abdulaziz Medical City, Riyadh, Saudi Arabia.

2.2. Study subjects

Inclusion criteria were used to select all Saudi non-syndromic OFC patients with a complete medical history who visited the Oral and Maxillofacial Surgery Department at King Abdulaziz Medical City from January 1, 2015 to December 31, 2018. Criteria were applied to exclude non-Saudi patients, patients seen outside the Oral and Maxillofacial Surgery Department of King Abdulaziz Medical City, and/or patients seen before 2015 or after 2019 and/or patients with syndromic OFCs; where OFCs are associated with syndromes such as Pierre Robin Sequence, Treacher Collins syndrome, cleidocranial syndrome and Apert syndrome.

2.3. Ethical considerations

Institutional Review Board (IRB) approval was obtained from King Abdullah International Medical Research Center (KAIMRC); approval number: (SP-19-056/R).

2.4. Data collection

Data were retrospectively collected using the BestCare system and the files of patients who fit the inclusion criteria were reviewed. Excel was used to record the required data. Gender was recorded as male or female, age was recorded as numerical data, The type of OFC was recorded as cleft lip (CL), cleft palate (CP) or cleft lip and palate (CLP), The side of the OFC was recorded as unilateral or bilateral, associated congenital malformations were recorded as one or more of the following: CHD, musculoskeletal, auricular, urogenital, ocular, and/or nasal and CHD type was recorded as one or more of the following: atrial septal defect (ASD), ventricular septal defect (VSD), pulmonary valve stenosis (PVS), mitral valve prolapse (MVP), transposition of great arteries (TGA), aortic valve stenosis (AVS) and/or tetralogy of Fallot.

2.5. Statistical analysis

Data were transferred to SPSS version 23 for statistical analysis. Frequency tests were mainly used to analyze the data. No other tests were required.

3. Results

A total of 168 OFC patient files were retrieved. Syndromic OFC patients represented 23% (38/168) of the total retrieved files and were excluded from the study. Non-syndromic OFC patients accounted for 77% (130/168) of the total retrieved files and were included, reviewed and analyzed. The sample consisted of 62% (81/130) males and 38% (49/130) females. The age of the subjects ranged from 1 to 17 years with a mean of 4 ± 3 years.

Unilateral CLP was the most prevalent side and type of OFC in both the males 21% (27/130) and females 13% (17/130) with a total of 34% (44/130), followed by bilateral CLP 22% (28/130) (Table 1).

The prevalence of associated congenital malformations was 41% (54/130). These 54 patients had either one or more associated congenital malformations, which resulted in a total of 95 different malformations predominately CHDs 35% (33/95) (Fig. 1). Bilateral CLP was the most common side and type of the non-syndromic OFCs associated with congenital malformations 31% (17/54), followed by unilateral CLP 26% (14/54) (Table 2).

In terms of CHD, the associated 33 cases were reviewed. The prevalence of CHD associated with non-syndromic OFCs was 19% (24/130), whereas the rest of the sample 81% (106/130) had no associated CHD. Unilateral CLP was the most common side and type of non-syndromic OFC associated with CHD 33% (8/24), followed by bilateral CLP at 21% (5/24) and unilateral CP at 21% (5/24) (Table 3). ASDs were the most common type of CHD associated with non-syndromic OFCs 37% (12/33), followed by VSDs 24% (8/33), with TGA, AVS and tetralogy of Fallot being the least common diseases with equal percentages of 6% (2/33) (Fig. 2).

Table 1 Distribution of different types and sides of non-syndromic OFCs in terms of gender.

Type: / Side:	Unilateral	Bilateral	Total
CL	M = 12% (16/130) F = 8% (10/130) Sum = 20% (26/130)	M = 3% (4/130) F = 2% (3/130) Sum = 5% (7/130)	M = 15% (20/130) F = 10% (13/130) Sum = 25% (33/130)
CP	M = 4% (5/130) F = 7% (9/130) Sum = 11% (14/130)	M = 5% (7/130) F = 3% (4/130) Sum = 8% (11/130)	M = 9% (12/130) F = 10% (13/130) Sum = 25% (19/130)
CLP	M = 21% (27/130) F = 13% (17/130) Sum = 34% (44/130)	M = 17% (22/130) F = 5% (6/130) Sum = 22% (28/130)	M = 38% (49/130) F = 18% (23/130) Sum = 55% (72/130)
Total	M = 37% (48/130) F = 28% (36/130) Sum = 65% (84/130)	M = 25% (33/130) F = 10% (13/130) Sum = 35% (46/130)	M = 62% (81/130) F = 38% (49/130) Sum = 100% (130/130)

OFCs, orofacial clefts; CL, cleft lip; CP, cleft palate; CLP, cleft lip and palate; M, male; F, female.

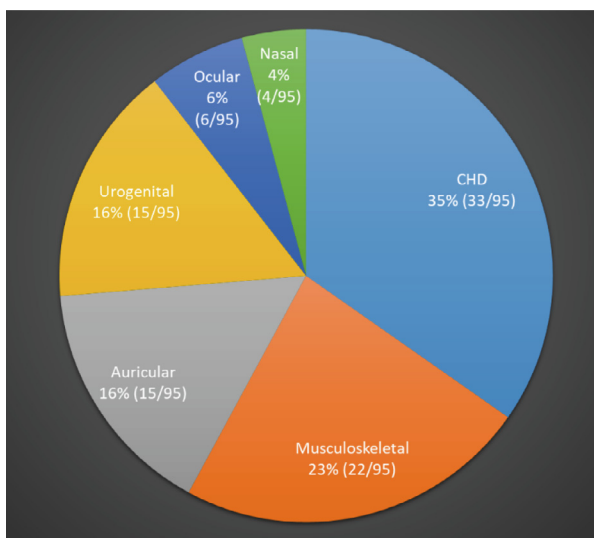


Fig. 1 Congenital Malformations: Prevalence of different types of congenital malformations associated with non-syndromic OFCs. *OFCs, orofacial clefts; CHD, congenital heart disease.*

Table 2 Distribution of congenital malformations in terms of type and side of non-syndromic OFCs.

Type: / Side:	Unilateral	Bilateral	Total
CL	11% (6/54)	2% (1/54)	13% (7/54)
CP	15% (8/54)	15% (8/54)	30% (16/54)
CLP	26% (14/54)	31% (17/54)	57% (31/54)
Total	52% (28/54)	48% (26/54)	100% (54/54)

OFCs, orofacial clefts; CL, cleft lip; CP, cleft palate; CLP, cleft lip and palate.

Table 3 Distribution of congenital heart diseases in terms of type and side of non-syndromic OFCs.

Type: / Side:	Unilateral	Bilateral	Total
CL	8% (2/24)	0% (0/24)	8% (2/24)
CP	21% (5/24)	17% (4/24)	38% (9/24)
CLP	33% (8/24)	21% (5/24)	54% (13/24)
Total	63% (15/24)	38% (9/24)	100% (24/24)

OFCs, orofacial clefts; CL, cleft lip; CP, cleft palate; CLP, cleft lip and palate.

4. Discussion

Infants with non-syndromic OFCs presented with a significantly higher risk for any type of congenital anomaly (Corona-Rivera et al., 2018). CHD is the most common congenital anomaly associated with OFCs (Aljohar et al., 2008; Hadadi et al., 2017; Munabi et al., 2017). Newborns who are classified as having a non-syndromic OFC do not usually undergo protocols for congenital anomaly evaluation, which potentially increases their risk of being discharged home with an undiagnosed CHD. Due to a lack of research in the preva-

lence of non-syndromic OFCs with CHD in Saudi Arabia, and due to its great impact and clinical significance, this research was therefore conducted.

The Oral and Maxillofacial Surgery Department of King Abdulaziz Medical City, Riyadh, Saudi Arabia is one of the largest government medical facilities in Riyadh and is a referral center for children born with OFCs. There have been previous publications from this center (Hadadi et al., 2017).

The current study found that the occurrence of non-syndromic OFCs (77%) was around 3-fold higher than syndromic OFC cases that accounted only for only (23%). This was in agreement with Hadadi et al. where non-syndromic OFCs comprised 81%, while syndromic cases were only (19%) (Hadadi et al., 2017). This highlights that non-syndromic OFC patients constitute a large proportion of all OFC patients, and therefore congenital anomalies should be always anticipated and screened. Non-syndromic OFC patients presented with a male predominance of (62%) compared to females (38%). Also, Fakhim et al. reported that OFCs were more common in males (58%) than females (42%) (Fakhim et al., 2016). Among both genders, CLP was the most common type (55%) of OFC, which was consistent with Aljohar et al. who also found that CLP was more common (48%) than the other types of OFCs in Saudi Arabia (Aljohar et al., 2008). However, this contradicted Sabbagh et al. and Hadadi et al. where CL and CP, respectively, were the most common types (Sabbagh et al., 2015). In the current study, unilateral OFCs (65%) were more common than bilateral OFCs (35%), which is in agreement with Butali et al. (2014). Similar to the findings of Ajami et al., unilateral CLP (34%) was the most prevalent in terms of side and type (Ajami et al., 2017).

The present study found that (41%) of patients had one or more associated congenital malformation. Furthermore, Sun et al. stated that the prevalence of congenital anomalies associated with OFCs was (30%) (Sun et al., 2013). The current study reported that CHD was the malformation most commonly associated with OFCs (35%), which supports the findings of previously published research (Aljohar et al., 2008; Hadadi et al., 2017; Munabi et al., 2017; Panamonta et al., 2015; Sun et al., 2013). In the current study, CHD was most commonly associated with unilateral CLP, which was also in agreement with other studies (Kasatwar et al., 2018). This could be attributed to the fact that in our sample, unilateral CLP was the most common phenotype, hence, it has greater chance of having CHD.

In respect to CHD, Noori et al. reported an overall prevalence of 25% in OFC patients, which is slightly higher than our results (19%) (Noori et al., 2016). The association between CLP and CHD has been proposed to result from a common genetic relationship in the deleted T-box 1 gene (TBX1) (Friedman et al., 2011). It has been shown, for example, that modulating genes such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF8) can act on the same pathway as genes from the commonly deleted region at 22q11.2, thereby influencing the expression of primarily deleted genes, such as TBX (Friedman et al., 2011). ASDs were the most prevalent of the CHD types (37%), which is comparable to the findings of Sun et al. (40%) (Sun et al., 2013). A noticeable lack of literature data was observed regarding the precise genetic mechanism of occurrence between OFCs and ASDs.

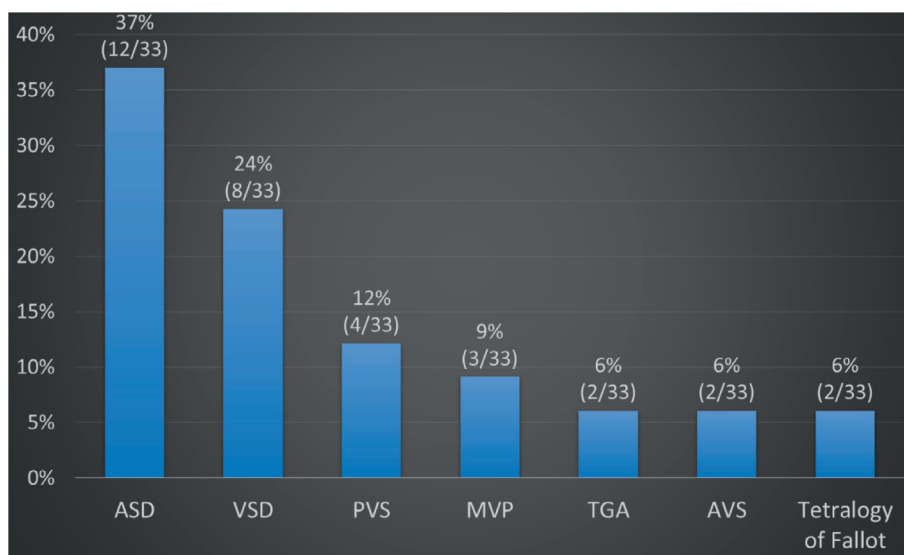


Fig. 2 Congenital heart diseases: Distribution of different congenital heart disease types associated with non-syndromic OFCs. *OFCs*, orofacial clefts; *ASD*, atrial septal defect; *VSD*, ventricular septal defect; *PVS*, pulmonary valve stenosis; *MVP*, mitral valve prolapse; *TGA*, transposition of great arteries; *AVS*, aortic valve stenosis.

This study has encountered some limitations. A retrospective study collecting data from records presents expected errors with regards to missing or lost data and inaccurate recording or record keeping. Another limitation was the inability to calculate the sample power. The number of records studied were 168 and the prevalence was reported as 77%. No comparison was made and p-value which indicates statistical significance was not reported. Hence our study is descriptive and reported only the prevalence, this might have an influence on the generalization of the results. Also, the study was conducted in a single tertiary hospital population and therefore, results cannot be generalized or representative of the population across Saudi Arabia. Further comprehensive multicenter research in all regions of Saudi Arabia to describe the prevalence of CHD in non-syndromic OFC patients is warranted. Finally, the study did not analyze and compare left sided OFC and right sided OFC.

5. Conclusion

There are few studies on the prevalence, characteristics and risk factors of non-syndromic OFCs and associated congenital malformations in Saudi Arabia. Further investigations are highly encouraged to provide domestic statistics of such cases in all facilities in Saudi Arabia. Thorough understanding of the association between CHD and OFC cases is considerably important to the health and welfare of these patients. The early detection of CHDs identifies cases for surgical intervention and reduces the consequences where these diseases are left unoperated. Global screening protocols designed for congenital malformations in non-syndromic OFC newborns are needed to eliminate the late diagnosis of crucial or fatal CHDs and to prevent the operative risks of anesthesia and surgical procedures.

Ethical committee approval

Ethical approval was obtained from King Abdullah International Medical Research Centers (KAIMRC). IRB Approval number (SP-19-056/R).

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Declaration of Competing Interest

Authors declare that there is no conflict of interest.

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