

Article

Dental Agenesis in Repaired Craniofacial Cleft Patients: Influence of Cleft Type, Sex, and Skeletal Pattern

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Abstract

Background: Congenital tooth agenesis is a common dental anomaly in individuals with orofacial clefts and may be related not only to cleft type but also to skeletal growth characteristics. This study aimed to investigate whether the number of congenitally missing permanent teeth is associated with cleft type, sex, and sagittal and vertical skeletal patterns in non-syndromic cleft patients. **Materials and Methods:** A retrospective cross-sectional analysis was conducted on 60 patients aged ≥ 17 years (36 males, 24 females; mean age 19.5 ± 1.8 years) with surgically repaired cleft lip and/or palate, based on clinical records collected over a long-term follow-up period. Sagittal (Class I, II, III) and vertical (normal, deep bite, open bite) skeletal patterns were extracted from available orthodontic records based on routine cephalometric assessment. The number of congenitally missing permanent teeth, excluding third molars, was recorded. Statistical analysis included non-parametric tests and Poisson regression. **Results:** The distribution of missing teeth deviated significantly from normality according to the Shapiro–Wilk test ($p < 0.001$). In the Poisson regression model, sex ($p = 0.011$) and cleft type ($p < 0.001$) were significantly associated with the number of congenitally missing teeth, whereas sagittal skeletal pattern ($p = 0.338$) and vertical skeletal pattern ($p = 0.281$) were not significant predictors. **Conclusions:** In this retrospective record-based analysis, the number of congenitally missing teeth appeared most consistently associated with cleft type, while sex showed a model-dependent association in the adjusted regression analysis.

Keywords: cleft lip and palate; congenital tooth agenesis; hypodontia; skeletal malocclusion; vertical skeletal pattern



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1. Introduction

Craniofacial clefts, including cleft lip (CL), cleft palate (CP), cleft lip and palate (CLP), and related forms, are congenital conditions frequently associated with disturbances in

craniofacial growth and dental development. Even after surgical repair during childhood, individuals with clefts often present long-term alterations in dentofacial morphology that require comprehensive orthodontic management in adolescence or adulthood.

Among the dental anomalies observed in these patients, congenital tooth agenesis represents one of the most prevalent findings [1]. Tooth agenesis, defined as the congenital absence of one or more permanent teeth (excluding third molars), is a developmental condition with multifactorial etiology involving genetic, epigenetic, and environmental influences [1,2]. Third molars were excluded because of their highly variable developmental pattern and the relatively high prevalence of physiological absence in the general population, which may complicate the diagnosis of true congenital agenesis. It may occur as an isolated finding or in association with craniofacial disorders. Beyond its clinical implications for occlusion and aesthetics, hypodontia has been linked to variations in craniofacial morphology and skeletal growth patterns [3]. Experimental and clinical evidence suggests that disturbances affecting neural crest cell migration and epithelial–mesenchymal interactions during early embryogenesis may simultaneously influence odontogenesis and maxillofacial growth [4,5]. This shared developmental origin may partly explain the frequent coexistence of dental agenesis and craniofacial anomalies in cleft populations. Studies in non-cleft orthodontic populations have demonstrated significant associations between tooth agenesis and sagittal skeletal discrepancies, particularly Class III relationships, as well as vertical growth variations [3]. In individuals with orofacial clefts, the prevalence and distribution of tooth agenesis are substantially higher than in the general population and appear to vary according to cleft type and extent [6,7]. A recent meta-analysis reported that individuals with orofacial clefts have approximately 14-fold higher odds of presenting tooth agenesis than unaffected individuals [6]. Epidemiological data indicate that agenesis in cleft patients most commonly affects teeth adjacent to the cleft site, particularly maxillary lateral incisors and premolars, reflecting the vulnerability of the fusion zones during craniofacial development [8,9]. Cross-sectional analyses have shown that patients with more extensive cleft involvement, especially CLP, exhibit a higher frequency of missing permanent teeth [6]. A recent meta-analysis further confirmed distinct patterns of agenesis in cleft populations, highlighting the influence of cleft morphology on dental development [7]. Additionally, retrospective radiographic evaluations in patients with craniofacial disorders support the concept that dental agenesis may reflect broader disturbances in craniofacial developmental processes [10].

Contemporary morphometric studies have emphasized that cleft phenotype severity correlates with increased variability in craniofacial growth patterns, reinforcing the biological interrelationship between cleft morphology and dental development [11]. Previous studies conducted in non-cleft populations have reported significant associations between tooth agenesis and skeletal malocclusion patterns, particularly Class III skeletal relationships and variations in vertical growth patterns [3]. However, comparable evidence regarding the relationship between agenesis severity and skeletal malocclusion patterns in non-syndromic cleft populations remains limited. Although the association between cleft type and dental agenesis has been widely documented, limited evidence exists regarding whether the severity of agenesis, expressed as the number of congenitally missing teeth, is related to skeletal malocclusion classification, particularly in adolescent and adult non-syndromic cleft patients. Most available studies focus on prevalence rather than on quantitative assessment of agenesis severity or its interaction with sagittal and vertical skeletal patterns [12]. Given that odontogenesis and craniofacial morphogenesis share overlapping developmental pathways [1,2], it is plausible that variations in the number of missing teeth may correlate not only with cleft type but also with sagittal and vertical skeletal patterns.

A clearer understanding of this relationship is clinically relevant. Identifying potential associations between dental agenesis, cleft morphology, and skeletal growth characteristics may enhance orthodontic diagnosis, improve risk assessment, and support individualized interdisciplinary treatment planning in cleft patients.

Therefore, the present retrospective cross-sectional study aimed to investigate the association between congenital tooth agenesis and skeletal malocclusion patterns in non-syndromic individuals with surgically repaired cleft lip and/or palate. Specifically, this study evaluated whether the number of congenitally missing permanent teeth differs according to sex, cleft type (cleft lip [CL], cleft lip and alveolus [CLA], cleft lip and palate [CLP], cleft palate [CP], and submucous cleft [SC]), sagittal skeletal classification (Class I, II, III), and vertical skeletal pattern (normal, deep bite, open bite).

2. Materials and Methods

2.1. Study Design and Ethical Considerations

This retrospective cross-sectional study was conducted at the Department of Orthodontics, Faculty of Dental Sciences, Aldent University, Tirana, Albania, and was based on clinical records of patients with craniofacial clefts treated in a multidisciplinary setting, including the University Hospital Centre “Mother Teresa”, over a long-term period as part of routine clinical care.

The data included in this study were originally collected over several years during standard diagnostic and therapeutic procedures and were not initially organized for research purposes. These records were accumulated progressively during long-term patient follow-up and subsequently identified as suitable for retrospective analysis.

Ethical approval was granted by the Institutional Review Board of Aldent University (protocol no. 13/5; approval date: 5 March 2026) for the retrospective use, anonymization, and analysis of pre-existing clinical records collected during routine patient care. The clinical data had been accumulated over several years as part of standard multidisciplinary management of patients with craniofacial clefts and were subsequently identified as suitable for retrospective research analysis. Following ethical approval, the dataset was anonymized and prepared for statistical analysis in accordance with the approved study protocol.

Written informed consent had been obtained from all patients at the time of their treatment, allowing for the use of their clinical data for scientific and research purposes, in accordance with institutional protocols and the principles of the Declaration of Helsinki (2013 revision).

2.2. Study Sample and Eligibility Criteria

The study sample consisted of 60 patients aged 17 years or older (36 males and 24 females; mean age: 19.5 ± 1.8 years) with a history of surgically repaired craniofacial cleft. All participants had undergone primary surgical closure of the cleft defect during childhood and had been followed clinically over time within a multidisciplinary care pathway.

Patients with craniofacial clefts represent a relatively low-prevalence population requiring long-term, multidisciplinary management from early childhood through adolescence and adulthood. Consequently, the availability of comprehensive clinical and radiographic records suitable for research purposes is typically achieved over extended periods of patient follow-up rather than within short timeframes.

Because this was a retrospective study based on an existing clinical database, no a priori sample size calculation was performed. Instead, all eligible patients who met the inclusion criteria and had complete clinical and radiographic records available at the time of data collection were included in this study. Given the relatively low prevalence of craniofacial clefts and the requirement for long-term follow-up to obtain complete orthodontic records,

inclusion of all available eligible patients was considered the most appropriate sampling strategy. A post hoc power analysis was also performed using G*Power software (version 3.1.9.2; Franz Faul, Universität Kiel, Kiel, Germany). Based on four predictors and an effect size of 0.85, calculated from the model partial R^2 , the available sample size provided a statistical power greater than 95%. Inclusion criteria comprised age ≥ 17 years, complete surgical repair of cleft lip (CL), cleft lip and alveolus (CLA), cleft lip and palate (CLP), cleft palate (CP), or submucous cleft (SC), and availability of comprehensive orthodontic records including clinical documentation and lateral cephalometric radiographs. The age threshold of 17 years was selected to ensure complete development of the permanent dentition, excluding third molars, thereby allowing for a reliable diagnosis of congenital tooth agenesis and minimizing the risk of misclassifying late-developing teeth as congenitally missing. Patients presenting systemic conditions known to affect craniofacial growth and dental development, such as craniofacial syndromes, endocrine disorders, or other developmental disorders, a history of facial trauma, or incomplete or poor-quality clinical or radiographic records were excluded.

2.3. Data Collection and Variables

The dataset was retrospectively assembled from clinical files, orthodontic charts, and radiographic documentation derived from both university-based and hospital-based clinical settings, accumulated over multiple years of patient follow-up. The recorded variables included demographic characteristics (age and sex), type of cleft (CLP, CL, CLA, CP, SC), sagittal skeletal pattern, vertical skeletal pattern, and dental agenesis. Cleft type was categorized according to the anatomical extent of the cleft and was based on the clinical diagnosis established by the multidisciplinary cleft team and documented in the patients' medical records. Patients were classified as cleft lip (CL), cleft lip and alveolus (CLA), cleft lip and palate (CLP), cleft palate (CP), or submucous cleft (SC). Sagittal skeletal classification was extracted from the available orthodontic records and was based on the comprehensive cephalometric assessment routinely performed during clinical care, including SNA, SNB, ANB, and Wits appraisal [13–15]. Patients were categorized as skeletal Class I, II, or III according to the combined interpretation of these cephalometric parameters and the overall orthodontic diagnosis documented in the clinical records. Reference cephalometric norms included SNA values of approximately $82^\circ \pm 2^\circ$, SNB values of approximately $80^\circ \pm 2^\circ$, and ANB values of approximately $2^\circ \pm 2^\circ$ for skeletal Class I relationships. Increased ANB values ($>4^\circ$) were generally indicative of Class II skeletal patterns, whereas ANB values below 0° were suggestive of Class III relationships. However, because this was a retrospective study based on pre-existing clinical records, patients were not reclassified using a newly applied standardized protocol with predefined cephalometric cut-off values.

Vertical skeletal pattern was assessed from the available orthodontic records using cephalometric measurements, including SN-MP and FMA, together with clinical evaluation of overbite. Patients were classified as having a normal bite, deep bite, or open bite according to the combined clinical and cephalometric assessment documented by the treating orthodontists.

Importantly, in this repaired cleft population, the recorded skeletal and vertical classifications should be interpreted as treatment-record-based classifications rather than as standardized measurements of the original untreated craniofacial phenotype. Many patients with cleft lip and/or palate undergo surgical repair, orthopedic or orthodontic treatment, alveolar bone grafting, and, in some cases, orthognathic surgery during growth and development [16]. Therefore, the skeletal classification available in the clinical record may have been influenced by previous treatment and may not fully reflect the patient's initial craniofacial growth pattern. This limitation may introduce misclassification bias and

limits the reproducibility of the skeletal classification process. For this reason, analyses involving sagittal and vertical skeletal pattern should be interpreted as exploratory.

Cephalometric measurements and skeletal classifications were performed by two orthodontists experienced in cephalometric analysis. In cases of disagreement, records were reviewed jointly and a consensus classification was reached. However, because of the retrospective nature of this study and the use of pre-existing clinical records, no formal intra-examiner or inter-examiner reliability assessment was performed for skeletal or vertical classification. Therefore, examiner agreement statistics could not be calculated, and the reproducibility of the skeletal classification process could not be quantitatively assessed. Congenital tooth agenesis was assessed through a combination of panoramic radiographic evaluation, clinical examination, and patient-reported dental history. Teeth were classified as congenitally missing when they were absent on panoramic radiographs and patients reported no history of extraction of the corresponding tooth. Information obtained during the clinical examination and patient interview was used to distinguish congenital absence from teeth previously extracted for orthodontic, restorative, traumatic, or other clinical reasons. Whenever available, historical orthodontic records and radiographic documentation obtained during earlier stages of dental development were also reviewed to support the diagnosis of congenital tooth agenesis and to minimize the risk of misclassification. Only permanent teeth were considered, while third molars (FDI 18, 28, 38, and 48) were excluded in accordance with established diagnostic criteria for congenital hypodontia. The position of missing teeth was recorded using the Fédération Dentaire Internationale (FDI) two-digit numbering system (ISO 3950:2016) [17]. Similarly, no formal examiner calibration procedure, intra-examiner reproducibility assessment, or inter-examiner agreement analysis was performed for the diagnosis of congenital tooth agenesis. The diagnosis was based on the combined interpretation of panoramic radiographs, clinical examination, patient-reported dental history, and available clinical records. Although available historical records were reviewed to reduce the risk of misclassifying extracted teeth as congenitally missing, the absence of formal reliability testing should be considered a methodological limitation.

2.4. Statistical Analysis

For analytical purposes, the primary outcome variable was defined as the total number of congenitally missing permanent teeth per patient.

Statistical analysis was performed using IBM SPSS Statistics, version 20.0 (IBM Corp., Armonk, NY, USA). The normality of the dependent variable (number of congenitally missing teeth) was assessed using the Shapiro–Wilk test. As the distribution deviated significantly from normality, non-parametric methods were applied for two-group comparisons. Descriptive statistics, including mean, standard deviation, median, minimum, and maximum values, were calculated separately for males and females. To preliminarily examine whether the distribution of cleft types differed according to sex, Pearson’s chi-square test was performed. Because some expected cell counts were below 5, Fisher’s exact test was also performed. To evaluate the association between multiple predictors and the number of congenitally missing teeth, a Poisson regression model with log link function was applied, as the dependent variable represented count data. The independent variables included sex, cleft type, sagittal skeletal pattern, and vertical skeletal pattern. The results are presented as exponentiated regression coefficients, corresponding to incidence rate ratios (Exp(B)), with 95% confidence intervals (95% CI). Exploratory unadjusted comparisons were also performed. Sex-based differences in the number of congenitally missing teeth were evaluated using the Mann–Whitney U test. Pairwise comparisons across cleft types were explored using one-way analysis of variance (ANOVA) followed by Games–Howell

post hoc tests when the assumption of homogeneity of variances was violated. Statistical significance was established at $p < 0.05$.

3. Results

3.1. Distribution and Normality of the Number of Congenitally Missing Teeth

Normality testing using the Shapiro–Wilk test revealed that the variable number of congenitally missing teeth was not normally distributed in either sex group ($p < 0.001$ for both males and females; Table 1). The distribution was positively skewed, with a predominance of zero values and a limited number of high observations. Since the data were not normally distributed, non-parametric tests were used for two-group comparisons.

Table 1. Normality Testing (Shapiro–Wilk Test).

Group	N	Shapiro–Wilk Statistic	<i>p</i> -Value
Females	24	0.717	<0.001
Males	36	0.672	<0.001

3.2. Descriptive Statistics—Females

A total of 24 female patients were included in the analysis (Table 2). The mean number of congenitally missing teeth was 1.50 ± 2.23 , with a median of 0.50 (Figure 1). The values ranged from 0 to 8 missing teeth.

Table 2. Descriptive Statistics for Females.

Statistic	Value
N	24
Mean	1.50
Standard deviation	2.23
Median	0.50
Minimum	0
Maximum	8

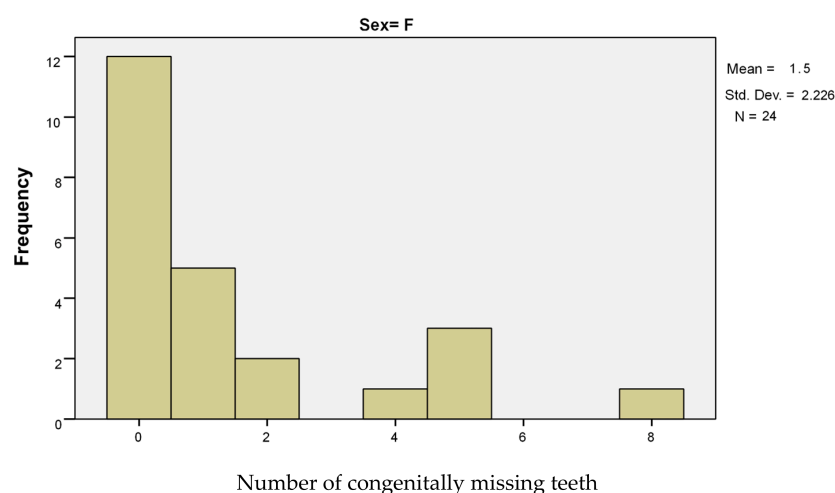


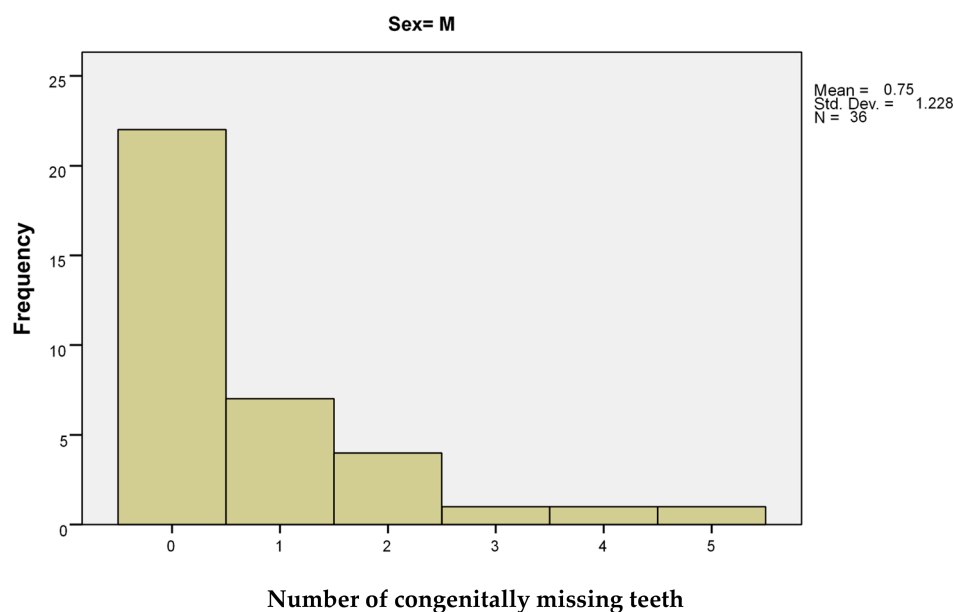
Figure 1. Distribution of the number of congenitally missing teeth in female patients.

3.3. Descriptive Statistics—Males

Thirty-six male patients were analyzed (Table 3). The mean number of congenitally missing teeth was 0.75 ± 1.23 , with a median of 0.00. The values ranged from 0 to 5 missing teeth (Figure 2).

Table 3. Descriptive Statistics for Males.

Statistic	Value
N	36
Mean	0.75
Standard deviation	1.23
Median	0.00
Minimum	0
Maximum	5

**Figure 2.** Distribution of the number of congenitally missing teeth in male patients.

3.4. Sex-Based Differences in Cleft Type

The distribution of cleft type according to sex is presented in Table 4. Pearson's Chi-square test revealed no statistically significant association between sex and cleft type ($\chi^2 = 1.415$, $df = 4$, $p = 0.842$), indicating a balanced distribution of cleft categories across sexes. Because some expected cell counts were below 5, Fisher's exact test was also performed and confirmed the absence of a statistically significant association between sex and cleft type ($p = 0.853$).

Table 4. Distribution of cleft type according to sex and results of Pearson's Chi-square and Fisher's exact tests.

Cleft Type	Females (n = 24)	Males (n = 36)	Total (n = 60)
CLP	8	13	21
CL	5	7	12
CLA	2	3	5
CP	4	9	13
SC	5	4	9
Total	24	36	60

Chi-square test: $\chi^2 = 1.415$, $df = 4$, $p = 0.842$; Fisher's exact test: $p = 0.853$.

3.5. Factors Influencing the Number of Congenitally Missing Teeth

A Poisson regression model was performed to evaluate the association between sex, cleft type, sagittal skeletal pattern, and vertical skeletal pattern and the number of congenitally missing teeth (Table 5). The model was statistically significant compared with the intercept-only model (likelihood ratio $\chi^2 = 76.065$, $df = 9$, $p < 0.001$). The goodness-of-fit indices did not indicate marked overdispersion (deviance/ $df = 1.217$; Pearson $\chi^2/df = 1.194$). In the tests of model effects, sex (Wald $\chi^2 = 6.476$, $df = 1$, $p = 0.011$) and cleft type (Wald $\chi^2 = 21.134$, $df = 3$, $p < 0.001$) were significantly associated with the number of congenitally missing teeth. In contrast, sagittal skeletal pattern (Wald $\chi^2 = 2.172$, $df = 2$, $p = 0.338$) and vertical skeletal pattern (Wald $\chi^2 = 2.541$, $df = 2$, $p = 0.281$) were not significant predictors. The estimated incidence rate ratios (Exp(B)) and corresponding 95% confidence intervals are reported in Table 5.

Table 5. Poisson regression model for the number of congenitally missing teeth.

Predictor/Category	Wald χ^2	df	p-Value	Exp(B)	95% CI for Exp(B)
Sex	6.476	1	0.011	—	—
Female vs. male	6.476	1	0.011	2.153	1.193–3.887
Cleft type	21.134	3	<0.001	—	—
CLP vs. SC	12.929	1	<0.001	16.345	3.564–74.950
CL vs. SC	—	—	—	Not estimable	—
CLA vs. SC	0.005	1	0.946	1.088	0.097–12.263
CP vs. SC	5.662	1	0.017	6.495	1.391–30.331
Sagittal skeletal pattern	2.172	2	0.338	—	—
Class I vs. Class III	2.160	1	0.142	1.950	0.800–4.750
Class II vs. Class III	0.036	1	0.849	1.142	0.293–4.454
Vertical skeletal pattern	2.541	2	0.281	—	—
Deep bite vs. open bite	0.193	1	0.661	0.807	0.311–2.099
Normal bite vs. open bite	1.825	1	0.177	0.512	0.194–1.352

Exp(B) represents the incidence rate ratio. Reference categories were male sex, submucous cleft (SC), skeletal Class III, and open bite. The CL parameter was not reliably estimable because of sparse/zero counts in this category.

3.6. Exploratory Post Hoc Analysis

The Mann–Whitney U test showed no statistically significant difference between males and females in the number of congenitally missing teeth ($U = 365.50$, $Z = -1.116$, $p = 0.265$). This finding should be interpreted as an unadjusted comparison between sexes. Therefore, the sex-related result observed in the adjusted Poisson regression model, which simultaneously accounted for cleft type, sagittal skeletal pattern, and vertical skeletal pattern, should be considered model-dependent and interpreted with caution.

To evaluate whether the number of congenitally missing teeth differed among cleft types (CLP, CL, CLA, CP, SC), a one-way analysis of variance (ANOVA) was performed. The analysis revealed a statistically significant difference between groups ($F(4,55) = 6.358$, $p < 0.001$), indicating that the number of missing teeth varied according to cleft type. The assumption of homogeneity of variances was tested using Levene's test and was found to be violated ($p < 0.001$); therefore, Games–Howell post hoc comparisons were applied, as this test does not assume equal variances (Table 6). Post hoc analysis demonstrated that patients with cleft lip and palate (CLP) exhibited a significantly higher number of congenitally missing teeth compared with:

- Cleft lip (CL) (mean difference = 2.286, $p = 0.001$);
- Cleft lip and alveolus (CLA) (mean difference = 2.086, $p = 0.003$);

- Submucous cleft (SC) (mean difference = 2.063, $p = 0.004$).

Table 6. Games–Howell Post hoc Comparisons for Cleft Type.

Comparison (I vs. J)	Mean Difference (I–J)	<i>p</i> -Value	Significant
CLP vs. CL	2.286	0.001	Yes
CLP vs. CLA	2.086	0.003	Yes
CLP vs. CP	1.363	0.197	No
CLP vs. SC	2.063	0.004	Yes

Dependent variable: Number of congenitally missing teeth.

No statistically significant difference was observed between CLP and cleft palate (CP) ($p = 0.197$). It should be noted that the CLP group represented the largest subgroup within the sample ($n = 21$).

4. Discussion

In the present study, the number of congenitally missing permanent teeth demonstrated a non-normal, positively skewed distribution, with most patients presenting no or few missing teeth and a smaller subgroup exhibiting multiple agenesis. This distribution pattern is consistent with recent investigations in cleft populations, which report that dental agenesis tends to cluster in a limited number of individuals rather than being evenly distributed across patients [7,18]. Such variability reflects the heterogeneous biological expression of dental developmental disturbances in non-syndromic cleft patients, where the severity of agenesis may differ according to individual developmental and morphological factors. Previous radiographic and cross-sectional analyses have similarly shown that although the overall prevalence of agenesis is elevated in cleft populations, the number of missing teeth per patient varies considerably [7,10]. The predominance of zero values in the present cohort indicates that not all repaired cleft patients exhibit agenesis, supporting the concept that cleft morphology alone does not uniformly determine dental absence. Given the skewed distribution of this count variable, the application of non-parametric statistical methods for group comparisons was appropriate and ensured that the analyses were not influenced by violations of normality assumptions.

In the descriptive analysis, female patients showed a higher mean number of congenitally missing teeth than males; however, this difference did not reach statistical significance in the unadjusted Mann–Whitney U test. In contrast, sex was significantly associated with the number of congenitally missing teeth in the adjusted Poisson regression model, which simultaneously accounted for cleft type and skeletal characteristics. Therefore, the sex-related finding should be interpreted as a model-dependent exploratory association rather than as definitive evidence of an independent sex effect. The influence of sex on dental agenesis remains inconsistent in the literature. Some epidemiological studies have reported a slightly higher prevalence of hypodontia in females in both cleft and non-cleft populations, potentially reflecting differences in craniofacial developmental timing, skeletal maturation, or genetic expression [19,20]. Conversely, other investigations in cleft cohorts have failed to demonstrate significant sex-based differences in the distribution or severity of missing teeth, emphasizing instead the dominant role of cleft morphology and laterality [21,22]. Overall, the present findings support the multifactorial nature of dental agenesis in repaired cleft patients and suggest that sex may represent one possible component within a broader developmental context. However, this association should be interpreted cautiously and requires confirmation in larger multicenter studies.

The present Poisson regression model showed that sex and cleft type were significantly associated with the number of congenitally missing permanent teeth, whereas sagittal and vertical skeletal classifications were not significant predictors of agenesis severity in this retrospective record-based analysis. Because the outcome variable was a count variable, Poisson regression provided a more appropriate analytical approach than a linear model. Effect estimates were expressed as incidence rate ratios with 95% confidence intervals, allowing for interpretation of both the magnitude and precision of the observed associations. The significant association with cleft type supports previous reports showing that more extensive cleft phenotypes, particularly cleft lip and palate, are associated with increased prevalence and severity of dental anomalies [12,23,24]. However, the findings related to sagittal and vertical skeletal classifications should be interpreted with particular caution. In the present retrospective study, skeletal and vertical classifications were derived from available orthodontic records and therefore may reflect treatment-record-based or treatment-modified craniofacial relationships rather than the original untreated skeletal phenotype. This is especially relevant in repaired cleft patients, whose craniofacial growth may be influenced by surgical intervention, scar formation, orthopedic or orthodontic treatment, alveolar bone grafting, and growth modification protocols [25–27].

Therefore, the absence of a significant association between skeletal classification and agenesis severity in the present study should not be interpreted as definitive evidence that no developmental relationship exists between dental agenesis and the original craniofacial skeletal pattern. Rather, these findings indicate that, within the limitations of the available retrospective clinical records, sagittal and vertical skeletal classifications were not significant predictors of the number of congenitally missing teeth. Given the relatively small number of patients in some subgroups and the potential for treatment-related modification in skeletal relationships, nonsignificant findings related to skeletal classifications should be considered exploratory and should be confirmed in larger multicenter studies using standardized cephalometric re-evaluation protocols and predefined diagnostic thresholds.

Exploratory pairwise analysis by cleft type further showed that patients presenting cleft lip and palate (CLP) exhibited a higher agenesis burden compared with CL, CLA, and SC. These findings indicate that the anatomical extent and morphological complexity of the cleft defect play a decisive role in determining the severity of dental developmental disturbances. The higher number of missing teeth observed in the CLP group is consistent with previous clinical investigations reporting increased prevalence and severity of dental anomalies in more extensive cleft forms [12,24]. In particular, cross-sectional analyses have shown that cleft extension involving both lip and palate is associated with a broader spectrum of structural dental anomalies and higher rates of hypodontia compared with isolated cleft lip or less extensive cleft variants [12]. Similarly, Somani et al. [24] reported differences in the distribution of dental anomalies among cleft subtypes, supporting the concept that cleft phenotype directly influences dental developmental outcomes. The absence of a statistically significant difference between CLP and CP in the present study may reflect shared developmental mechanisms affecting palatal structures. Although CLP involves both the primary and secondary palates, cleft palate alone may still disrupt odontogenesis within the maxillary developmental field. Previous investigations analyzing agenesis patterns in unilateral clefts have demonstrated that missing teeth frequently cluster near the cleft site and within fusion zones, suggesting localized embryologic vulnerability rather than a strictly lip-dependent mechanism [28]. These findings support the notion that palatal involvement alone may be sufficient to influence dental development severity. Moreover, earlier studies examining dental anomaly prevalence in unilateral and bilateral cleft lip and palate populations have shown that the number and pattern of missing teeth vary according to cleft type and laterality [28,29]. Although some of these investigations reported

differences between unilateral and bilateral presentations, they consistently emphasize the role of cleft morphology as a primary determinant of dental phenotype expression. Taken together, the present findings align with the existing literature in demonstrating that cleft type represents a central determinant of agenesis severity. The gradient observed in the current sample, where CLP exhibited the highest number of missing teeth, supports the hypothesis that increasing cleft extension is associated with greater disruption of odontogenesis. These results reinforce the importance of early and comprehensive dental monitoring in patients with more extensive cleft phenotypes, particularly those with CLP.

The relatively small sample size and retrospective cross-sectional design may limit the generalizability of the findings and preclude causal inferences. In addition, sagittal and vertical skeletal classifications were based on available orthodontic records rather than on a standardized re-evaluation of pretreatment cephalometric records using predefined diagnostic thresholds. Consequently, these classifications may not fully represent the original untreated craniofacial phenotype and may have been influenced by previous cleft-related treatment. This represents a potential source of misclassification bias and limits the reproducibility of the skeletal classification process. Another limitation is the absence of formal intra-examiner and inter-examiner reliability testing. Although skeletal classifications were performed by two experienced orthodontists and disagreements were resolved through consensus discussion, no agreement statistics were calculated. Therefore, the reproducibility of skeletal and vertical classification could not be quantified. Similarly, congenital tooth agenesis was diagnosed using panoramic radiographs, clinical examination, patient-reported dental history, and available clinical records, but no formal calibration procedure or examiner agreement analysis was performed for this diagnostic process. Consequently, the magnitude of potential diagnostic or classification errors within the dataset cannot be estimated. This limitation should be considered when interpreting the study findings. Because this was a retrospective analysis of clinical records, blinding was not feasible; however, consensus classification by two orthodontists reduced potential bias. Furthermore, because this study was based on retrospectively available clinical records from a single treatment center, a degree of selection bias cannot be excluded. In addition, genetic information was not available for the included patients; therefore, the potential influence of genetic factors on the severity of dental agenesis could not be evaluated. Furthermore, some cleft subgroups contained a limited number of patients, which may have reduced the statistical power to detect associations involving sagittal and vertical skeletal patterns. Therefore, nonsignificant findings related to skeletal classifications should be interpreted with caution and confirmed in larger multicenter cohorts.

Future multicenter studies with larger samples and standardized surgical histories are warranted to clarify the relationships among cleft morphology, skeletal growth, and dental agenesis severity. Longitudinal investigations integrating genetic and morphometric analyses may provide further insight into the developmental mechanisms underlying tooth agenesis in cleft populations.

5. Conclusions

Within the limitations of this retrospective study, cleft type was the most consistent factor associated with the number of congenitally missing permanent teeth in non-syndromic repaired-cleft patients, while sex showed a model-dependent association in the adjusted regression analysis. More extensive cleft phenotypes, particularly cleft lip and palate, were associated with a greater agenesis burden. Because skeletal classifications may have been influenced by previous cleft-related treatment, these findings should be interpreted as exploratory and should not be considered definitive evidence regarding the relationship between dental agenesis and the original untreated craniofacial phenotype. These findings

support the role of cleft morphology as a major factor associated with dental developmental disturbances and indicate that, in this retrospective record-based analysis, skeletal malocclusion classification alone was not a reliable marker of agenesis severity. Early and individualized interdisciplinary assessment is therefore particularly important in patients with more extensive cleft forms.

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References

1. Rakhshan, V. Congenitally missing teeth (hypodontia): A review of the literature concerning the etiology, prevalence, risk factors, patterns and treatment. *Dent. Res. J.* **2015**, *12*, 1–13. [[CrossRef](#)] [[PubMed](#)]
2. Meade, M.J.; Dreyer, C.W. Tooth agenesis: An overview of diagnosis, aetiology and management. *Jpn. Dent. Sci. Rev.* **2023**, *59*, 209–218. [[CrossRef](#)] [[PubMed](#)]
3. Costa, A.M.G.; Trevizan, M.; Matsumoto, M.A.N.; da Silva, R.A.B.; da Silva, L.A.B.; Horta, K.C.; Romano, F.L.; Nelson-Filho, P.; Küchler, E.C. Association between Tooth Agenesis and Skeletal Malocclusions. *J. Oral Maxillofac. Res.* **2017**, *8*, e3. [[CrossRef](#)] [[PubMed](#)]
4. Cobourne, M.T.; Sharpe, P.T. Diseases of the tooth: The genetic and molecular basis of inherited anomalies affecting the dentition. *Wiley Interdiscip. Rev. Dev. Biol.* **2013**, *2*, 183–212. [[CrossRef](#)] [[PubMed](#)]
5. Modafferi, C.; Tucci, I.; Bogliardi, F.M.; Gimondo, E.; Chiurazzi, P.; Tabolacci, E.; Grippaudo, C. Genetic Aspects of Tooth Agenesis. *Genes* **2025**, *16*, 582. [[CrossRef](#)] [[PubMed](#)]
6. Marzouk, T.; Alves, I.L.; Wong, C.L.; DeLucia, L.; McKinney, C.M.; Pendleton, C.; Howe, B.J.; Marazita, M.L.; Peter, T.K.; Kopycka-Kedzierawski, D.T.; et al. Association between Dental Anomalies and Orofacial Clefts: A Meta-analysis. *JDR Clin. Trans. Res.* **2021**, *6*, 368–381. [[CrossRef](#)] [[PubMed](#)]
7. Howe, B.J.; Pendleton, C.; Withanage, M.H.H.; Childs, C.A.; Zeng, E.; van Wijk, A.; Hermus, R.; Padilla, C.; Hecht, J.T.; Poletta, F.A.; et al. Tooth Agenesis Patterns in Orofacial Clefting Using Tooth Agenesis Code: A Meta-Analysis. *Dent. J.* **2022**, *10*, 128. [[CrossRef](#)] [[PubMed](#)]
8. Antonarakis, G.S.; Suri, S. Prevalence and patterns of permanent tooth agenesis in patients with nonsyndromic Pierre Robin sequence. *Am. J. Orthod. Dentofac. Orthop.* **2014**, *145*, 452–460. [[CrossRef](#)] [[PubMed](#)]
9. Papaefthymiou, P.; Agrafioti, M.; Yilmaz, H.N. Correlation of Dental Anomalies with Cleft Type and Gender in Non-Syndromic Oral Cleft Patients: A Cross-Sectional Study. *Cleft Palate Craniofac. J.* **2024**, *61*, 284–294. [[CrossRef](#)] [[PubMed](#)]
10. Weise, C.; Lehmann, M.; Schulz, M.C.; Reinert, S.; Koos, B.; Weise, H. Tooth agenesis in German orthodontic patients with non-syndromic craniofacial disorder: A retrospective evaluation of panoramic radiographs. *Clin. Oral Investig.* **2022**, *26*, 5823–5832. [[CrossRef](#)] [[PubMed](#)]
11. Schraad, F.; Schwahn, C.; Krey, K.F.; Doberschütz, P.H. Craniofacial morphological variability in orthodontic patients with non-syndromic orofacial clefts: An approach using geometric morphometrics. *Clin. Oral Investig.* **2024**, *28*, 409. [[CrossRef](#)] [[PubMed](#)]
12. Konstantonis, D.; Alexandropoulos, A.; Konstantoni, N.; Nassika, M. A cross-sectional analysis of the prevalence of tooth agenesis and structural dental anomalies in association with cleft type in non-syndromic oral cleft patients. *Prog. Orthod.* **2017**, *18*, 20. [[CrossRef](#)] [[PubMed](#)]

13. Zawiaślak, A.; Wędrychowska-Szulc, B.; Grocholewicz, K.; Janiszewska-Olszowska, J. Craniofacial Cephalometric Morphology in Polish Adolescents with Cleft Palate Only. *J. Clin. Med.* **2024**, *13*, 4507. [[CrossRef](#)] [[PubMed](#)]
14. Nerurkar, S.; Kamble, R.; Shrivastav, S.; Sanchla, A.; Kaiser, J.; Mathew, J.; Toshniwal, N. The Comparative Evaluation of the Morphology and Dimensions of the Sella Turcica in Skeletal Class III Patients and Patients With Unilateral Cleft Lip and Palate in Post-Pubertal Age Group. *Cureus* **2022**, *14*, e29730. [[CrossRef](#)] [[PubMed](#)]
15. Proffit, W.R.; Fields, H.W.; Larson, B.; Sarver, D.M. *Contemporary Orthodontics*, 6th ed.; Elsevier: St. Louis, MO, USA, 2018.
16. Isufi, I.; Isufi, A.; Meto, A.; Alushi, A.; Esposito, R.; Tepedino, M. Orthognathic Surgery in Adults with Craniofacial Clefts: Evaluating the Need for Maxillary Advancement and Facial Aesthetic Improvement. *Appl. Sci.* **2025**, *15*, 9505. [[CrossRef](#)]
17. ISO 3950:2016; Dentistry—Designation System for Teeth and Areas of the Oral Cavity. International Organization for Standardization: Geneva, Switzerland, 2016.
18. das Neves, L.T.; de Carvalho, I.M.M.; Cobourne, M.T.; Gomide, M.R. Dental anomalies in non-syndromic orofacial clefts: A clinical approach. *Oral Dis.* **2022**, *28*, 1351–1368. [[CrossRef](#)] [[PubMed](#)]
19. Garib, D.G.; Rosar, J.P.; Sathler, R.; Ozawa, T.O. Dual embryonic origin of maxillary lateral incisors: Clinical implications in patients with cleft lip and palate. *Dent. Press J. Orthod.* **2015**, *20*, 118–125. [[CrossRef](#)] [[PubMed](#)]
20. Rodrigues, A.S.; Teixeira, E.C.; Antunes, L.S.; Nelson-Filho, P.; Cunha, A.S.; Levy, S.C.; Araújo, M.T.S.; Ramos, A.G.C.; Cruz, G.V.; Omori, M.A.; et al. Association between craniofacial morphological patterns and tooth agenesis-related genes. *Prog. Orthod.* **2020**, *21*, 9. [[CrossRef](#)] [[PubMed](#)]
21. Jamilian, A.; Lucchese, A.; Darnahal, A.; Kamali, Z.; Perillo, L. Cleft sidedness and congenitally missing teeth in patients with cleft lip and palate patients. *Prog. Orthod.* **2016**, *17*, 14. [[CrossRef](#)] [[PubMed](#)]
22. Premkumar, S.; Mohan, G. Pattern of dental anomalies in nonsyndromic clefts and its relationship to neural crest developmental fields. *J. Cleft Lip Palate Craniofac. Anomal.* **2015**, *2*, 123–128. [[CrossRef](#)]
23. Fonseca-Souza, G.; de Oliveira, L.B.; Wambier, L.M.; Scariot, R.; Feltrin-Souza, J. Tooth abnormalities associated with non-syndromic cleft lip and palate: Systematic review and meta-analysis. *Clin. Oral Investig.* **2022**, *26*, 5089–5103. [[CrossRef](#)] [[PubMed](#)]
24. Somani, R.S.; Patel, D.; Jain, M. Prevalence of dental anomalies in different cleft lip and palate groups: A survey. *J. Cleft Lip Palate Craniofac. Anomal.* **2022**, *9*, 36–40. [[CrossRef](#)] [[PubMed](#)]
25. Cabrera, C.T. A Review of Orthodontic Considerations before and after Alveolar Bone Grafting in Patients with Cleft Lip and Palate. *Acta Medica Philipp.* **2024**, *58*, 7–19. [[CrossRef](#)] [[PubMed](#)] [[PubMed Central](#)]
26. Naqvi, Z.A.; Shivalinga, B.M.; Ravi, S.; Munawwar, S.S. Effect of cleft lip palate repair on craniofacial growth. *J. Orthod. Sci.* **2015**, *4*, 59–64. [[CrossRef](#)] [[PubMed](#)]
27. Celie, K.B.; Włodarczyk, J.; Naidu, P.; Tapia, M.F.; Nagengast, E.; Yao, C.; Magee, W., 3rd. Sagittal Growth Restriction of the Midface Following Isolated Cleft Lip Repair: A Systematic Review and Meta-Analysis. *Cleft Palate Craniofac. J.* **2024**, *61*, 20–32. [[CrossRef](#)] [[PubMed](#)]
28. Bartzela, T.N.; Carels, C.E.; Bronkhorst, E.M.; Kuijpers-Jagtman, A.M. Tooth agenesis patterns in unilateral cleft lip and palate in humans. *Arch. Oral Biol.* **2013**, *58*, 596–602. [[CrossRef](#)] [[PubMed](#)]
29. Rullo, R.; Festa, V.M.; Rullo, R.; Addabbo, F.; Chiodini, P.; Vitale, M.; Perillo, L. Prevalence of dental anomalies in children with cleft lip and unilateral and bilateral cleft lip and palate. *Eur. J. Paediatr. Dent.* **2015**, *16*, 229–232. [[PubMed](#)]

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