Clinical issues in orofacial clefts in Ecuadorian children

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Abstract

Background: Orofacial clefts are one of the most common human malformations worldwide and comprise cleft lip (CL), cleft palate (CP), and cleft lip with cleft palate (CLP) phenotypes.
Objective: To analyze the clinical features and genetics in Ecuadorian children patients with orofacial clefts.
Design: Observational, cross-sectional, cases series study.
Subjects and Setting: It analyzed 475 children patients of less of 5 years presenting orofacial clefts. The data arose of public hospitals from the 22 provinces around the country.
Interventions: It designed a survey to gather information from inpatient records of the hospitals. Data was collected during a six month period in 2010.
Results: Male cases were 64.8%, the ratio male:female was 1.84:1. Children of less of 1 year comprise the 21.7% (103/475) of cases and, 80.2% of the cases (381/475) were Mestizos. CL phenotypes were the most common orofacial cleft, alone in 42.7% (203/475) or in association with CP in 19.2% of cases (91/475). CP alone was 38.1% of cases (181/475). Unilateral CL was present in 38.4% of cases (78/203), the left side was the most affected in 64.1% (50/78); the ratio left to right side was 1.78:1. There was a correlation between orofacial clefts and multiple gestations above 4 gestations, low maternal age below 15 years, high paternal age above 45 years, intrauterine growth retardation, positive use of anticonvulsivants and frequent maternal alcohol consumption.
Conclusion: In Ecuadorian Mestizo children affected by orofacial clefts, unilateral, incomplete, CL of the left side was the most frequent finding followed by cleft hard palate with cleft soft palate. Further evaluation is needed to understand more widely the multifactorial etiology of this problem.

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Abbreviations used:
CL= *cleft lip only.* ***CP=*** *cleft palate only.* ***CLP=*** *cleft lip and palate.* ***BPR=*** *birth prevalence ratio.*

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Características clínicas de las hendiduras orofaciales en niños ecuatorianos

Resumen

Contexto: Las hendiduras orofaciales son malformaciones humanas comunes en todo el mundo e incluyen fenotipos de labio leporino (LL), paladar hendido (PH) y labio leporino con paladar hendido (LPH).
Objetivo: Analizar las características clínicas y genéticas de pacientes pediátricos ecuatorianos con hendiduras orofaciales.
Diseño: Estudio observacional y transversal de serie de casos.
Lugar y sujetos: Se analizaron 475 pacientes pediátricos menores de 5 años que presentaban hendiduras orofaciales. Los datos procedieron de los hospitales públicos de las 22 provincias del país.
Mediciones principales: Se diseñó una encuesta para recopilar información de los registros de hospitalización de los hospitales. Los datos fueron recogidos durante un período de seis meses en 2010.
Resultados: Los casos de sexo masculino fueron 64.8%, la razón hombre:mujer fue de 1.84:1. Los niños de menos de 1 año constituyeron el 21.7% (103/475) de los casos y, el 80.2% de los casos (381/475) eran mestizos. El LL fue la hendidura orofacial más común, presentándose único en 42.7% (203/475) o en asociación con PH en 19.2% de los casos (91/475). El PH fue 38.1% de los casos (181/475). El LL unilateral estuvo presente en el 38.4% de los casos (78/203), el lado izquierdo fue el más afectado en el 64.1% (50/78); la razón izquierda:derecha fue 1.78:1. Existió correlación entre las hendiduras orofaciales y embarazos múltiples por encima de 4 gestaciones, la baja de la edad materna menor de 15 años, alta edad paterna de más de 45 años, el retraso del crecimiento intrauterino, el uso positivo de anticonvulsivantes y el consumo materno de alcohol frecuente.
Conclusión: En niños mestizos ecuatorianos afectados por hendiduras orofaciales, unilaterales, incompletas, el LL del lado izquierdo fue el hallazgo más frecuente, seguido de paladar duro leporino con paladar hendido. Se necesitan más evaluaciones para comprender más ampliamente la etiología multifactorial de este problema.

Palabras clave:
Malformaciones congénitas, Hendiduras orofaciales, Labio leporino, Paladar hendido, Niños, Ecuador.

Introduction

The aim of this study is to analyze the clinical features and genetics in Ecuadorian children with orofacial clefts of Ecuador. This is the first study performed in their class that approaches this specific problem. Birth defects in our country are an important concern for the Public Health authorities and researchers, especially because they are related with mental retardation and development disabilities, an emerging and neglected problem that it has increased due the disparities inside of the population [1].

Orofacial clefts are one of the most common human malformations worldwide and comprise cleft lip (CL), cleft palate (CP), and cleft lip with cleft palate (CLP) phenotypes [2]. These birth defects affect the upper lip and roof of the mouth and are the most common disease affecting children with variable phenotype [3]. They result from a failed fusion of the medial, lateral and maxillary processes, which should occur from the 6th to the 10th week of intrauterine life [4].

The birth prevalence rate (BPR) of these phenotypes in US is estimated at 1/750 [5], with variability identified by ethnicity [6]. It is among the most common congenital anomalies, occurring approximately 1-2/1000 live births worldwide [7]. Native Indians of North America and Asians have the highest prevalence rates (1/500), while Caucasian populations have intermediate rates (1/1000) and, African derived populations have the lowest prevalence rates (1/2500) [8]. The prevalence in Latino Americans is lower than in Caucasians and Native Indians of North America [9].

In Ecuador, according with the ECLAMC study [10] the BPR of cleft palate without cleft lip is 4.2/100,000 and cleft lip with or without cleft palate is 18/100,000; in other study published by our research team the BPR was 1.91 and 3.24 respectively [11, 12]. For CLP, high BPR clusters were associated with high altitude above sea level, Amerindian ancestry, and low socioeconomic strata [13]. Cleft individuals in South America present a higher frequency of Amerindian mitochondrial haplotypes, in particular haplotype-D; reduced folate carrier 1 is associated with cleft of the lip [14].

Subjects and methods

Study design: This is an observational, cross-sectional, cases series study. It analyzed 475 children patients, of less of 5 years presenting orofacial clefts of Ecuador. It designed a survey to gather the information from inpatient records of public hospitals that reported CL, CP and CLP cases to the Ministry of Public Health. The data was collected during a six month period in 2010, of hospitals arising from the 22 provinces around the country. Data were gathered and analyzed by our research team.

Analysis: The generated descriptive statistics included major parameters for continuous data and, for categorical data did report frequencies and percentages.

Some definitions used: *Cleft palate without cleft lip (CP),* a congenital malformation characterized by a closure defect of the hard and/or soft palate behind the foramen incisivum without cleft lip. *Cleft lip with or without cleft palate (CL)*, a congenital malformation characterized by partial or complete clefting of the upper lip, with or without clefting of the alveolar ridge or the hard palate. It used also ICD-10 classification of PAHO/WHO and their definitions.

Results

Table 1 shows the distribution of the demographic factors found it. Most of the patients analyzed were born in Quito, 33.3% (158/475), and remain patients were born in one of the 22 provinces of our country. Male cases were 64.8% (308/475), the ratio male:female was 1.84:1. Children of less of 1 year comprise the 21.7% (103/475) of cases and, 80.2% of the cases (381/475) were Mestizos who are descendants from an admixture between Native Amerindians and European Caucasians.

Table 2 reports the distribution of the maternal and pregnancy risk factors related with the prenatal stage. In 48.6% of cases (231/475) the child was the product of the first pregnancy and, in 8.6% (41/475) of the cases the mother of the affected child had 4 or more pregnancies. In relation a relatives with a congenital malformation 33.3% (158/475) did not report any, in 12.9% (61/475) reported at least one relative with malformation being the most frequent a cousin. However, 53.9% (256/475) of the patients did not know if some relative had a congenital defect. At least 10.9% of the mothers

(52/274) ingested a medication during the pregnancy, from them 7.2% (34/475) ingested some kind of antibiotics. In relation to maternal consumption of alcohol, tobacco products or recreational drugs during pregnancy, were in all cases less of 5%. Positive maternal smoking was 3.5% (17/475), alcohol consumption was 4.2% (20/475) and recreational drugs only the 0.4% (2/475).

In 85.5% of cases the medical care was appropriated and the inter-gestational period was between 12 to 24 months in 19.4% of cases (93/475) being more of that time in 30.2% (139/475) of cases. In relation of the age of the mother, most of them were between 18 to 25 years, 49.3% of cases (144/475) but 11.6% of cases were (55/475) less of 18 years, and even more 8 cases were reported in women of less of 15 years. Most of the fathers were in the group of 25 to 35 years counting the 40.2% of cases (191/475), only 14 cases were between 45 to 57 years, 2.9% of cases. Children were born by normal delivery in 79.6% of cases (378/475) and in 65.1% did weight between 2,500 to 3,500 grams. Twin pregnancy counted in 4 cases only, and low weight at birth was found in only 24.6% (117/475).

Table 1. Distribution of the demographic factors (n= 475).

Place of birth (province)	n	%
Pichincha, Quito	158	33.3
Imbabura	63	13.3
Guayas	39	8.2
Cotopaxi	36	7.6
Tunguragua	33	6.9
Chimborazo	23	4.8
Loja	23	4.8
Santo Domingo	20	4.2
Pichincha, rest of province	15	3.2
Napo	12	2.5
Esmeraldas	10	2.1
Francisco de Orellana	8	1.7
Manabí	8	1.7
Bolívar	7	1.5
El Oro	7	1.5
Los Ríos	3	0.6
Azuay	2	0.4
Macas	2	0.4
Zamora	2	0.4
Cañar	1	0.2
Carchi	1	0.2
Galápagos	1	0.2
Pastaza	1	0.2

Gender	n	%
Female	167	35.2
Male	308	64.8

Age in years	n	%
Less to 1	103	21.7
1	88	18.5
2	77	16.2
3	76	16.0
4	70	14.7
5	61	12.8

Ethnic group	n	%
Native Amerindian	74	15.6
White caucasian	12	2.5
Mestizo	381	**80.2**
Black afroecuadorian	8	1.7

Table 2. Maternal and pregnancy risk factors (n=475).

Gesta	n	%
1	231	48.6
2	126	26.5
3	77	16.2
4	24	5.1
5	7	1.5
6	4	0.8
8	1	0.2
9	2	0.4
10	1	0.2
12	2	0.4

Relative with malformation	n	%
Siblings	2	0.4
Uncles/aunts	6	1.3
Parents	10	2.1
Cousins	43	9.1
Unknown	256	53.9
None	158	33.3

Medication during pregnancy	n	%
Unknown antibiotics	17	3.6
Anihistaminic	6	1.3
Vaginal antibiotics	6	1.3
Cefalexine	5	1.1
Ampicillin	3	0.6
OCPs	3	0.6
Aminophillin	2	0.4
Aspirin	2	0.4
Ciprofloxaxine	2	0.4
Antihypertensives	2	0.4
Antifungi	1	0.2
Anticonvulsivants	1	0.2
Antidepressants	1	0.2
Antispasmodics	1	0.2
Gentamycin	1	0.2
Antiemetics	1	0.2
Penicillin	1	0.2

Maternal smoking	n	%
Yes	17	3.6
No	458	96.4
Habitual smoker	10	2.1
Ocassional	7	1.5

Maternal alcohol consumption	n	%
Yes	20	4.2
No	455	95.8
1 time/week	16	3.4
2-3 times/week	4	0.8

Inter-partum period (mos)	n	%
0-12	43	9.1
12-24	93	19.6
24-48	59	12.4
>48	49	10.3
non applicable	31	6.5

Prenatal medical care	n	%
Yes	406	85.5
No	69	14.5

Maternal recreational drugs	n	%
Inhaling glue or contact cement	2	0.4
None	473	99.6

Type of delivery	n	%
Normal delivery	378	79.6
Cesarean-section	97	20.4
Twins pregnancy	4	0.8

Weight at birth in grams	n	%
<2500	117	24.6
2500-3500	309	65.1
>3500g	49	10.3

Mother age (yrs)	n	%
<15	8	1.7
15-18	47	9.9
18-25	234	49.3
25-35	144	30.3
35-45	40	8.4
>45	2	0.4

Father age (yrs)	n	%
<15	0	0
15-18	17	3.5
18-25	186	39.2
25-35	191	40.2
35-45	67	14.1
45-57	14	2.9

Table 3 shows the distribution of the main medical problems during the pregnancy, during the delivery and during the perinatal stage. In 53.7% of cases (255/475) the mothers reported a problem during pregnancy being urinary tract infections the most frequent medical problem reported in 51.4% of cases (131/255), followed by threatened abortions in 12.5% (32/255) and sexual transmitted diseases in 11.4% (29/255). In 7.8% of cases (37/475) mothers had problems during the delivery or in the days before the delivery, of them in 30% of cases (9/37) were preeclampsia, in 26.7% acute fetal distress (8/37) and in 23.3% (7/37) were a preterm labor with a premature delivery.

Also 30% of the children (143/475) showed problems in the perinatal period, being the most important breastfeeding problem in 39% of cases (57/143), followed by upper respiratory tract infections in 21% (30/143) and newborn respiratory distress in 11.2% of cases (16/143). During the development 43.6% of patients (207/475) showed a problem, being the speech problem the most important with 53.6% of cases (111/207) and followed by the complications of the surgical procedure in 19.3% (40/207) and, periodontal problems in 14.5% of patients (30/207). Talking of the surgical procedure, 80.6% of patients (383/475) were under a surgical reconstruction and of them 30.9% (147/475) required at least a surgical procedure twice.

Table 3 Distribution of the main medical problems during the pregnancy, delivery and perinatal stage.

Pregnancy problems	n=255	%
UTI	131	51.4
Threatened abortion	32	12.5
STDs	29	11.4
Preclampsia	20	7.8
Pesticides exposure	8	3.1
Anemia	6	2.4
Preterm labor	6	2.4
Fetal diagnostic of malformation	5	2.0
Placenta previa	3	1.2
URTIs	3	1.2
Placental abruption	2	0.8
Oligohydramnios	2	0.8
Premature rupture of membranes	2	0.8
Trauma	1	0.4
Convulsion	1	0.4
Major depressive disorder	1	0.4
Gestational diabetes	1	0.4
Hepatitis	1	0.4
Hypothyroidism	1	0.4

Problems during delivery	n=37	%
Preclampsia	9	30.0
Acute fetal distress	8	26.7
Premature delivery	7	23.3
Abnormal bleeding	4	13.3
Fetus misplaced	3	10.0
Premature rupture of membranes	2	6.7
Fibroids + hysterectomy	1	3.3
Oligohydramnios	1	3.3
Polyhydramnios	1	3.3
Septate uterus	1	3.3

Perinatal problems in the child	n=143	%
Breastfeeding problems	57	39.9
URTIs	30	21.0
Newborn respiratory distress	16	11.2
Desnutrition	13	9.1
Otitis	9	6.3
Anemia	6	4.2
Other congenital malformation	6	4.2
Convulsions	2	1.4
Hypoglicemia	1	0.7
Neck abcess	1	0.7
Hemophilia	1	0.7
Muscular flaccidity	1	0.7

Development problems	n=207	%
Speech	111	53.6
Post surgical complications	40	19.3
Periodontal	30	14.5
Chronic desnutrition	25	12.1
Death of patient	1	0.5

Surgical procedure	n=475	%
One time	236	49.7
Twice	147	30.9
None	92	19.4

Pregnancy problems - 255/475 (53.7%); problems during delivery - 37/475 (7.8%); perinatal problems - 143/475 (30%); UTI= urinary tract infections; STDs= sexual transmitted diseases; URTIs= upper respiratory tract infections

Table 4 indicates the main clinical findings in the sample analyzed. CL phenotypes were the most common orofacial cleft, alone in 42.7% (203/475)) or in association with CP in 19.2% of cases (91/475). Both counted 61.9% of the cases. CP alone was 38.1% of cases (181/475). In relation of CL, the most common presentation was unilateral in 38.4% of cases (78/203), the side most affected was the left in 64.1% (50/78), the ratio left to right side was 1.78:1. The incomplete shapes were the most frequents, bilateral incomplete in 75.4% of patients (49/65). With CP the phenotype more frequent was cleft hard palate with cleft soft palate combined in 70.7% of patients (128/151). CLP combined counted by 19.2% of cases (91/475) and, the most common presentation was cleft hard/soft palate with bilateral cleft lip in 59.3% of cases (54/91).

Table 4. Main clinical findings.

General		**n=475**	**%**
Q35	Cleft lip	203	42.7
Q36	Cleft palate	181	38.1
Q37	Cleft lip + palate	91	19.2
Cleft lip		**n=203**	**%**
Q36.9	Unilateral	78	38.4
Q36.0	Bilateral	65	32.0
Q36.1	Median	60	29.6
	Affected side	**n=78**	**%**
	Right	28	35.9
	Left	50	64.1
	Shape		
	Unilateral incomplete	48	61.5
	Unilateral complete	30	38.5
	Bilateral incomplete	49	75.4
	Bilateral complete	16	24.6
Cleft palate		**n=181**	**%**
Q35.1	Cleft hard palate	35	19.3
Q35.3	Cleft soft palate	18	10.0
Q35.5	Cleft hard palate with cleft soft palate	128	70.7
	Affected side (cleft hard or soft palate alone)	**n=53**	**%**
	Right	31	58.5
	Left	22	41.5
Q35.7	Cleft uvula	3	
Cleft lip + cleft palate		**n=91**	**%**
Q37.4	Cleft hard/ soft palate + bilateral cleft lip	54	59.3
Q37.5	Cleft hard/soft palate + unilateral cleft lip	37	40.7

Finally, **table 5** shows other malformations found it and related with this primary malformation. 24.1% of cases (115/475) presented one or more additional malformations and, 15.16% (72/475) of cases were affecting multiple systems. Most common associated malformation was microcephaly in 6.9% of cases (15/115), followed by microtia in 6.5% of cases (14/115) and fissured, notched and cleft nose in 5.1% of cases (11/115). It also found CL or CP cases as a part of well described syndromes such as Pierre-Robin sequence, Silver-Russel, Patau, Cornelia de Lange and Down syndromes.

In relation with the etiology and the risk factors, this study found positive correlations between orofacial clefts and different factors, such as multiple gestations above 4 gestations (41/475), low maternal age below 15 years (8/475), high paternal age above 45 years (14/475), low weight at birth below 2,500 gs (117/475) which is related with intrauterine growth retardation, positive use of anticonvulsivants (1/475), frequent maternal alcohol consumption of 2-3 times per week (4/475).

Table 5. Other malformations found it.

ICD-10	Main malformations found it	n=115	%
Q02	Microcephaly	15	6.9
Q17.2	Microtia	14	6.5
Q30.2	Fissured, notched and cleft nose	11	5.1
Q21.0	Cardiac septal malformations	9	4.2
Q69	Polydactily	8	3.7
Q90	Down's syndrome	6	2.8
Q70	Sindactily	5	2.3
Q65	Congenital deformities of hip	4	1.9
Q18.3	Webbing of neck	4	1.9
K07.1	Prognathism / Retrognathism	3	1.4
Q66.0	Talipes equinovarus	3	1.4
Q53	Undescended testicle	3	1.4
Q35.7	Cleft uvula	3	1.4
Q42.3	Imperforate anus	2	0.9
Q38.5	Absence of uvula	2	0.9
Q79.2	Exomphalus	2	0.9
Q87.0	Pierre Robin sequence	2	0.9
Q87.1	Silver-Russell syndrome	1	0.5
Q91.7	Patau's Syndrome	1	0.5
Q87.1	Cornelia de Lange syndrome	1	0.5
Q04.0	Agenesis of corpus callosum	1	0.5
H54.0	Amaurosis	1	0.5
Q56.4	Ambiguous genitalia	1	0.5
Q39.0	Atresia of oesophagus	1	0.5
Q66.8	Club foot	1	0.5
Q43.2	Congenital dilation of colon	1	0.5
Q43.6	Congenital fistula of rectum and anus	1	0.5
Q03.0	Congenital hydrocephalus	1	0.5
Q76.3	Congenital scoliosis	1	0.5
Q30.3	Congenital perforated nasal septum	1	0.5
Q38.2	Macroglossia	1	0.5
Q38.3	Microglossia	1	0.5
Q11.2	Microphtalmus	1	0.5
Q67.6	Pectus excavatum	1	0.5
Q73.1	Phocomelia	1	0.5
Q60.2	Renal agenesis	1	0.5

24.1% (115/475) presented one or more additional malformations.
15.16% (72/475) of cases were affecting multiple systems.

Discussion

In this study most of the patients arose from Quito because they were born there and the biggest children hospital is located in that city. However, sampling was made with a national perspective covering 22 provinces. In relation with ethnicity this study did not find any relevant correlation, even when most of the patients were Mestizos descending of Native Amerindians and European Caucasian, with a major component indigenous how we did show in a former study [15]. Most of cases found were men in agreement with the scientific literature.

In relation with the etiology and the risk factors, we think there are positive correlations between orofacial clefts and different factors, such as multiple gestations above 4 gestations, low maternal age below 15 years, high paternal age above 45 years, low weight at birth below 2,500 g which is related with intrauterine growth retardation, positive use of anticonvulsivants and frequent maternal alcohol consumption. It could say that in all these cases the cause is a preventable environmental factor that with be fixed with proper health policies. It found also a high prevalence of UTIs during the pregnancy and, its subsequent ingestion of oral antibiotics. Some of these medications

could de contributed to the origin of these birth defects. There is no correlation with Vitamin A ingestion, even when all patient mothers ingested multivitamins preparation during the pregnancy.

CLP may not be life-threatening but many functions such as feeding, digestion, speech, middle-ear ventilation, hearing, respiration and facial and dental development can be disturbed because of the structures involved. Their etiology remains largely unknown, with only a few cases associated with identified rare syndromes or secondary to recognized teratogen exposure. There is strong evidence that several environmental factors, e.g., alcohol consumption [16], tobacco [17], and anticonvulsants [18] increase the risk of CLP. In contrast, folic acid may have a protective effect on CLP and neural tube defects. The evidence of an association between maternal tobacco smoking and orofacial clefts is strong enough to justify its use in anti-smoking campaigns. In this study it found only 1 case related with the use of anticonvulsivants.

According with Yu [19], approximately 70% of orofacial clefts cases are non-syndromic cases, occurring as an isolated condition without association with any recognizable anomalies, while the remaining 30% are present in association with deficits or structural abnormalities occurring outside the region of the cleft. This data is compatible with our results partially; it found syndromic association only in 15% of cases. However, our team believe in it exists important congenital syndromes hidden and not identified properly in the first physical examination mainly due to the lack of experience of the primary care physicians in the genetics field.

Over 400 Mendelian disorders have been reported in OMIM in which clefting occurs as part of the overall clinical presentation [20]. In some studies, the frequency of CLP/CP differs with regard to sex and side of clefting with 2:1 (male:female) ratio and a 2:1 (left side:right side) ratio for clefting in unilateral clefts. CP alone has a 0.73:1 (male: female) ratio among the Caucasian population [21].

Non-syndromic orofacial cleft is an example of a genetically complex trait. The majority of affected patients have no positive family history and the evaluation of inheritance patterns in the familial cases has not revealed a simple Mendelian mode of inheritance. It is also clear that there is reduced or incomplete penetrance and variable expression pattern on a homogeneous genetic background. However, there is solid evidence that CLP is a genetic trait since there is a 40 fold risk for CLP amongst first degree relatives of an affected individual [22], and there is greater concordance in identical (monozygotic) compared to fraternal (dizygotic) twins. In twin studies, the observed concordance rate of 40–60% in monozygotic (MZ) twins is much higher than the 3–5% concordance rate in dizygotic (DZ) twins [23].

Compared with other birth defects, orofacial clefts have a high rate of familial recurrence. One study described the risk of cleft recurrence in first degree relatives was 32 for cleft lip and 56 for cleft palate alone compared to the reference populations, suggesting a stronger genetic basis for cleft palate compared with cleft lip [24]. In this study, it does not find cases among first relatives. Unilateral, incomplete, CL of the left side was the most frequent finding followed by cleft hard palate with cleft soft palate, in agreement with other series analyzed.

Conclusion

In Ecuadorian Mestizo children affected by orofacial clefts, unilateral, incomplete, CL of the left side was the most frequent finding, followed by cleft hard palate with cleft soft palate. There is correlation between orofacial clefts and multiple gestations above 4 gestations, low maternal age below 15 years, high paternal age above 45 years, intrauterine growth retardation, positive use of anticonvulsivants and frequent maternal alcohol consumption. Further evaluation is needed to understand more widely the multifactorial etiology of this problem.

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Contribution of the autors

All authors contributed equally to the conception, design, analysis and interpretation of data, drafting the article, further revision of this paper, and critical review of the content.

Founding

None

Competing Interest

The authors declare that they have no competing interests

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