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“Bioglass 45S5, a relevant alternative to autogenous harvesting for secondary alveolar bone grafts in clefts? Retrospective study of one hundred surgeries.”

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Bioglass 45S5, a relevant alternative to autogenous harvesting for secondary alveolar grafts in clefts?

Retrospective study of one hundred surgeries.

Summary

The secondary alveolar bone grafting (SABG) step restores the continuity of the alveolar bone necessary for dentition. Faced with the complications of autografts, synthetic biomaterials such as Bioglass (BG) 45S5 have been proposed. The objective was to evaluate the success rate of SABG with the addition of BG 45S5 and to highlight the prognostic factors. Patients operated on between 2015 and 2021 and had follow-up CBCT were analyzed. Multivariate analysis was performed to determine factors influencing radiographic success. 102 SABG were analyzed. They were unilateral total cleft lip and palate (49, 48.0%). The mean age of surgery was 9.32 ± 3.09 years. They were performed mainly outside a syndromic context and without a family history after orthodontic preparation. The radiographic success rate at 1 year was 80.4%. Mixed dentition stage (OR = 7.3, $p = 0.024$), absence of syndromic context (OR = 20.7, $p = 0.024$) and female sex (OR = 4.88, $p = 0.021$) were predictive factors for surgical success. The use of BG 45S5 instead of autograft is relevant for SABG with a one-year success rate of over 80%. The stage of mixed dentition, the absence of syndromic context and the female sex were factors of good prognosis.

Key-words: cleft palate, secondary alveolar bone graft, biomaterial, bioglass

Introduction

Cleft lip and palate is the fourth most common congenital malformation and the first craniofacial anomaly (Ysunza, Pamplona, and Repetto 2015). Cleft lip and/or palate (CL/P) are divided into two groups: isolated cleft palate, and cleft lip without or with cleft palate (Merritt 2005; Shkoukani, Chen, and Vong 2013). In France, the incidence of CL/P in all clinical forms is 1 per 700 to 1000 births (CCMR MaFace and Filière de santé maladies rares TeteCou 2021). Cleft palate is characteristic of over 200 well-defined congenital malformation syndromes (Ysunza, Pamplona, and Repetto 2015). Nearly 70% of cases are considered non-syndromic (Stanier and Moore 2004). At present, the described etiologies are multifactorial and involve genetic and environmental factors (Dixon et al. 2011; Martinelli et al. 2020).

It is not yet possible to completely prevent the onset of these embryopathies which, if left untreated, have a considerable impact on the quality of life of children (Rando et al. 2018; Karki et al. 2021; Leopoldo-Rodado et al. 2021). In France, to optimize the care pathway, a national diagnosis and care protocol (PNDS) was published in November 2021 (CCMR MaFace and Filière de santé maladies rares TeteCou 2021). The goal of cleft lip and palate repair is to restore oral anatomy and velum function (L. Ma et al. 2021). It takes place through three surgical steps.

The first step is primary cheilo-rhinoplasty associated with intraveloplasty. It takes place between three and six months. The second step is the closure of the residual bone gap, scheduled between 12 and 18 months. The third step, called secondary alveolar bone grafting (SABG), takes place between 4 and 6 years of age after orthodontic preparation. This key step

provides support to the maxillary arch for dentition and mastication by preventing transverse collapse (Weissler et al. 2016; X.-L. Liu et al. 2017).

The use of bone grafts or synthetic substitutes is described. They can be of natural origin, such as autografts or allografts. Autogenous harvesting can come from different sites: the most common is the iliac crest, but the tibia, mandible or skull can also be used (Thuaksuban, Nuntanaranont, and Pripatnanont 2010). The inconvenience is due to the complications related to the harvesting: postoperative pain, difficulty in walking, nerve damage, hematoma and infections (Cricchio and Lundgren 2003; Sbitany et al. 2010; Hayes et al. 2011; Chang et al. 2017; Sequera-Ramos et al. 2019; Tache and Mommaerts 2021).

In this context, alternatives were sought (Liang et al. 2018; Wu et al. 2018). Researchers are proposing the use of various bone substitutes: β -tricalcium phosphate (TCP), bioactive silicates, calcium phosphate, recombinant human bone morphogenic proteins-2 and 7 (rhBMP-2 and rhBMP-7) ⁴(Osorio et al. 2020; Brézulier et al. 2021). Among bioactive silicates, Bioglass® (BG) 45S5 provides promising results in a study of 58 cases (Graillon et al. 2018). However, literature is poor on its use in SABGs.

The primary aim of this study was to determine the success rate of SABG with BG supply. The secondary objectives were to test the predictive value of different parameters on the success of this approach by uni- and multivariate models.

1 Materials and methods

1.1 Study Design and Participants

A retrospective cross-sectional observational study was conducted according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) recommendations. The approval of the Ethics Committee of the Hospital of Rennes was obtained (opinion n°22.31). Data collection took place from November 2021 to July 2022.

Data from 124 SABG with BG 45S5 (GlassBone, Noraker, France), consecutively conducted in the pediatric surgery department of the South Hospital of the University Hospital of Rennes between July 2015 and 2021, by two surgeons, were used in the study. The surgical technique was always the same. First, a vestibular approach allows exposure of the bony cleft. The nasal mucosal plane is closed tightly in case of a fistula, whether it is known or discovered during surgery. The palatal fibromucosal plane is then closed tightly. The bone margins are then enhanced by corticotomies. Briefly, corticotomies are performed with the tip of an 11-blade scalpel on both bone margins, at a distance from the dental germs, until blood suffusion is obtained, but without bone avulsion. The bony cleft is filled with BG, followed by gingivoperiostoplasty to ensure tight closure.

Inclusion criteria were: (1) SABG of a facial cleft; (2) with a BG 45S5 bone substitute (GlassBone, Noraker, France); (3) performed in patients with a complete medical and radiographic record.

Exclusion criteria were: (1) absence of pre- or postoperative three-dimensional X-ray imaging at 1 year, (2) unreadable postoperative three-dimensional imaging at the six sites evaluated, (3) use of another type of graft, and (4) incomplete medical records.

1.2 Studied variables

The variables were divided into six blocks. The first described the sample: patient's age at SABG, gender, syndrome, history of familial clefts.

The second described the characteristics of the operated cleft: type, laterality.

The third described the dental data in relation to the cleft: orthodontics, formula (normal, lateral incisor agenesis, supernumerary tooth), stage of dentition at the time of SABG (temporary, mixed, adolescent), temporary teeth in the cleft and time of their extraction (pre- or per-operative), preoperative fistula.

The fourth one reported on the surgical procedure: fistula closure, operator, ambulatory character, anesthesia by supra-zygomatic block.

The fifth part consisted of postoperative data: residual fistula, antibiotics, infections.

The sixth section, which develops the radiographic data, is presented below.

1.3 Radiographic evaluation and definition of the operative result

The last set of variables was composed by measurements on CBCTs at 1 year. The three planes, orthogonal, 2 mm thick, were selected as follows (Figure 1). A first plane connected the two

teeth adjacent to the cleft. A second described the long axis from the mesial tooth to the cleft. A third traveled the cleft path on an anteroposterior axis.

Scoring by thirds (apical, medial, cervical) was performed in the horizontal and vertical dimensions. Therefore 6 sites were evaluated. The score was a discrete variable with three modalities: "1" for the absence of detectable bone in the area of interest, "2" in the presence of bone not filling the area on either side, "3" in the presence of bone filling the area of interest. In case of artifacts or blurring making the area non-evaluable, the score "NA" was assigned.

Inter- and intra-examiner reproducibility was assessed on 11 CBCTs by 4 practitioners (OA, TDB, DB, and AS) using Fleiss kappa and Cohen's kappa. It was complemented by reproducibility analyses by pair of examiners. Postoperative CBCTs were then all read separately by the two practitioners with the highest inter-rater reproducibility. Examinations with score discrepancies were re-evaluated by the two examiners associated with a third in a joint reading.

From these measurements, the outcome of the surgical procedure was defined by a binary variable taking the modalities: "failure" if the number of sites with score "1" was greater than or equal to 3 out of 6; "success" in all other cases.

1.4 Statistical analysis

Data were compiled in a Microsoft Excel® spreadsheet. Statistical analysis was performed with RStudio® software v1.4.1103 (RStudioTeam) in R language v4.0.2 (RCore Team). Categorical

data were reported as proportions and counts. χ^2 tests were performed for comparison. Univariate and multivariate logistic regression analyses were performed. Covariates from the univariate analysis were entered into top-down stepwise multivariate regression analyses. A p value ≤ 0.05 was considered significant.

2 Results

2.1 Descriptive analysis of the sample

2.1.1 Characteristics of surgical procedures

The study included 124 SABG surgeries with BG 45S5 performed on 97 patients. 22 were excluded: 16 had no control CBCT at 1 year and for 6, it was unusable (6 of the 6 sites were "NA"). This left a sample of 102 procedures in 79 patients, performed by two experienced operators with a ratio of 3:7. Of this sample, 95 (93.1%) procedures were a primary SABG procedure and 7 (6.9%) were a revision. The procedures were performed at a mean age of 9.32 ± 3.09 years and carried out 34 times in girls and 68 times in boys, i.e., 33.3% and 66.7% respectively. In 96 (94.1%) procedures, the cleft was isolated and 85 (83.3%) had no family history. The majority of the procedures were performed under general anesthesia on an outpatient basis (96 cases; 94.1%) with suprazygomatic block for 82 cases (80.4%). The majority of cases received 1 cubic centimeter of bioglass (99 cases; 97.1%), the remaining cases required 2 cc. These procedures were almost all under antibiotic coverage (99 cases; 97.1%). Three procedures (2.9%) developed a postoperative infection. The mean age of the follow-up CBCT for this study was 1.58 ± 0.94 years.

2.1.2 Characteristics of operated clefts

The majority of the surgeries involved unilateral clefts (57.8%) located on the left in 66 (64.7%) cases. They involved 49 (48.0%) unilateral CLP, 4 (3.9%) bilateral CL, 10 (9.8%) unilateral CL, 4 (3.9%) asymmetrical bilateral CLP and 35 (34.3%) symmetrical CLP.

An orthodontic preparation phase preceded 96 (94.1%) of the surgeries. For all of them and to avoid contraction of the fragments after the graft, the patients were fitted with a Hawley plate or a trans-palatal arch or quad'helix after the surgery. In 40 (39.2%) patients, the maxillary lateral incisor was agenetic. In contrast, 15 (14.7%) cases had supernumerary teeth or odontomas near the cleft. 36 (35.3%) cases had a primary tooth in the cleft path. Moreover, in 12 (11.8%) surgeries, a tooth near the cleft was extracted.

Oral-nasal fistulas were visible before the operation in 51 cases (50.0%). They were either closed before the procedure (3 cases; 5.9%) or during the procedure (48; 94.1%). Also, two fistulas (3.9%) of incidental discovery were closed during surgery, leading to 53 closure procedures.

2.1.3 Assessment of surgical success rate

Firstly, each rater read 11 CBCTs twice, one month apart. Intra-rater reproducibility ranged from 0.77 to 0.89. Intra-group reproducibility by Fleiss kappa was 0.71. The pair with the best reproducibility (0.85) then evaluated all CBCTs.

At the end of the inter-examiner consensus, 9 (1.52%) evaluated sites had artifacts, 8 in the horizontal dimension (1 apical, 2 medial, 5 cervical) and 1 in the vertical (cervical). They were

found in 5 patients, respectively 2, 2 and 1 subject with 1, 2 or 3 missing values. For the further analysis, the score "1" was assigned to the artifactual sites.

Scores 2 and 3 were most often attained in both dimensions with one exception in the cervical third, with the minimum score (1) most present in the horizontal dimension (Table 1).

Using the definition of surgical outcome described previously, 82 (80.4%) procedures were successful and 20 (19.6%) were failures. More precisely, among the 95 first operative steps, 77 (81.1%) were successful and among the 7 revision surgeries, 5 (71.4%) were successful ($p = 0.6$).

Considering the orthodontic aspect and the possibility of moving teeth within the graft zone, only 59 of the patients in the cohort were now old enough to receive braces. Of these, 39 (66.1%) are currently being treated without any particular complication regarding tooth displacement.

2.2 Univariate analysis of factors impacting success

Initially and after exclusion of the only case with a median cleft (surgical success), a univariate analysis was conducted to explain a successful outcome of SABG using the factors: sex, laterality of the cleft, type of cleft (transformed into "cleft lip/alveolar" or "cleft palate"), syndromic context, surgical step, family history, number of teeth, extraction of teeth, repair of a fistula, and stage of dentition (Table 2). The univariate analysis approach reported no parameters affecting success.

2.3 Multivariate analysis of factors impacting success

Initially, a complete model was used to conduct the multivariate analysis (Figure 2). Factors predictive of radiographic success were (1) mixed dentition stage (OR = 7,30, IC = 1,67-42,5, p = 0,024); (2) non-syndromic status (OR = 20,7, IC = 1,48-393, p = 0,024); and (3) female gender (OR = 4,88, IC = 1,26-23,2, p = 0,021). The Hosmer-Lemeshow test concluded that the model had good predictive value ($\chi^2 = 10.55$; p = .23).

In a second step, the stepwise top-down selection technique was used to simplify the explanatory model, generating a reduced model (p = 0.74). Only the factors: dentition stage, sex and syndrome were retained in this model. It had an Akaike Information Criterion (AIC) of 100.33 versus 112.32 for the full model. Pour ce modèle le test de Hosmer-Lemeshow reached ($\chi^2 = 1.10$; p = .998).

3 Discussion

The anterior iliac crest is the preferred donor site for SABG (Schaaf et al. 2010; Gjerde et al. 2020). However, postoperative pain is reported in 38% of cases. Some patients report walking difficulties, haematomas, paresthesias and infections (Eufinger and Leppänen 2000; Nkenke et al. 2004; Swan and Goodacre 2006; Hernigou et al. 2014; Jessop et al. 2015; Brudnicki et al. 2019). This leads to 4.3 ± 3.5 days of hospitalization and 20.2 ± 18.5 days of work absence (Gjerde et al. 2020). Ultimately, it degrades patients' quality of life (Reissmann et al. 2013).

The benefits of using a biomaterial are multiple: no donor site, no limited quantity of material (Janssen et al. 2014), reduction in operating time and the ambulatory nature of general anesthesia. The use of BG 45S5 makes the surgical protocol studied here completely innovative. This synthetic material is a silicate network (45 wt% SiO₂) incorporating 24.5 wt% Na₂O, 24.5 wt% CaO, and 6 wt% P₂O₅ (Hench 2006). It binds rapidly to bone and promotes osteoblasts differentiation. Its dissolution fluids is responsible for the creation of a suitable pH for the nucleation of hydroxyapatite (Sanders and Hench 1973). BG 45S5 also has an inhibitory effect on the activity of osteoclasts ("Abstracts of the 35th European Symposium on Calcified Tissues" 2008). This biochemistry makes it an excellent candidate for surgical applications with a limited cost (Graillon et al. 2018; Al Tamami et al. 2020). One of the problems with this type of substitute is its granular form, which does not ensure good mechanical properties. An orthodontic follow-up is therefore necessary.

The main objective of this study was to establish the success rate of SABG with BG 45S5. As this technique is not yet widely used, a retrospective analysis was chosen as it is faster, economic and easier to implement. This primary objective requires a reliable outcome

measure. Although the clinical criterion of success is the placement of teeth in the operated area, a radiographic evaluation is imperative, in particular to argue the need for a surgical revision. The evaluation of the success of the graft have been discussed for a long time, reflecting its complexity due to the radiographic technique and the growth of patients (Kamperos et al. 2020; Shaheen et al. n.d.; Stasiak, Wojtaszek-Słomińska, and Racka-Pilszak 2021; Chen et al. 2021). Bergland's two-dimensional classification method is historically the most widely used (Bergland, Semb, and Abyholm 1986; Witherow et al. 2002; Hynes and Earley 2003). It gives excellent results (majority of graft height > 50% of the cleft height) (Newlands 2000; Matic and Power 2008). However, it does not take into account the sagittal dimension where most of the resorption takes place (Dissaux et al. 2016). Three publications point out that 2D evaluation overestimates results (Van der Meij et al. 2001; Hamada et al. 2005; Feichtinger et al. 2008). These findings make 3D diagnostics an appropriate tool for this purpose. Specifically, cone-beam CT (CBCT) is preferred over CT because of its lower radiation dose (Amirlak et al. 2013). The evaluation of a percentage or volume of reconstruction during SABG remains extremely complex. First, because percentage ratios do not provide a spatial assessment of the architecture of the bone bridge (Zhang et al. 2012; Dissaux et al. 2016; Stasiak, Wojtaszek-Słomińska, and Racka-Pilszak 2019; B. Liu et al. 2020). Secondly, because this type of evaluation requires defining anatomical landmarks, which are non-standardized criteria and delicate to implement in a growing patient (Feng et al. 2017). Based on these findings, our study replicated the Suomalainen protocol (Suomalainen et al. 2014). It allows the precise localization of the graft in three dimensions. It has been used in a recent study (Padwa et al. 2022). The evaluation was conducted on CBCT taken on average 1 year after surgery as recommended in the literature (Stasiak, Wojtaszek-Słomińska, and Racka-Pilszak 2019).

Taking all of these elements into account, the success rate of SABG varies from 32% to 95%. This wide variability is due to the different definitions of success (Tan et al. 1996; Kumar et al. 2017). It is also due to the length of follow-up. Studies conducted in the short term, less than one year, show a higher success rate. A study using the same protocol showed a 94% success rate (Padwa et al. 2022). According to a 2022 meta-analysis, the total percentage of SABG success in the follow-up period of at least 1 year according to the Bergland index was 76.52% and the total percentage of bone filling after 1 year and according to CBCT was approximately 63.38% (Jahanbin et al. 2022).

The protocol with BG 45S5 led here to a success rate of 80%, higher than that found in the literature for this type of procedure with autogenous graft. Moreover, this score should be weighted by the fact that the artifactual sites were given a score of "1" by default, which leads to an underestimation of the success rate. In addition, the very low complication rate is significantly lower than reported with autografts. Only one other study used the same surgical protocol. In a smaller sample (58 patients) and with an assessment of bone continuity on CBCT at 1 year by linear measurements, the success rate was fewer than ours (Graillon et al. 2018). From an orthodontic point of view, the young age of the cohort meant that no reliable long-term conclusions could yet be drawn. However, the first 39 cases showed that it was possible to move teeth through the grafted area.

Secondly, we sought to establish the parameters influencing the outcome. A univariate and then multivariate approach was conducted. It is regularly used in medicine for these purposes (Bell et al. 2014; Mishra et al. 2021). Nevertheless, a preliminary description of the sample is essential. Concerning the gender of the patients, 66.7% of the interventions concerned boys, which is comparable to a systemic review (Li Ma et al. 2021). The mean age of 9.32 years at

the time of surgery has been found in another study (Chen et al. 2021). The majority of the clefts were located on the left, in agreement with the literature. One of the particularities here is the high proportion of bilateral clefts (42.2%), since the incidence of unilateral clefts is normally double that of bilateral ones (Martelli-Junior et al. 2007). As in the literature, clefts were associated with a syndrome in 5.9% of cases (“Prevalence at Birth of Cleft Lip with or without Cleft Palate: Data from the International Perinatal Database of Typical Oral Clefts (IPDTC)” 2011). Van der Woude syndrome was the most common in this sample. It is the leading cause of syndromic cleft lip and palate. It associates clefts, fistulas of the lower lip and sometimes hypodontia (Ural et al. 2019).

The univariate analysis approach reported no parameters influencing surgical success. The data were then included in a multivariate model. The syndromic context was then shown to be an unfavorable element for the success of SABG. The literature on this subject is not abundant. The vast majority of studies exclude patients with syndromes (Chetpakdechit et al. 2021; Thiruvengkatachari et al. 2021). Concerning the Van der Woude syndromes, a recurrent inflammatory context complicate the care (Dissemond et al. 2004; Etöz and Etöz 2009). Another parameter that emerged from this approach was the stage of dentition reached at the time of surgery. The stage of mixed dentition, i.e. after evolution of the permanent lateral incisor but before eruption of the canine, offered the best prognosis (Ozawa et al. 2007; Zhang et al. 2012; Borba et al. 2014). The eruption of the lateral incisor would initiate osteoinductive activities resulting in better bone formation and less resorption (Ozawa et al. 2007). In parallel, rapid closure of the space and eruption of the canine through the grafted area were associated with maintenance of the thickness and width of the bone volume (Feichtinger, Mossböck, and Kärcher 2006; 2007; Elhaddaoui et al. 2017; Miller et al. 2010). A 3D analysis showed a higher success rate of bone grafting around 5 years of age

(Dissaux et al. 2016). This age is younger than the study cohort. With the first ones dating back to 2015, orthodontic expansion was complex. The age of surgery is decreasing as advances in orthodontics make it easier to manage very young patients. The impact of the adjacent tooth is essential and directly influences the success rate of the bone graft, regardless of age (Feichtinger, Mossböck, and Kärcher 2006; 2007; Pinheiro et al. 2020). Finally, male sex was found to be a predictive factor for failure. Our hypothesis is that young boys have poorer oral hygiene control and inflammatory conditions around the graft. Girls brush their teeth more often and tend to have better oral hygiene and dental care (Vallejos-Sánchez et al. 2008; Angelopoulou et al. 2015; Costa et al. 2022). Although we did not collect this parameter from patients, several studies have associated poor hygiene with SABG failure (Jabbari et al. 2015; Lundberg, Levring Jäghagen, and Sjöström 2021; Chalien, Mark, and Rizell 2022).

Despite the reported success rate of about 80%, the limitations of this study should be noted. First of all, radiographic success does not predict clinical success, especially the good evolution of the teeth in the grafted areas with a healthy aspect of the periodontal mucosa. Secondly, the histo-physiology of the newly formed bone remains unknown. Further work in this area is required.

Conclusion

We can affirm that the innovative approach to clefts using BG 45S5 substitute offers a very interesting success rate, greater than 80%. A multivariate analysis retained the following predictive factors for a favorable outcome: mixed dentition stage, absence of syndromic context and female gender. The earlier the SABG was performed, the more favorable the outcome, always before the evolution of the permanent canines. To reinforce these good results, we believe it is essential to implement appropriate oral hygiene measures.

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Captions

Figure 1: Positioning of 2mm-thick CBCT slices in vertical and horizontal dimensions.

Figure 2: Complete multivariate analysis model and reduced model using the step-down selection technique for successful 1-year radiographic outcome of SABG.

Table 1: Distribution of scores on the six sites evaluated on CBCTs at 1 year after SABG in the vertical and horizontal dimensions at the apical, medial, and cervical thirds. Unreadable or artifactual sites were given a score of 1.

Table 2: Univariate regression analysis for successful 1-year radiographic outcome of SABG.

Score	Vertical			p-value ²	Horizontal			p-value ²
	1, N = 76 ¹	2, N = 129 ¹	3, N = 101 ¹		1, N = 84 ¹	2, N = 149 ¹	3, N = 73 ¹	
Thirds				<0.001				<0.001
<i>Apical</i>	17 (16.7%)	39 (38.2%)	46 (45.1%)		18 (17.6%)	52 (51.0%)	32 (31.4%)	
<i>Medial</i>	16 (15.7%)	47 (46.1%)	39 (38.2%)		16 (15.7%)	61 (59.8%)	25 (24.5%)	
<i>Cervical</i>	43 (42.2%)	43 (42.2%)	16 (15.7%)		50 (49.0%)	36 (35.3%)	16 (15.7%)	

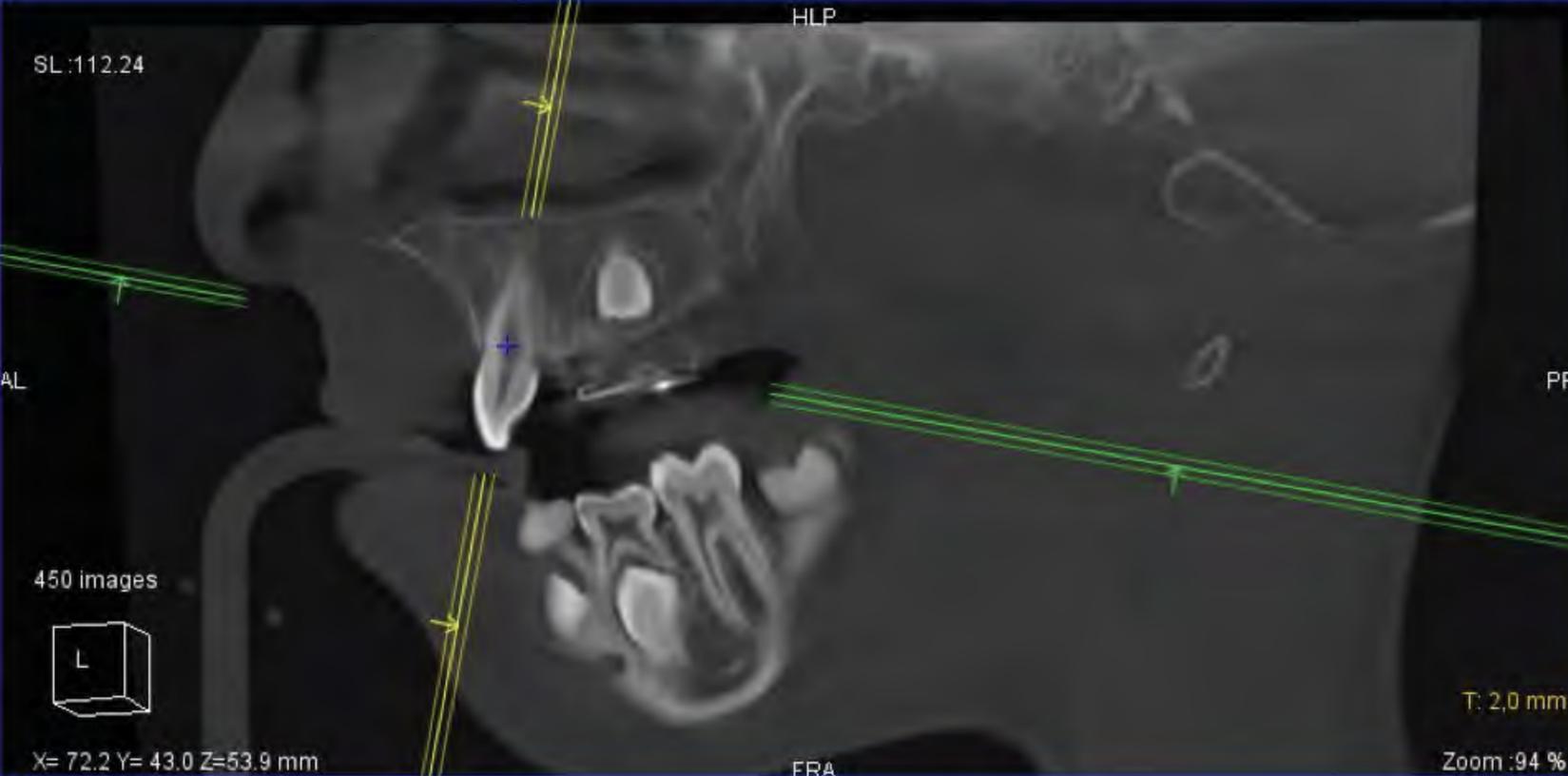
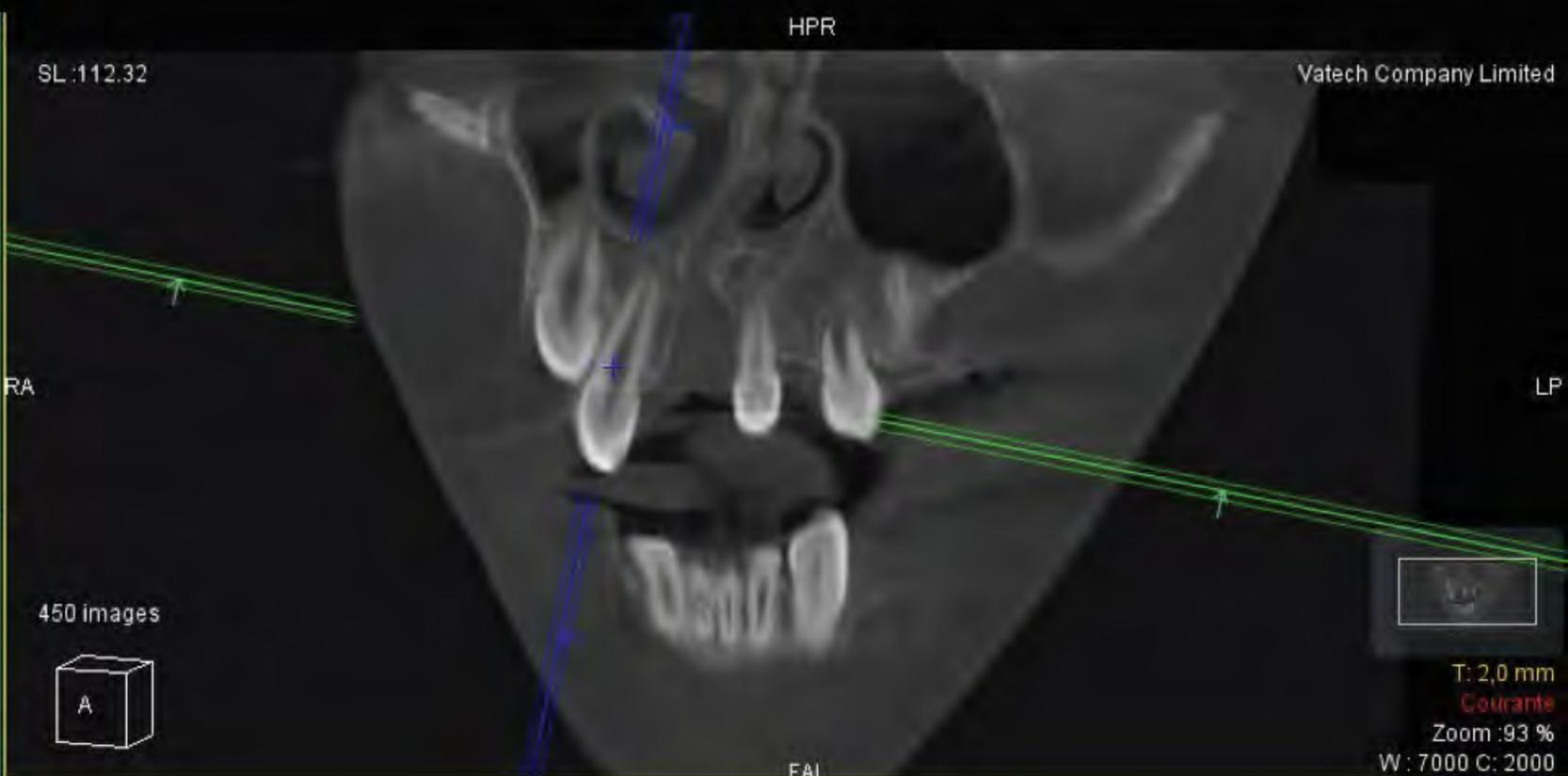
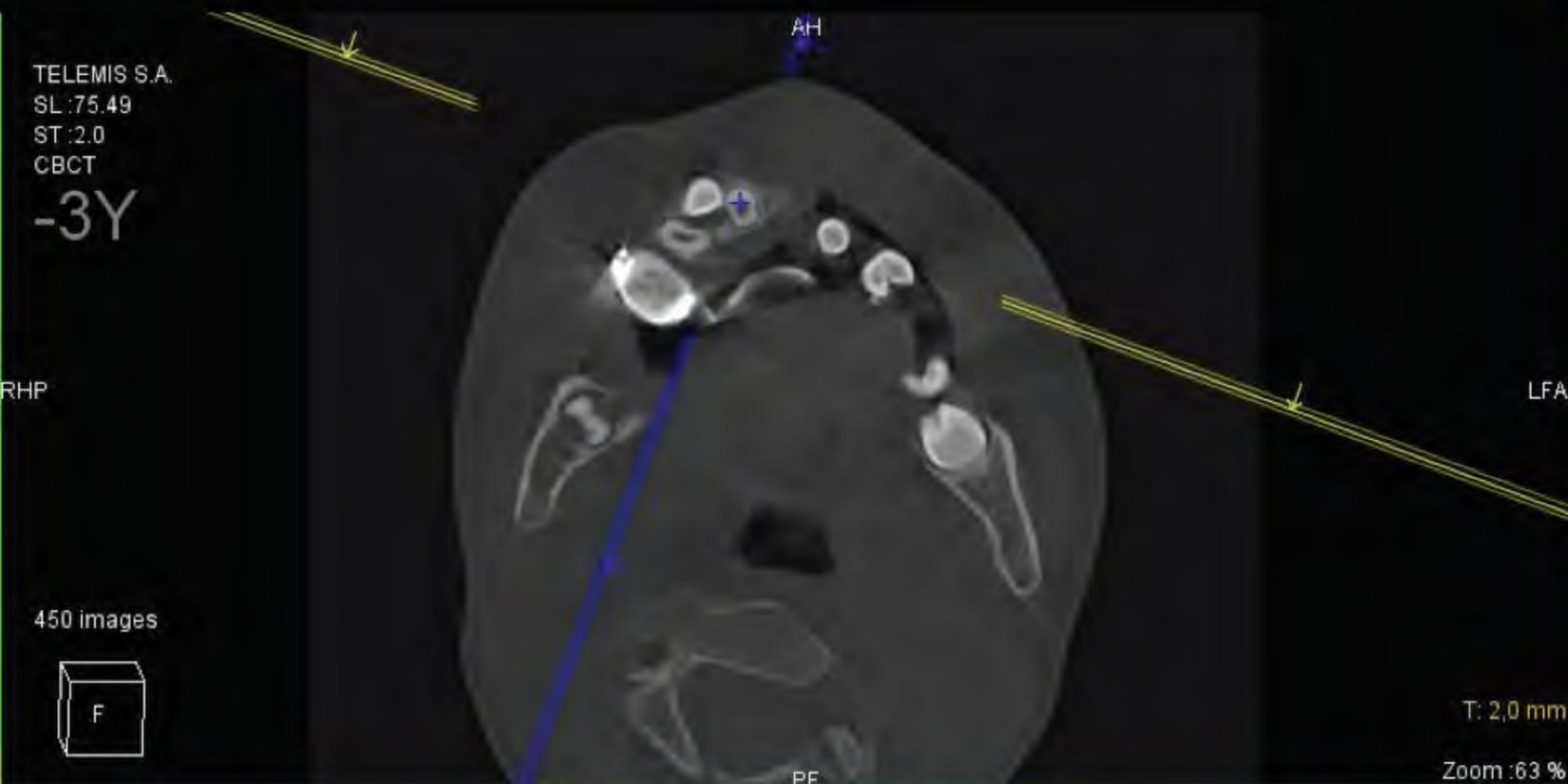
¹ n (%)

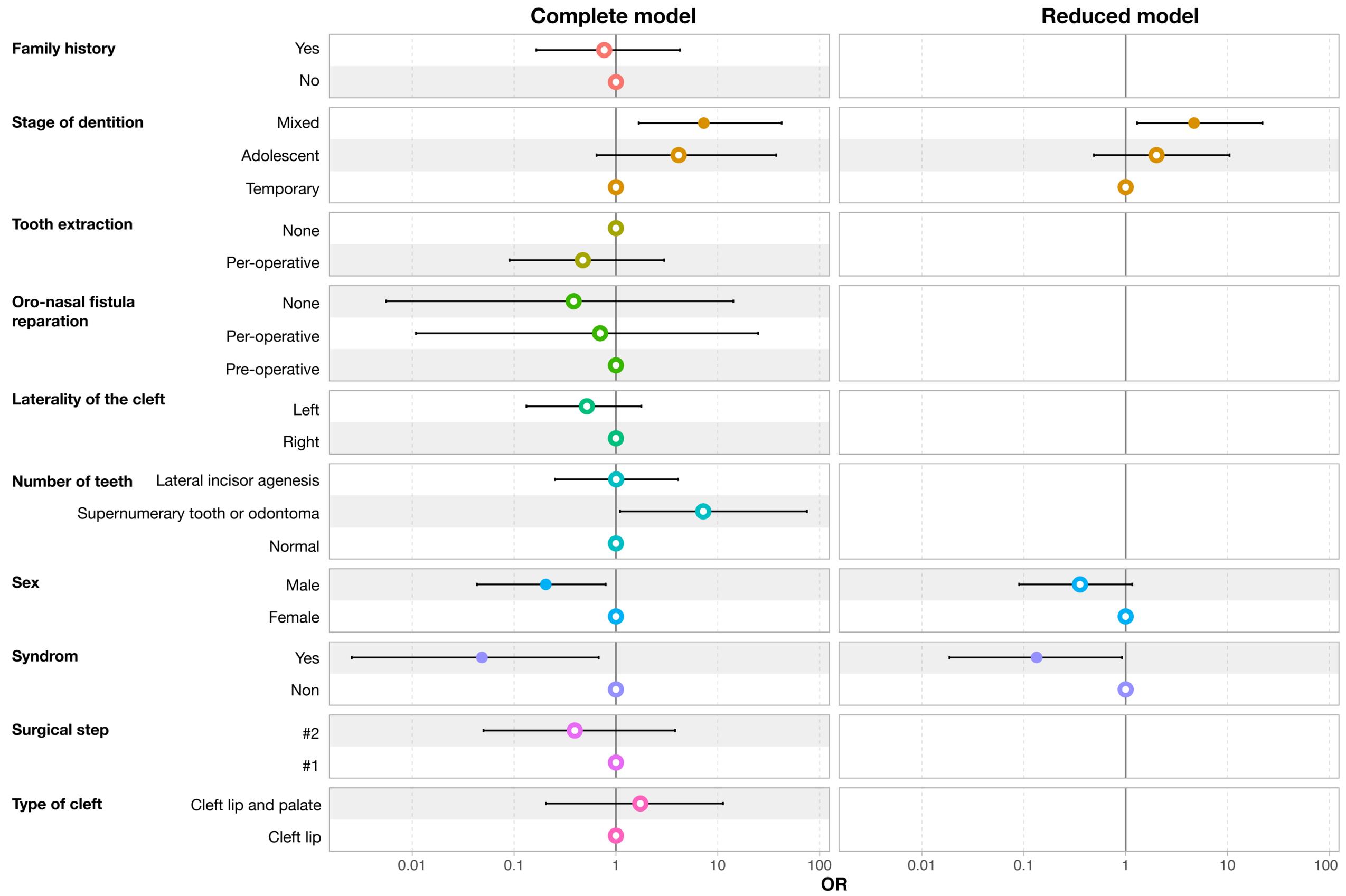
² Pearson's Chi-squared test

Parameters	N	Event N	OR ¹	95% CI ¹	p-value
Sex	101				0.16
<i>Female</i>		29	—	—	
<i>Male</i>		52	0.45	0.12, 1.36	
Laterality of the cleft	101				0.97
<i>Right</i>		28	—	—	
<i>Left</i>		53	1.02	0.35, 2.79	
Type of cleft	101				0.56
<i>Cleft lip</i>		12	—	—	
<i>Cleft lip and palate</i>		69	0.64	0.09, 2.63	
Syndrom	101				0.086
<i>No</i>		78	—	—	
<i>Yes</i>		3	0.22	0.04, 1.26	
Surgical step	101				0.56
<i>#1</i>		76	—	—	
<i>#2</i>		5	0.59	0.12, 4.36	
Family history	101				0.68
<i>No</i>		68	—	—	
<i>Yes</i>		13	0.76	0.23, 2.99	
Number of teeth	101				0.59
<i>Normal</i>		35	—	—	
<i>Lateral incisor agenesis</i>		33	1.48	0.52, 4.46	
<i>Supernumerary tooth or odontoma</i>		13	2.04	0.46, 14.4	
Tooth extraction	101				0.64
<i>None</i>		72	—	—	
<i>Per-operative</i>		9	0.71	0.19, 3.44	
Oral-nasal fistulas reparation	101				0.80
<i>Pre-operative</i>		2	—	—	
<i>None</i>		37	1.90	0.08, 21.9	
<i>Per-operative</i>		41	2.28	0.10, 26.4	
Stage of dentition	101				0.20

<i>Mixed</i>	33	—	—
<i>Adolescent</i>	12	0.36	0.07, 1.75
<i>Temporary</i>	36	0.36	0.09, 1.16

¹ OR = Odds Ratio, CI = Confidence Interval





● $p \leq 0.05$ ○ $p > 0.05$