Epidemiologic Trends of Infants With Orofacial Clefts in a Multiethnic Country: A Retrospective Population-based Study

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Abstract

Objectives: To establish the population-based prevalence and trends of cleft live births, evaluate associated malformations and infant mortality rate (IMR), and delineate the orofacial cleft (OFC) topography, ethnic and gender-specific features of the resident-population in Singapore from 2003 to 2012. Cleft-births surveillance and data of affected individuals, families, ethnic groups, locations and environment are essential in upstream healthcare planning. Well-informed decisions supported by data are all-important in health policies.

Methods: Resident population-based data were compiled from the National Birth Defects Registry (NBDR). The Registry's data was established from multiple sources: cytogenetics and histopathology laboratories, neonatal wards and maternity hospitals, medi-claims, birth defects, death certificates with reported congenital anomalies, stillbirths and abortuses (spontaneous and elective). The significance level of trend testing was set at $p < 0.05$.

Results: Prevalence per 10 000 for all cleft live births was 16.72; isolated clefts with no associated malformations, cleft lip, cleft palate, and cleft lip with cleft palate were 8.77, 6.85, 3.16, and 6.71, respectively. Prevalence in cleft live births was sexually dimorphic and ethnic-specific: Male, 17.72; Female, 15.78; Chinese group, 17.17; Malay group, 16.92; Indian group, 10.74; and mixed ethnicity group, 21.73. Infants with isolated clefts, non-isolated clefts with other malformations, and syndromic clefts were 52.5%, 42.1%, and 5.4%, respectively. Upward trend in infants with non-isolated clefts was significant ($p = 0.0287$). The mortality rate in infants with clefts was 4.76%.

Conclusions: The population-based prevalence for cleft live births was 16.72 per 10 000 with no significant upward trend. Co-occurrence of malformations and syndromes was found in almost half of all cleft live births. The IMR of infants with OFC was double that of the population norm.

Introduction

Orofacial clefts (OFC) are common birth defects with wide-ranging prevalences in the world [1]. There is much heterogeneity in OFC birth defects and the aetiologies of the various cleft-types are distinct involving different embryological origins and timing of development [2, 3]. Laterality is featured in individuals with OFC and unilateral left-sided findings are more common [4]. Identification of the different subphenotypes and cleft laterality is important in understanding the genetics, epigenetics, and environmental factors to identify individuals at risk and triggers [5].

Comparisons of perinatal mortality rate (PNMR) and IMR of infants, with and without associated anomalies, revealed higher mortality rates for the latter than the population norm [6]. Long-term survival of individuals with OFC was reduced [7] and their overall health status were not good [8]. These indicators inform the health systems and actions required to serve the healthcare needs, but more importantly, the key issues are to identify the patterns attributable to modifiable or non-modifiable factors in strategizing future treatment and prevention. The first step to change the corollary is data tracking to understand the

affected pregnancy outcomes. For upstream healthcare, cleft-births surveillance and data of affected individuals, families, ethnic groups, locations and environment are essential. Well-informed decisions are all-important in health policies to drive prevention programs.

The objectives of the present study were to establish the resident population-based prevalence and trends of cleft live births in Singapore from 2003 to 2012, delineate the ethnic and gender-specific features, and evaluate associated congenital malformations and IMR.

Materials And Method

Data sources comprised government organizations, public and private healthcare institutions. The method of data collection by the National Birth Defects Registry (NBDR) in Singapore was previously described [9]. Field visits were conducted by the Registry Coordinators (RC) at the medical records offices of restructured and private hospitals for data collection. The NBDR system was purpose-built for electronic data capture with case-entry matching against existing records in the system. The merging functions and contradiction modules checked, verified, and handled inconsistencies to resolve discrepancies and duplication. Data extractions were done in accordance to the NBDR guidelines and all data were entered directly and secured in the database. Annual audits were done to standardise the definitions of data items and abstraction rules to ensure standards of consistency and accuracy in data collection. Inter-rater reliability (IRR) audits of similar cases abstracted by multiple RCs were checked for levels of agreement.

The International Classification of Diseases 9th Edition (ICD-9) with Extension of the British Paediatric Association (BPA) Classification of Diseases (1979) Coding of Birth Defects [10] was used for subjects registered from 1993 to 2011. Individuals registered from 2012 onwards were coded using the International Classification of Diseases 10th Edition (ICD-10) Chapter XVII Royal College of Paediatric Child and Health Extension [11]. Extractions from the Registry's database were done by using the following codes in ICD-9: 749, and in ICD-10: Q35-Q37. Cleft laterality (side of the cleft), submucous cleft, bifid uvula and severity grading of the cleft defects were not classifiable by the codes and could not be recorded. Identifiers were removed for data anonymization.

The count of infants with clefts was by live pregnancy outcomes of Singaporean mothers grouped by ethnicity and who were resident citizens or permanent residents living in Singapore in the period 2003 to 2012. Live births of foreigners in Singapore and Singaporeans who did not reside in the country were excluded. Stillbirths and abortions (spontaneous and elective) were also excluded. The denominator was population live births per 10 000. Statistical analysis was performed using the SAS version 9.3 (SAS Institute, Cary, NC, USA). Linear regression was used in trend tests and the significance level was set at $p < 0.05$.

Results

From 2003 to 2012, the multiethnic population live births comprised 242 414 (66.7%) Chinese, 67 630 (18.6%) Malay, 33 373 (9.2%) Indian, and 20 216 (5.6%) mixed ethnicity groups. The prevalence and trend of cleft live births in the ethnic groups are in Fig. 1. Annualised prevalence and trends are in Fig. 2.

Cleft-type and prevalence

The distribution of cleft-types is in Table 1 and consisted of 41.0% (N = 249) cleft palate (CP), 40.1% (N = 244) cleft lip and palate (CL/P), and 18.9% (N = 115) cleft lip (CL) groups. The denominator was resident population live births for prevalence of cleft live births: 6.85, 6.71 and 3.16 per 10 000 for the CP, CL/P and CL groups.

Table 1
Live births by cleft-type and gender.

Type of Cleft		Livebirths		
		Male	Female	Total
Cleft Palate Only		97	152	249
Cleft lip only	Unilateral	49	34	83
	Bilateral	9	4	13
	*NOS	14	5	19
Cleft lip and palate	Unilateral	86	58	144
	Bilateral	39	26	65
	*NOS	18	17	35
Total		312	296	608
*NOS – not otherwise specified cleft sub-type in ICD 9 & 10.				

Cleft-type and gender

Table 1 also shows the gender distribution for the CP group, which consisted of 39% (N = 97) males and 61.0% (N = 152) females; the CL/P group comprised 58.6% (N = 143) males and 41.4% (N = 101) females; and the CL group comprised 62.6% (N = 72) males and 37.4% (N = 43) females. The CL/P sub-types comprised 59.0% (N = 144) unilateral, 26.6% (N = 65) bilateral, and 14.3% (N = 35) were not otherwise specified (NOS). The CL sub-types comprised 72.2% (N = 83) unilateral, 11.3% (N = 13) bilateral, and 16.5% (N = 19) NOS.

Cleft-type and ethnicity

Table 2 shows the ethnic group distribution for the cleft sub-types. The CP group consisted of 72.3% (N = 180) Chinese, 15.3% (N = 38) Malay, 4.8% (N = 12) Indian, and 7.6% (N = 19) mixed ethnicity. The CL/P group consisted of 65.6% (N = 160) Chinese, 20.9% (N = 51) Malay, 6.6% (N = 16) Indian, and 7.0% (N = 17)

mixed ethnicity. The CL group consisted of 67.0% (N = 77) Chinese, 20.9% (N = 24) Malay, 7.0% (N = 8) Indian, and 5.2% (N = 6) mixed ethnicity.

Table 2
Ethnic groups and cleft sub-types – with and without malformations and syndromes.

Type of Cleft		Isolated Clefts				Clefts with Associated Malformations				Syndromic Clefts				Total
		C	M	I	O	C	M	I	O	C	M	I	O	
Cleft palate only		73	17	5	14	96	19	6	4	11	2	1	1	249
Cleft lip only	Unilateral	42	5	1	2	14	8	6	3	1	1	0	0	83
	Bilateral	3	3	0	0	3	0	0	0	2	2	0	0	13
	*NOS	9	2	0	0	3	3	1	0	0	0	0	1	19
Cleft lip and palate	Unilateral	65	10	5	7	31	12	6	6	1	1	0	0	144
	Bilateral	17	10	2	1	17	9	1	2	5	1	0	0	65
	*NOS	21	5	0	0	2	2	2	0	1	1	0	1	35
Total		230	52	13	24	166	53	22	15	21	8	1	3	608
*NOS – not otherwise specified cleft sub-type in ICD 9 & 10.														
C: Chinese group; M: Malay group; I: Indian group; O: Mixed ethnicity group.														

Cleft-type and associated malformations/syndromes

Table 2 shows infants with isolated clefts and no chromosomal or genetic anomalies formed 52.5% (N = 319) of cleft live births and 47.5% (N = 289) were associated with other malformations or syndromic clefts. Syndromic clefts were 5.4% (N = 33) of cleft live births. The malformations comprised 31.5% heart anomalies, 24.2% musculoskeletal system anomalies, and 7% central nervous system anomalies. Other malformations coded for infants with clefts were ear, face and nose (EFN) anomalies, respiratory system anomalies, gut, integument, eye, and urinary system anomalies. The prevalence of isolated clefts was 8.77 and upward trend was not significant ($p = 0.0883$). The prevalence of non-isolated clefts with other malformations was 7.04 with significant upward trend ($p = 0.0287$), and syndromic clefts was 0.90 with no significant upward trend ($p = 0.1908$).

Infant Mortality

Infant deaths under one year of age (< 365 days after birth) involved 17 males and 12 females. All deaths of infants with non-isolated clefts involved infants with syndromic clefts (N = 13) and clefts associated with other malformations (N = 15) except for one. The one infant with isolated cleft perished in the early neonatal period, less than 7 days after birth. All infants with syndromes (N = 13) died in the neonatal period of less than 28 days. Thirteen infants with non-syndromic and non-isolated clefts died in the

neonatal period, and two infants in the post-neonatal period before the age of one year. Overall, the cleft neonatal mortality rate (NMR) was 3.45%, and the cleft infant mortality rate (IMR) was 4.76%.

Discussion

Population prevalence

The population-based prevalence for cleft live births of the resident population, without stillbirths and abortuses, was 16.7 per 10 000 and no significant upward trend ($p = 0.317$). The population-based prevalence in the previous decade, from 1993 to 2002, was 18.7 per 10 000 with significant upward trend that included all notified cleft births that included, stillbirths and abortuses of residents, non-residents, and foreigners in Singapore [12]. However, the prevalence in both decades were high, above the global average of 9.92 per 10 000 (range 2.89 to 23.85) reported in the period 2000 to 2005 [1].

Ethnic-specific prevalence

Singapore has a multiethnic population constituted by immigrants from the neighbouring countries of China, India and Malaysia. Among the four ethnic groupings in Singapore, the group with mixed ethnicity had the highest prevalence of 21.73 per 10 000, and prevalence in the groups with Chinese, Malay and Indian ancestries were 17.17, 16.92, and 10.74 per 10 000, respectively. This was also reflected in the population-based study of the previous decade, from 1993 to 2002 [12], which reported similar patterns in the order of prevalence for the ethnic groups.

The present study found the prevalence of Chinese Singaporeans to be high, 17.17 per 10 000, which was close to the reported prevalence for the ethnic Chinese in China of 16.63 per 10 000 [13]. Pooled cleft prevalences from cross-sectional studies of Indians across India was 13.0 per 10 000 [14]. In comparison, the prevalence of Indian Singaporeans was lower, 10.74 per 10 000. Cohorts of consecutive cleft live births for Indian Singaporeans ($N = 36$) as well as the Singaporean group with mixed ethnicities ($N = 42$) in this study were small, which might not be representative of the actual prevalence in these groups. The Malay Singaporean's prevalence of 16.92 per 10 000 in this study was closer to the prevalence of 18.5 per 10 000 of the Malay group reported in northwest Malaysia [15]. Despite the small difference in frequencies, the Malay groups in both countries featured similarly high prevalence of OFC births.

Variations in ethnic group prevalence could be due to different reasons. Population demographics could have changed due to migratory patterns. Differences in study designs and sampling, i.e. population-based, hospital-based or treatment centre sampling, inclusion and exclusion criteria, different nominators and denominators in determining prevalence, early or late registration of subjects with OFC were among many reasons that might change prevalence values. The prevalence of the ethnic groups with OFC in this study resembled those in the old countries of their forebears. This corroborates with findings that indicate ethnic-specific prevalence of OFC seemed to be linked to ancestral genes [16].

Gender

The prevalences for male and female cleft live births were 17.72 and 15.78 per 10 000, respectively; upward trends for both were not significant ($p = 0.650$ and $p = 0.294$, respectively). Distribution by gender was 1.1:1.0 male to female ratio. Gender-specific cleft types of CL and CL/P were 1.7:1.0 and 1.4:1.0, respectively, with a predisposition for males. This was reversed in CP with a 1.6:1.0 female to male ratio. Males infants tended to present with CL and CL/P phenotypes and females with the CP phenotype. The role of gender in different cleft phenotypes was postulated to be due to the timing of embryological development, and slower palatal development could result in more cleft palate defects in females [17]. Gender also represented a substantial estimated population attributable fraction in non-modifiable factors for OFC [18].

Cleft-types

Cleft palate defects were the most common cleft type among live births in this study. Distribution by cleft-type was 2.2:2.1:1.0 for CP, CL/P and CL, respectively. The Global Registry and Database on Craniofacial Anomalies reported findings of Asian OFC registries with low CP prevalence and high CL/P rates; CL/P to CP were 4 to 6 times higher in Asia [19]. In this study, prevalences for CP and CL/P were almost, 6.86 and 6.71 per 10 000, respectively. This could be a reflection of the pooling effect of the multiethnic variations in cleft-types. The multifactorial threshold (MFT) model predicted greater genetic liability within a population with higher overall cleft prevalence that predisposed to greater occurrence of severe cleft types [20]. There were suggestions of CL and CL/P as defects of different severities in the same aetiological spectrum but the evidence was not conclusive. The two entities of CL and CL/P were suggested to be classified separately [21]. Syndromic clefts in this study were associated with bilateral CL/P than unilateral CL/P. In this population with high overall cleft prevalence, there should be a greater number of cases with increased cleft defect severity. However, unilateral CL/P occurred four times more often than bilateral CL/P. Even in countries with low overall prevalence of less than 10 per 10 000, subjects with CL/P were more common than those with CL [1].

Associated malformations

The number of non-isolated clefts in this study was high and constituted 42.1% of cleft live births. They accounted for almost half (47.5%) of cleft live births when grouped with syndromic clefts (5.4%). Prevalence of non-isolated clefts with other malformations was 7.04 per 10 000 with a rising trend ($p = 0.0287$). Syndromic clefts were more commonly associated with CP defects (55.6%) and half of infants with CP (50.2%) were associated with other malformations. The findings concurred with other reports on the high frequency of associated anomalies with CP cases that should be routinely examined for additional malformations [22, 23, 24, 25]. The associated anomalies of infants with CP in the present study involved mostly the musculoskeletal system and heart anomalies. In infants with non-isolated CL and CL/P, associated anomalies were twice more frequent in the latter and involved heart anomalies. The IPDTC Working Group [1] reported 15.9% and 7.3% of individuals with clefts had other malformations and syndromes, respectively.

Neonatal and infant mortality rate

Neonatal and infant death registrations by the Singapore Registry of Births and Deaths were of infants who lived less than 28 days and 365 days, respectively [26]. Cleft neonatal mortality rate (NMR) was 3.5%, similar to the NMR of the general population in the same period, from 2003 to 2012. However, the infant mortality rate (IMR) at 4.8% was more than double compared to the population IMR of 2.1%. Infants with associated malformations and syndromic clefts formed 96.6% of deaths with one death involving an infant with isolated cleft palate, which was not a common occurrence. There could have been a missed diagnosis of an associated anomaly or Pierre Robin Sequence in the one infant with isolated cleft palate who died. Infants with clefts who perished comprised 49.4% with CL/P, 37.3% with CL, and 13.3% with CP.

In a Danish population study of 678 consecutive live birth infants with OFC from 1977 to 1981, 24 infants (3.5%) died before the age of 22 months [4], the causes of death were not specified. The mortality rate of cleft infants in Denmark was mildly raised compared to the population post-neonatal mortality rate of 3.0 to 3.2 within a similar period [27]. A national study of Dutch infants with orofacial clefts reported the overall IMR to be elevated at 2.09%, which was significantly higher than the Dutch general population IMR of 0.45% [28]. In another report by the East of England Cleft Network of 638 children with clefts, the causes of deaths were reported to be from associated anomalies (61%) and infections (17%), and the IMR was 3.6% for children with clefts [29]. The IMR for children with clefts in all studies was consistently higher than that of the general population. It indicated the relevance of thorough medical examination of all infants born with OFC for associated anomalies that could have fatal consequences.

Study limitations

The main limitations in this study were the coding systems, early registration at or soon after birth, and no histories of family members with OFC. The registry lacked registration data in maternal, paternal and family histories of OFC to link heredity to the affected pregnancy outcomes. The ICD-9 and ICD-10 coding systems were not structured to record the heterogeneity of OFC subphenotypes. This limitation was faced by other researchers as well and there was a call for revision of the ICD coding system to include classification of the different OFC sub-types and possible aetiologies [30]. The call was heeded and the newly launched ICD-11 [31] had been reorganised for classifications that could individuals with heterogeneous OFC conditions in the chapter on Developmental Anomalies. Isolated structural developmental anomalies, multiple developmental anomalies and syndromes classifications are augmented by inclusions for genetic or cytogenetic aetiologies in chromosomal or genetic anomalies with the flexibility to add granular details of the complex OFC subphenotypes.

The findings in this study are based on diagnostic data soon after birth. The probability of under-reporting cleft live births and associated malformations is likely to be due to early registrations. Certain primary and secondary cleft palate defects can prove to be diagnostically challenging and easily missed in small infants, especially the soft tissue cleft defects. Associated developmental comorbidities can take time to manifest and may be missed in infants under one year. Our team proposes a lifelong open date registration of individuals with OFC. Continual data updates to the registry will minimise missed diagnoses and improve accuracy in ascertainment.

Conclusions

Population-based cleft live birth prevalence was 16.72 per 10 000 with sexual dimorphism, 17.72 and 15.78 in males and females, respectively. There was no significant upward trend of cleft live births. Prevalence varied for the cleft-types: cleft palate, 6.85; cleft lip, 3.16; and cleft lip with cleft palate, 6.71. Ethnic-specific prevalence in the Chinese, Malay and Indian groups were 17.17, 16.92 and 10.74, respectively. In the group with mixed ethnicities, the prevalence was 21.73. The upward trend in cleft live births with associated malformations was significant. The mortality rate of infants with clefts more than doubled the IMR of the population norm and infants with associated malformations were mostly affected.

Abbreviations

BPA

British Paediatric Association; CIRB:Centralized Institutional Review Board; CL:Cleft Lip; CL/P:Cleft Lip and Palate; CP:Cleft Palate; EFN:Ear, Face and Nose; ICD:International Classification of Diseases; IMR:Infant Mortality Rate; IPDTC:International Perinatal Database of Typical Oral Clefts; IRR:Inter-rater Reliability; MFT:Multifactorial Threshold; NBDR:National Birth Defects Registry; NC:North Carolina; NMR:Neonatal Mortality Rate; OFC:Orofacial Cleft; PNMR:Perinatal Mortality Rate; RC:Registry Coordinator; SAS:Statistical Analysis Software; USA:United States of America

Declarations

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Authors' contributions

MY and GSHY conceived the idea and developed the conceptual framework of the study. MY, AJ and GSHY analysed, interpreted the data, and prepared the tables and figures. MY wrote the manuscript and AJ and GSHY provided critical feedback. All authors reviewed and approved the final manuscript.

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Availability of data and materials

Data supporting this study are at: <https://osf.io/5rw3f/files/>

Ethics approval and consent to participate

This study was approved by the SingHealth Centralized Institutional Review Board D (reference: 2014/2199). Informed consent was waived for this registry-based study because secondary data were used.

Consent for publication

Not applicable.

Competing interests

The authors declare they have no competing interests.

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Figures

Figure 1

Population-based prevalence by ethnic groups from 2003 to 2012. Chinese group 17.17 per 10 000. Upward trend is not significant ($p=0.692$). Malay group 16.92 per 10 000. Upward trend is significant ($p=0.008$). Indian group 10.74 per 10 000. Upward trend is not significant ($p=0.724$). Mixed ethnicity group 21.73. Upward trend is not significant ($p=0.606$).

Figure 1

Population-based prevalence by ethnic groups from 2003 to 2012. Chinese group 17.17 per 10 000. Upward trend is not significant ($p=0.692$). Malay group 16.92 per 10 000. Upward trend is significant ($p=0.008$). Indian group 10.74 per 10 000. Upward trend is not significant ($p=0.724$). Mixed ethnicity group 21.73. Upward trend is not significant ($p=0.606$).

Figure 2

Population-based cleft live birth prevalence by year from 2003 to 2012. Overall prevalence is 16.72. Upward trend is not significant ($p=0.317$).

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