T.C
YEDİTEPE UNIVERSITY
INSTITUTE OF HEALTH SCIENCES
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EVALUATION OF MAXILLARY SINUS PATHOLOGIES IN CHILDREN AND ADOLESCENTS WITH CLEFT LIP AND PALATE USING CONE BEAM COMPUTED TOMOGRAPHY: A RETROSPECTIVE STUDY

DOCTOR OF PHILOSOPHY THESIS

DENTIST
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Prof. Dr. Bayram YILMAZ

Director of Institute of Health Sciences

DECLARATION

I hereby declare that this thesis is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person nor material which has been accepted for the award of any other degree except where due acknowledgment has been made in the text.

AYŞE ÇELİK

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ABBREVIATIONS AND SYMBOLS

%: Percentage

2D: Two-dimensionally

3D: Three-dimensionally

ABRS: Acute bacterial rhinosinusitis

ARS: Acute Rhinosinusitis

ASAN: Anterior Superior Alveolar Nerve

BCL: Bilateral Cleft Lip

BCLP: Bilateral Cleft Lip and Palate

BMP4: Bone Morphogenetic Protein 4

CBCT: Cone Beam Computed Tomography

CL: Cleft Lip

CLP: Cleft Lip and Palate

CP: Cleft Palate

CRS: Chronic Rhinosinusitis

CT: Computed Tomography

FGFR1: Fibroblast Growth Factor 1

FGFR2: Fibroblast Growth Factor 2

LUCLP: Left Unilateral Cleft Lip and Palate

mL: Milliliter

mm: Millimeter

MR: Magnetic Resonance

MRI: Magnetic Resonance Imaging

MS: Maxillary sinus

MSAN: Middle Superior Alveolar Nerve

MSCT: Multi-slice Computed Tomography

MSX1: Msh Homeobox 1

MTHFR: Methylenetetrahydrofolate Reductase

NSCLP: Nonsyndromic Cleft Lip and Palate

OMS: Odontogenic Maxillary Sinusitis

PR: Panoramic Radiography

PSAA: Posterior Superior Alveolar Artery

PSAN: Posterior Superior Alveolar Nerve

RUCLP: Right Unilateral Cleft Lip and Palate

TGF: Transforming Growth Factor

TGFα: Transforming Growth Factor-α

TGFβ3: Transforming Growth Factor β3

TMJs: Temporomandibular Joints

UCLP: Unilateral Cleft Lip and Palate

VAS: Visual Analogue Scale

ABSTRACT

CELIK A. 2023. Evaluation Of Maxillary Sinus Pathologies in Children and Adolescents with Cleft Lip and Palate Using Cone Beam Computed Tomography, A Retrospective Study. Yeditepe University Institute of Health Sciences, Doctorate Thesis, Istanbul.

The aim of this study is to retrospectively evaluate maxillary sinus pathologies in children and adolescents with cleft lip and palate and compare them with those of a sex- and age-matched control group using Cone-Beam Computed Tomography (CBCT). For the sampling, the CBCT images of 7-18 aged patients between the years 2014 and 2022 were retrieved from the archives of the Department of Oral and Maxillofacial Radiology at Yeditepe University, the Faculty of Dentistry. Four hundred and two scans were reviewed initially. All scans were taken using the same imaging device (i-CAT Imaging Science International, Inc. Hatfield, PA, USA). Based on inclusion and exclusion criteria, groups were designed and matched according to gender and age. Then a total of 130 scans were considered eligible for this study. After evaluating the coronal, sagittal, and axial views of the scans, a yes/no scale was used to determine the presence or absence of sinus pathologies. Findings of the maxillary sinus were categorized into groups based on the level and pattern of sinus opacification. The groups were: (1) healthy, (2) mucosal thickening >3 mm, (3) polypoidal mucosal thickening, (4) partial opacification, and (5) complete opacification. Variations of polypoidal mucosal thickenings were subcategorized as small, large, and multiple. The right and left sinuses of the patients in the CLP and control groups were recorded separately for pathologies. Also, the cleft side of the CLP patients was noted to identify the relationship with the side of the pathology. Among 130 patients, polypoidal mucosal thickening (25.4%) was found as the most frequent sinus pathology, followed by mucosal thickening greater than 3 mm (19.2%), partial opacification (6.1%), and total opacification (1.6%). The comparison of the presence and absence of the pathologies, the comparison of the sides of the pathologies, and the comparison of the groups resulted only in the number of sinuses with mucosal thickening greater than 3 mm was significantly higher in the CLP than that of the control group ($p<0.05$). Comparing the frequency of pathology based on the sinuses according to cleft types and cleft sides showed no significant difference in any of the pathology groups ($p > 0.05$). In conclusion, CBCT plays a very important role in detecting incidental findings in the oral and maxillofacial region. For children with CLP, it's absolutely essential to get an early diagnosis of maxillary sinusitis.

Keywords: *Cleft Lip and Palate, Maxillary Sinus, Pathology, Children, CBCT*

ÖZET

ÇELİK A. 2023. Dudak Damak Yarıklı Çocuk ve Genç Hastaların Maksiller Sinüs Patolojilerinin Konik Işınlı Bilgisayarlı Tomografi ile İncelenmesi, Retrospektif Çalışma. Yeditepe Üniversitesi Sağlık Bilimleri Enstitüsü, Doktora Tezi, İstanbul.

Bu çalışmanın amacı; dudak damak yarıklı (DDY) çocuk ve genç hastaların maksiller sinüs patolojilerinin konik ışınlı bilgisayarlı tomografi (KIBT) ile retrospektif olarak incelenmesi ve cinsiyet ve yaş eşleştirmeli kontrol grubuyla karşılaştırmalı olarak değerlendirilmesidir. Örneklem için Yeditepe Üniversitesi Diş Hekimliği Fakültesi Ağız Diş ve Çene Radyolojisi Anabilim Dalı arşivinden 2014-2022 yılları arasındaki 7-18 yaş arası hastaların KIBT görüntüleri alınmıştır. Başlangıçta dört yüz iki görüntü incelenmiştir. Tüm görüntüler aynı görüntülüme cihazı (i-CAT Imaging Science International, Inc. Hatfield, PA, ABD) kullanılarak çekilmiştir. Dahil etme ve dahil etmeme kriterlerine göre gruplar planlanmış ve cinsiyet ve yaşa göre eşleştirilmiştir. Daha sonra toplam 130 hastaya ait görüntüler bu çalışma için uygun kabul edilmiştir. Görüntülerin koronal, sagital ve aksiyal kesitleri değerlendirildikten sonra sinüs patolojilerinin varlığını ve yokluğu belirlemek için evet/hayır skalası kullanılmıştır. Maksiller sinüs patolojileri, sinüs opasifikasyonunun düzeyi ve şekline göre gruplandırılmıştır. Gruplar: (1) sağlıklı, (2) mukozal kalınlaşma>3 mm, (3) polipoidal mukozal kalınlaşma, (4) kısmi tıkanıklık, (5) tam tıkanıklık olarak kaydedilmiştir. Polipoidal mukozal kalınlaşma varyasyonları ise küçük, büyük ve çoklu olarak alt kategorilerde incelenmiştir. DDY ve kontrol grubundaki hastaların sağ ve sol sinüsleri patolojiler açısından ayrı ayrı kaydedilmiştir. Ayrıca, DDY grubundaki hastaların yarık tarafları da patoloji tarafı ile ilişkisinin değerlendirilebilmesi açısından not edilmiştir. Toplam 130 hasta arasında polipoidal mukozal kalınlaşma (%25,4) en sık sinüs patolojisi olarak bulunurken, bunu 3 mm'den büyük mukozal kalınlaşma (%19,2), kısmi opasifikasyon (%6,1) ve total opasifikasyon (%1,6) izlemiştir. Patolojilerin varlığı ve yokluğunun karşılaştırılması, patolojilerin taraflarının karşılaştırılması ve grupların karşılaştırılması sonucunda yalnızca mukozal kalınlaşmanın 3 mm'den fazla olan sinüs sayısının DDY grubunda kontrol grubuna göre anlamlı derecede fazla olduğu bulunmuştur ($p<0.05$). Sinüslerdeki patoloji sıklığı, yarık tiplerine ve yarık tarafına göre karşılaştırıldığında hiçbir patoloji grubunda anlamlı bir fark bulunmamıştır ($p>0.05$). Sonuç olarak, KIBT ağız ve maksillofasiyal bölgedeki rastlantısal bulguların saptanmasında çok önemli bir rol oynamaktadır. Dudak damak yarıklı çocuklar için maksiller sinüzitin erken teşhisi başlıca önem taşımaktadır.

Anahtar Kelimeler: *Dudak Damak Yarığı, Maksiller Sinüs, Patoloji, Çocuk, KIBT*

1. INTRODUCTION AND PURPOSE

A cleft lip and palate (CLP) malformation is one of the most common developmental craniofacial anomalies. This anomaly occurs due to the failure of fusion of the developmental processes of the face, in the early embryological period (1). The frequency of CLP was found to be 1/800 in Turkey (2). Orofacial clefts include a wide range of deformities and are classified according to the location of the cleft and the affected tissues (3,4). These anatomical deficiencies are responsible for esthetic, functional, and psychosocial changes (5). CLP patients encounter challenges in speaking, nutrition, chronic upper airway infections, dentition, hearing, face morphology, and psychological aspects (6). A meta-analysis showed that the occurrence of dental anomalies is also higher in patients with CLP, compared with the normal population (7). Thus, children with CLP need multidisciplinary care from birth to adulthood (8). Management of these children requires efforts from nursing, paediatric dentistry, orthodontics, dentomaxillofacial radiology, maxillofacial surgery, plastic surgery, otolaryngology, audiology, speech therapy, counseling, psychology, and genetics (9).

Patients with CLP would experience alterations in morphology associated with the maxillary sinus (MS), one of the most significant midface structures (1). Previous studies analyzed the maxillary sinuses of patients with CLP using several imaging techniques, such as conventional radiography and multi-slice computed tomography (MSCT) (10–13). However, the two-dimensionally (2D) evaluation of a space which is a three-dimensional (3D) structure, would be potentially limited and prone to errors. In this regard, a 3D volumetric evaluation of the maxillary sinuses appears as a more eligible option to better assess these structures. Although the computed tomography (CT) is considered the golden standard, it brings about a high radiation dose which is a significant disadvantage, especially for children (14). Furthermore, cone beam computed tomography (CBCT), is also replacing CT in various studies, due to its several advantages (15). With the increased usage of CBCT in dentistry, more CLP patients are undergoing CBCT scanning before orthodontic treatment or alveolar bone grafting procedures. The CBCT image provides a 3D view by allowing visualization of structures in all three planes (16–18).

Evaluating the MS of the patients with CLP guides identifying differences, which may cause impairments, such as sinus diseases (10). Among sinus diseases, sinusitis related to the

maxillary sinus is frequently noted in patients with CLP (10–12). Studies reported a higher incidence of maxillary sinusitis in cleft patients at younger ages (11,19,20). But no factor has been proven to have a definitive effect on maxillary sinusitis (21). Several studies reported that among unilateral cleft lip and palate (UCLP) patients, the high incidence of MS disease may be seen due to several heterogeneous anatomical variations observed in the MSs (10). The most considered hypothesis is the occurrence of hypoplasia of MSs (22). To verify it, an evaluation of the anatomical features of the MSs should be performed with an extensive analysis of the 3D morphology. However, current studies with CLP patients mainly focus on the MS volume (6,21,23), whereas no consistent conclusion exists. n (24). Some researchers, who focused on MS size in children with a cleft or without clefts, found no differences (25-27), while other researchers found significant differences (28,29).

Therefore, the purpose of this study was to retrospectively evaluate maxillary sinus pathologies in children and adolescents with cleft lip and palate and compare them with those of a control group using CBCT.

The hypothesis of this study was that clefting might be a predisposing factor to the pathologies of the maxillary sinus in young patients. The null hypothesis (H_0) of this study was that there was no statistically significant relationship between clefting and maxillary sinus pathologies.

2. GENERAL INFORMATION

2.1. Cleft Lip and Palate

A cleft is described as an opening or division in some part of the anatomical structures that are normally not open or divided (30). In the maxillofacial region, CLP is one of the most severe and prevalent congenital anomalies, with a high frequency of 6.64 per 10,000 live births worldwide (31,32). It is defined as the failure of fusion of the upper lip and/or the soft and/or hard palate, which leads to an opening in the affected structures (2). The line of the cleft is generally seen between the maxillary lateral incisors and maxillary canines (33). The condition requires multiple surgical procedures and frequent outpatient treatment from birth to maturity (34).

2.1.1. Embryology

The facial development of humans begins to form during the 4^{th} week of the intrauterine period. The external face is completed by the 6^{th} week. In the 6^{th} -8^{th} weeks the development of the palate divides the nasal and oral cavities into sub-divisions. This development continues with the completion of the soft palate into the 12^{th} week (35). The facial appearance is becoming clear within 8 to 10 weeks. According to the studies, the cleft lip (CL) and/or palate (CLP), appears between the first 8th to 12th weeks of embryological development (33,36,37).

The medial nasal processes fuse to form the intermaxillary process which forms the philtrum of the upper lip (35). Then, the medial nasal process, lateral nasal process, and maxillary process combine to form the anatomical structures of the normal nose, upper palate, and lip. The merging of the medial nasal processes and the maxillary processes leads to the separation of the oral and nasal cavities (38). Facial cleft appears due to fusion failures of the processes during development. In the intrauterine period at the 11^{th} and 12^{th} weeks, fusion disturbances in the medial line of the maxillary bones cause cleft lip formation (35,39). A cleft lip generally occurs at either side of the upper lip at the junction between the central and lateral parts (40). If the disturbance of the fusion occurs only on one side, the definition is unilateral cleft lip, if it occurs on both sides, the definition is bilateral cleft lip (BCL) (33). The cleft may affect only the upper lip or extend deeper into the hard palate and the floor of the nose (40).

The maxillary palatal processes grow towards each other and rotate from the vertical position to the horizontal position during the 7th week and rise over the tongue to merge the midline (41,42). The cleft palate (CP) occurs with the failure of this fusion within 7 to 12 weeks

of gestation (42). The cleft palate can involve a soft palate and/or hard palate. The cleft of the primary palate always includes cleft lip and alveolar cleft. Whereas the cleft of the soft palate can appear as separate or combined with the cleft of the lip and primary palate (40).

2.1.2. Epidemiology

The most common craniofacial birth defects are orofacial clefts, and 65% of these defects comprise cleft lip and palate cases (43). CLP occurs in approximately one in 700-1000 births worldwide, with the incidence varying according to geographic location and race/ethnicity, gender, and socioeconomic status of the parents (44,45). Native American Indian population has the highest incidence of CLP, followed by Asians, whites, and blacks (45). The prevalence of cleft palate alone is 0.5 per 1000 births and does not vary with ethnicity (46).

Regarding gender and the side of the cleft, cleft lip and palate incidence rates vary. CLP occurs more often in males than females with a 2:1 ratio, whereas CP occurs more often in females than males with a 2:1 ratio (45). Unilateral clefts occur twice as often on the left side as on the right side and 80% of the deformity is unilateral (47). While Stoll et al. (48) reported more males are affected by bilateral clefts, Meskin et al. (49) and Henriksson (50) found that females had complete BCL more often than males.

CLP can be classified whether it is syndromic or nonsyndromic. Most studies regard that about 30% of CLP patients are syndromic and linked with other developmental anomalies, while 70% of CLP patients are nonsyndromic and occur without any other physical abnormalities (51-53).

2.1.3. Etiology

Cleft lip and palate is considered one of the most common developmental craniofacial anomalies that result in medical, social, and psychological problems which affect individuals and their families (54,55). The condition has a multifactorial etiology in which genetic or environmental factors, or a combination of both factors play a role (54-56).

2.1.3.1. Genetics

While there is ongoing research on the subject, evidence of genetic etiology for cleft lip and palate formation has been present for several years. Twin research and segregation analysis

provide scientific proof that genetics plays a part in the genesis of nonsyndromic cleft lip and palate (NSCLP) However, there is currently little progress in the identification of causative genetic role (53,57,58). When there is a supportive family history, the likelihood of clefting increases. An affected parent runs a 3-5% chance of having a kid with CLP; if they already have one affected child, they have a 40% chance of having another once more (45). On the other hand, there have been great improvements in identifying and understanding the genetic etiology of syndromic forms of cleft lip and palate (5).

Consanguineous marriage is also associated with an increased risk of CLP because of the similarity of the gene structures (59,60). ***Aquino et al.*** found that CLP was more frequent with a history of first-degree consanguinity (61). However, ***Paranaiba et al.*** evaluated the correlation between the clefting and possible risk factors and reported that the marriage of relatives and the story of familial cleft were not related to CLP in the Brazilian population (62).

Previous genetic studies have reported that abnormality in transforming growth factor (TGF) is a significant predisposition for clefting (63-65). In addition, transforming growth factor-alpha (TGFα), transforming growth factor β3 (TGFβ3) and Msh Homeobox 1 (MSX1) are the genes that are responsible for head and face development (66,67). However, ***Lidral et al.*** (68) and ***Passos-Bueno et al.*** (69) showed no association between TGFA with CLP in the non-Caucasian population. Moreover, resequencing studies identified specific variants of the candidate genes that might underlie statistical associations with clefting, and the best current evidence has been reported for mutations in MSX1, fibroblast growth factor receptor 1 (FGFR1), fibroblast growth factor receptor 2 (FGFR2), and bone morphogenetic protein 4 (BMP4). Similarly, ***Carinci et al.*** (70) demonstrated a significantly higher mutation frequency of methylenetetrahydrofolate reductase (MTHFR) in mothers of children with non-syndromic CLP. ***Aşlar et al.*** (71) supported these findings with a conducted study on the Turkish population.

In general, because of the genetic complexity of clefting, the genetic basis of CLP is still controversial. Results from previous studies showed the presence of multiple genes involved in the etiology of clefting. However, the integration of genetic factors and environmental risks using epigenetics is essential to characterize the genetic foundation of CLP.

2.1.3.2. Environmental Factors

Although it is generally accepted that genetic contributions to CLP are a more significant predictor, environmental factors are also efficient (41).

2.1.3.3. Nutritional Intake

Nutritional status is found to be associated with the risk of oral clefts (72). Some studies have shown that maternal malnutrition can increase the risk of having a CLP (73,74). In addition, some researchers demonstrated that multivitamin usage during pregnancy can reduce the risk of oral clefts (75-78). However, it remains unknown which nutrients are specifically responsible for the decrease. Though the strength of the evidence varies by region, low zinc levels have been linked in some studies to an increase in oral clefts (79-81).

McKinney et al. (72) conducted a study in Thailand and found that a decrease in liver consumption was associated with an increased risk of oral clefts. Whereas ***Mitchell et al.*** (82) found no association between clefting and liver intake in their study of the Denmark population, but they discovered that people with higher estimated vitamin A intake through supplement use and liver intake had a decreased likelihood of developing CLP. ***Johansen et al.*** (83) also observed a strong protective association between high maternal intake of vitamin A and the risk of isolated cleft palate.

Folate deficiency has also been indicated as a nutritional component that affects the incidence of CLP (84). ***Shaw et al.*** (85) reported that if folic acid and cobalamin as vitamin supplements were not taken during early pregnancy, the risk for CLP could be tripled. Moreover, ***Badovinac et al.*** (78) supported the protective effect of folic acid containing supplement intake on the risk of oral clefts during pregnancy. Despite these findings, there is inconclusive evidence about the mechanism of the protective effect of these supplements (57,75,78).

2.1.3.4. Medicine Intake

Orofacial clefts have been linked to systemic glucocorticoid therapy. This relationship has been theorized since the primate studies of ***Baxter and Fraser*** based on animal research showing that glucocorticoids can result in a cleft palate in different animal types (86). ***Rodriguez-Pinilla and Martinez-Frias*** revealed a correlation between maternal systemic

glucocorticoid usage and the birth of a child with CLP in a case-control study in Spain (87). Similar findings were reported in retrospective research by ***Pradat et al.*** (88), who discovered a link between systemic corticoid use in the first trimester of pregnancy and the prevalence of clefting.

Anticonvulsant use by mothers, particularly phenytoin or phenobarbital, has been associated with a higher risk of orofacial clefts (89-91).

In addition, the association between the usage of naproxen and clefting has shown formal statistical significance. However, since so many exposures were examined, it might still be a random discovery (92).

Lastly, ***Källén*** studied the association between maternal drug use in early pregnancy and CLP in the child and found only a small role of maternal drug use on the incidence (93).

2.1.3.5. Alcohol Intake

The research has been contradictory, yet exposure to maternal alcohol consumption has also been deemed a risk factor (94). A positive correlation between alcohol intake during pregnancy and clefting has been shown in several studies (59,95-97), but not in all (74,98,99). This disagreement in the results could be related to the need for excessive alcohol consumption for the expression of the anomaly, which is uncommon during pregnancy, resulting in a small percentage of women being exposed (96).

2.1.3.6. Smoking

Exposure to passive or environmental smoking may increase the risk of developing an oral cleft. The effects of maternal smoke exposure are difficult to distinguish from those of other types of smoke exposure, though (100).

The best-established environmental risk factor for oral clefts is maternal smoking. The association between the occurrence of oral clefts and maternal smoking has been researched in many studies which have shown a modest association (59,101,102). ***Neves et al.*** (99) established a significant association between maternal smoking and the occurrence of CLP in accordance with the findings of other researchers (59,98,101,102). In addition, in a conducted study by ***Honein et al.*** (103) the risk of CLP was found to be 1.3 times higher in children of a smoking mother than in children of non-smokers.

Globally, further investigation into the precise etiological variables and epidemiological data is still required to determine the most efficient means of lessening the disease's burden and improving the standard of care given to those who are affected.

2.1.4. Classification

Classifying clefts is essential for planning clinical interventions, predicting treatment needs, and evaluating treatment outcomes (104).

CL/CP can be unilateral (UCLP) or bilateral (BCLP), and incomplete or complete, depending on the extent of tissue involvement. When CL/CP affects only one side of the face, it is termed unilateral, and when both sides are affected, it is termed bilateral. If the cleft is unilateral, the affected side is noted. Incomplete CL and CP are determined as involving the lip and the anterior part of the maxilla. Complete CL and CP include the lip, anterior part of the maxilla, and the hard and soft palate (45).

In 1861, ***Forster*** (105) was the first to classify facial malformations. Nevertheless, the most accepted classification systems were those of ***Veau*** 106) and ***Davis and Ritchie*** (107) which can be used as examples of some of the problems represented by older systems (108). ***Davis and Ritchie*** termed the deformations as prealveolar, alveolar, and postalveolar in their classification method based on the position of the cleft in relation to the alveolar process in 1922 (107). After nine years, ***Veau*** defined a new classification for palatal clefts based on anatomical position: isolated soft palate, clefts up to the incisive foramen, clefts extending through the alveolar crest unilaterally, and clefts extending through the alveolar crest bilaterally (106). However, using Veau's system would be difficult to describe clefts of the lip and alveolus without palatal clefts.

In 1942, ***Fogh-Anderson*** introduced a classification based on embryological development as clefts of the lip – unilateral or bilateral, clefts of the lip and cleft palate (single or double), and clefts of the lip and palate up to the incisive foramen (109). ***Kernahan and Stark*** (1958) acknowledged the need for an embryology-based classification system rather than a morphology-based system (110).

In 1962, American Cleft Palate-Craniofacial Association has formulated a classification system with a committee chaired by ***Harkins*** (111). The Committee emphasized precise terms with clear definitions, specifically the usage of Greek and Latin terminology, which would be

universally understandable. Lastly, the Committee concluded on two main anatomical divisions and six subdivisions according to the affected tissues. Moreover, ***Pfeifer*** (1964) introduced the first symbolic representation of cleft lip and cleft palate (112,113). After one year, the International Confederation for Plastic and Reconstructive Surgery formed a subcommittee to establish a new Nomenclature and Classification which T. Ray Broadbent chaired. The Subcommittee devised a two-tier system that categorized clefts of the lip, alveolus, and palate in three main divisions (anterior, anterior and posterior, and posterior clefts) based on embryologic principles and four subdivisions for rare facial clefts based on topographic findings (114). Nevertheless, in 1973, Victor Spina suggested a revision for the terms of the anterior and posterior clefts. Spina offered to rename these terms as preforaminal, transforaminal, and postforaminal clefts. Accordingly, Spina argued that the classification system would be easier to understand if the terminology was based on Latin and kept referring to a specific anatomic structure (115). In 1971, a symbolic classification called 'the striped Y' was found by ***Kernahan*** (Fig 1). In this symbol, the right and left limbs of the Y represented the primary palate, while the stem of the Y represented the secondary palate. Also, the incisive foramen can be represented symbolically by a small circle with the dividing pointing between the primary and secondary palates in this classification system (116).

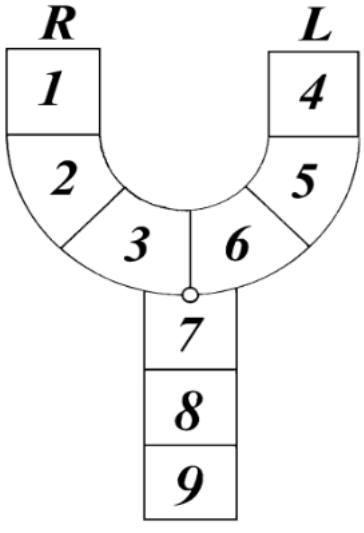

Fig. 1. The Kernahan striped Y classification of cleft lip and palate (126)
1 - Right lip; 2 – right alveolus; 3 – right premaxilla;
4 – left lip; 5 – left alveolus; 6 – left premaxilla;
7 – hard palate; 8 – soft palate; 9 – submucous cleft

Later, the classification was modified by other researchers ***Elsahy*** (117), ***Millard*** (118,119), and ***Friedman et al***.(120,121). In 1998, ***Smith et al.*** modified the Kernahan striped "Y" classification by simplifying the definition of the deformities and trying to implement digital coding (122). This classification can be found more comprehensive than the Kernahan "Y" classification (123).

Symbolic classifications indicate the presence of the cleft and its extensions within the hard tissues. However, the severity of the deformation and the relation with the soft tissues is critical. The classification system should define the deformation clearly for selecting preoperative orthopedic or surgical treatment approaches (120,124). Therefore, a new method that describes primary and secondary cleft palates with their severity and related soft tissues that have been affected has been proposed by ***Ortiz-Posadas et al*** (124). This method, however, has a broad and complicated structure with more than one scheme. To define a more precise and straightforward classification, ***Rossell-Perry*** developed the "Lima Clock Diagram" in 2009 (Fig 2). This schema, which is based on the surgical outcomes of 1043 patients with cleft lip and palate, categorizes pathology according to the degree of deformation of the nose, lip, and primary and secondary palate. As a result, in the same research, comparing with Kernahan's diagram (116), the Clock Diagram was found more effective to demonstrate a cleft's severity (125). However, the system is limited by the lack of lateral segment illustration on the clock diagram, and other components such as the maxilla and nasal septum.

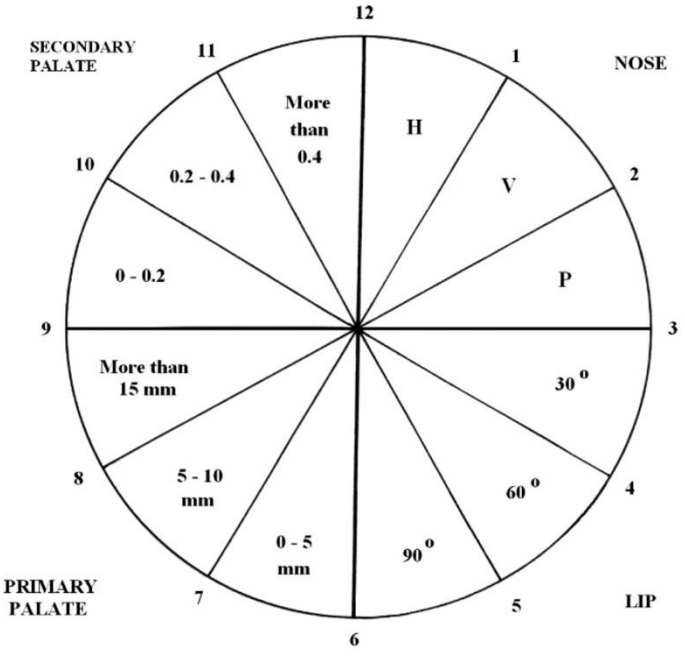

Fig. 2. The Clock Diagram

Lastly, in 2017, ***Elsherbiny and Mazeed*** presented a classification based on the Kernahan's striped Y diagram. This given classification system includes severity scores for each cleft component as well as additional details on the cleft extent. Thus, they aimed to introduce a universally accepted and accurate basic classification system for the primary diagnosis of CLP (126).

To conclude, the cleft classification is based on embryological progression and is determined by the physical involvement of the etiology and severity (45).

Causative categories are (1) syndromic cleft lip and/or palate, (2) syndromic cleft palate, (3) non-syndromic cleft lip and/or palate, and (4) non-syndromic cleft palate (30). Syndromic form is defined as the presence of a specific malformation pattern that includes the existence of several related anomalies in addition to CLP (9). On the other hand, non-syndromic CLP is described as no physical or development anomalies other than the CL/CP, and no confirmed teratogenic exposures that result in clefting. A summary of syndromes with CLP are provided in Table 1 (127-135).

Table 1. Syndromes with cleft lip-palate

Syndrome	Etiology	References
van der Woude syndrome	Autosomal dominant	Cervenka et al., 1967
Apert syndrome	Autosomal dominant	Cohen, 1975
Treacher Collins syndrome	Autosomal dominant	Gorlin et al., 1976
Cleidocranial dysplasia	Autosomal dominant	Gorlin et al., 1976
Ectodermal dysplasia	Autosomal dominant	Bixler et al., 1971
Stickler syndrome	Autosomal dominant	Herrmann and Opitz, 1975
Pierre Robin syndrome	Autosomal dominant	Shah et al., 1970
Oro-facial digital syndrome	X-linked dominant	Gorlin et al., 1976
Meckel syndrome	Autosomal recessive	Hsia et al., 1971
Christian syndrome	Autosomal recessive	Christian et al., 1971

2.1.5. Clinical Findings

Clinical findings in patients with CLP are categorized in two parts as extraoral and intraoral features.

The length, width, and height development of the maxilla are seen insufficient in extraoral examination (136). Due to maxillary hypoplasia, abnormal forward projection of the mandible beyond the common relation to the cranial base, also called prognathism, can be seen in individuals with CLP. Mandible has a significant downward and backward rotation associated with a wider gonial angle (137). Maxillary growth deficiencies reduce airway size, narrow the nasal floor, and increase airway resistance. Nasal deformities often compromise breathing, which leads to an increase in the prevalence of mouth breathers in cleft patients (138,139). Muscle phonation is affected by the dysfunction of the *m. levator veli palatini*. The most frequent finding is the retardant effect on consonant sounds (p, b, t, d, k, g). Difficulty in articulation and abnormal nasal resonance are other characteristic findings in CLP (140,141). Asymmetry of the face is another common feature in these cases (142).

In intraoral examination, shape, number, size, structural, positional, and developmental anomalies are commonly found in the dentition of CLP patients (143). In the cleft area, tooth agenesis is seen most frequently with the maxillary lateral incisors (144). However, in contrast with the normal population, microdontia of the maxillary lateral incisor is not rare among cleft patients (145). It has been shown that congenitally missing premolars are the second most common dental agenesis pattern in individuals with clefts (146,147). Although the frequency of the prevalence of hyperdontia is less than that of hypodontia, previous studies proved that it is the second most common dental anomaly seen in the cleft area (148,149). The alveolar crest was displaced towards the cleft side and the teeth on the cleft side were generally impacted. Bone support of the roots of the permanent teeth in the cleft area is insufficient. Early bone loss and periodontal problems can lead to loss of the teeth adjacent to the cleft area (150,151). Malocclusion with poor oral hygiene can be the reason of high caries prevalence (151).

2.1.6. Role of Dentists

Children with CLP should have specific treatment needs, and these should be met with a multidisciplinary team approach. Dental caries can be a serious further problem for these kids. Along with consultations between the mother and dentist early after the child's birth, good dietary awareness concerning dental caries should be maintained from an early age (152). Caries preventive measures should be performed. Also, before surgical interventions, patients

should have good oral health to eliminate the sources of infectious factors that may risk the surgical procedures. To preserve the bone tissue in the cleft area, extra and/or abnormally positioned deciduous teeth should be retained for as long as possible.

A paediatric dentist plays a critical role in achieving oral hygiene for CLP patients and maximizing the oral motor functions of these individuals. This includes, referral to a speech therapist for improving speech; facilitating nutrition; advancing oral morphology to provide optimal masticatory function and esthetics (153). Dental rehabilitation of the cleft patients is individual, and it is depending on the needs of each individual patient (154).

It is known that patients with CLP will have morphological alterations to their maxillary sinus. These alterations may lead to impairments such as sinus diseases (155). Dentists must be aware of each of the MS diseases as well as how they appear (156). Imaging technologies have become essential for the assessment and diagnosis of MS diseases. Panoramic radiography (PR) and CBCT should be known as diagnostic modalities (157).

2.2. Paranasal Sinuses

Paranasal sinuses are air-filled chambers that develop as nasal cavity invaginations. They encircle the nasal cavity and are given names based on the bones they occupy within such as: maxillary, ethmoid, sphenoid, and frontal. They begin to form in the 3rd and 4th fetal months, and after birth, the sinuses aerated. Enlargement of the sinuses occurs especially at puberty during the eruption of permanent teeth (158,159).

The majority of diseases that affect the paranasal sinuses are inflammatory in etiology. Primarily, a dentist will be requested for a differential diagnosis when the maxillary sinus is affected (160).

2.2.1. Maxillary Sinus

Leonardo da Vinci first described and illustrated the maxillary sinus in 1489, and English anatomist Nathaniel Highmore later documented them in 1651. The largest and first one to develop among the paranasal sinuses, the maxillary sinus is located within the maxillary bone. The inferior margin of the sinus is formed by the alveolar process of the maxilla, which also supports the dentition.

There are some important functions of the maxillary sinus, which are:

- Increasing resonance of the voice
- Heating and humidifying of inhaled air
- Regulating intranasal pressures
- Decreasing the weight of the skull
- Producing bactericidal lysosome into the nasal cavity for immunological defense (161).

2.2.1.1 Embryology

Only the maxillary and ethmoid sinuses are present at birth, even though paranasal sinus development begins in utero. The ethmoturbinals, a group of five to six ridges on the lateral nasal wall that indicate the formation of the paranasal sinuses, first occur around the 9^{th} week of pregnancy (162). The initial emergence of the six to seven folds of ethmoturbinals results in differential development and growth, but finally, only three to four ridges remain through regression and fusion (163). In the tenth week of intrauterine life, the maxillary sinus begins to form (164). During the eleventh week of development, the ethmoid infundibulum invaginations toward the mesenchyme merge to form a single oval cavity with smooth walls, the primordium of the maxillary sinus. Then, during the sixteenth week, the ossification of the sinus starts. The maxillary sinus has an anteroposterior depth of about 7 millimeters (mm), a height of 4.0 millimeters, and a width of 2.7 millimeters at birth. At ages 3 and 7 to 12 the maxillary sinus shows a biphasic growth pattern, equating with the maturing and eruption of permanent dentition and pubertal facial development. The maxillary sinus reaches its adult size at the age of 16, when it is depth of 39 mm, height of 36 mm, and width of 27 mm. The maxillary sinus's final size varies among individuals and can be affected by several factors (165). Morphological changes of maxillary sinuses by ages have shown in Figure 3 (159). Maxillary sinus hypoplasia is a relatively uncommon problem that has been linked to syndromes affecting the first branchial arch, trauma, tumors, severe infections, and irradiation (166).

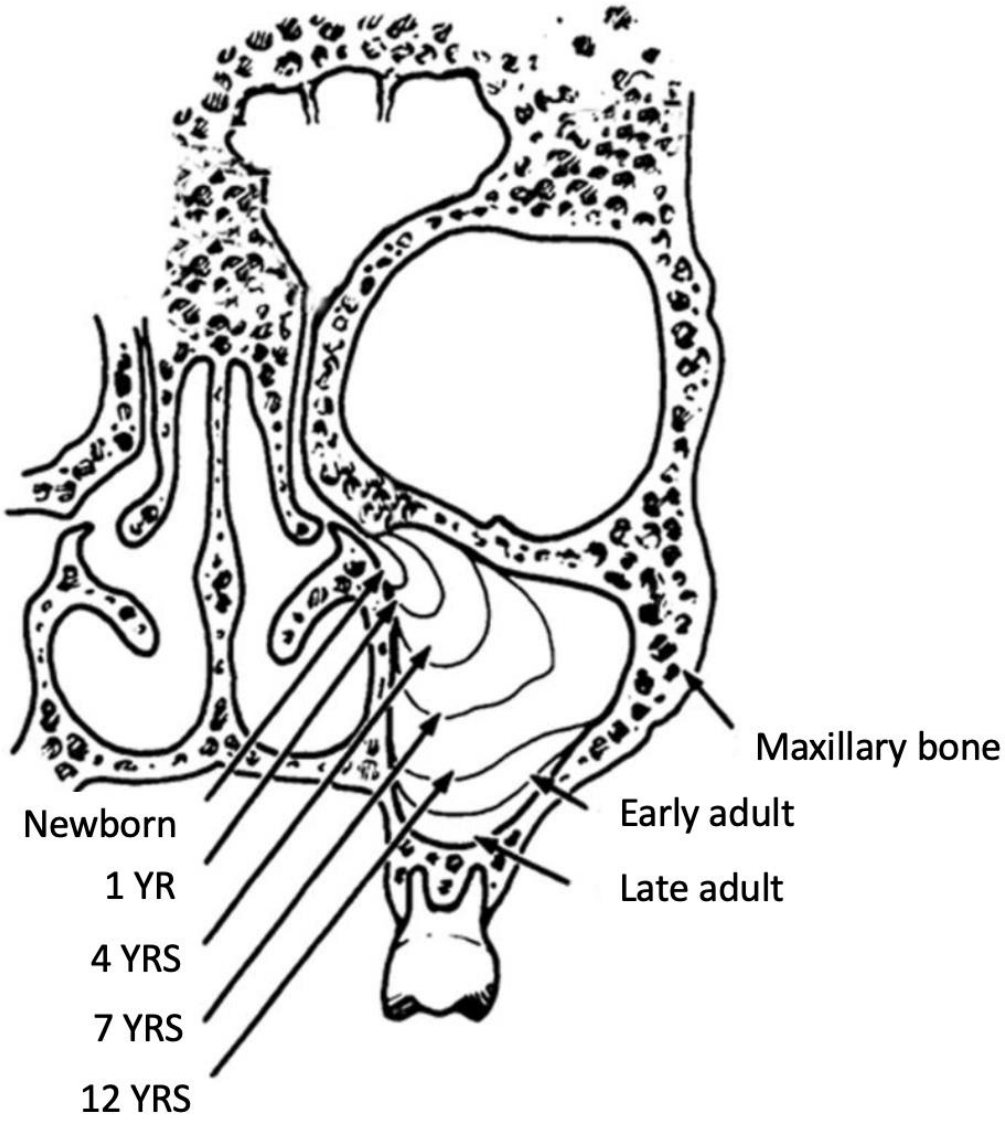

Fig. 3. Morphological changes of maxillary sinus by ages (modified from *Scuderi et al* (159).

2.2.1.2 Anatomy

The maxillary sinus commonly consists of a single, 15-milliliter (mL)-sized pyramidal chamber in adult life. The medial wall of the maxillary sinus is formed by a thin bony plate formed by the bones of the maxilla, inferior turbinate, uncinate process, perpendicular plate of the palatine bone, and lacrimal bone. The lateral apex widens into the zygomatic process of the maxillary bone or into the zygoma (167). The roof of the maxillary sinus is shaped by the floor of the orbital bone where the infraorbital nerve and artery courses through the infraorbital groove (168). The alveolar and palatal processes of the maxilla form the inferior boundary (167). Generally, compact bone separates the maxillary sinus floor from the molar teeth. The canine fossa, which is found directly above the canine tooth, and the infraorbital foramen are

located on the anterior wall of the sinus (169). The posterior wall of the maxillary sinus forms the anterior border of the pterygomaxillary fossa (167).

The posterior superior alveolar artery (PSAA), the infraorbital artery, and the posterior lateral nasal arteries supply the maxillary sinus. These arteries are the branches of the maxillary artery (159). Venous drainage passes through the facial vein anteriorly and the maxillary vein, as well as the jugular and dural sinus systems posteriorly (170). The posterior superior alveolar nerve (PSAN), which is the maxillary division of the trigeminal nerve, supplies most of the sensations in the maxillary sinus. The anterior superior alveolar nerve (ASAN) and middle superior alveolar nerve (MSAN) branching from the infraorbital nerve also innervates the sinus. The ASAN innervates the anterior part of the maxillary sinus where the MSAN contributes secondary mucosal innervation. The submandibular lymph nodes provide the lymphatic drainage system for the maxillary sinus (159,167).

2.2.1.3. Diseases of the maxillary sinuses

2.2.1.3.A. Inflammatory Diseases

Rhinosinusitis

Rhinosinusitis is described as the inflammation of the nose and paranasal sinuses. Certain symptoms must be part of the diagnosis. In paediatric patients, rhinosinusitis is defined by two or more symptoms one of which should be either nasal obstruction or nasal discharge:

- ± pain or pressure feeling in the facial region
- ± cough

and either

- endoscopic signs of:
  - nasal polyps, and/or
  - mucopurulent discharge primarily from middle meatus and/or
  - oedema/mucosal obstruction primarily in middle meatus

and/or

- CT changes:
  - mucosal changes within the ostiomeatal complex and/or sinuses

Based on the score of the visual analogue scale (VAS), the disease can be divided into Mild, Moderate, and Severe. The duration of the disease determines whether it is acute (<3 months) or chronic (≥ 3 months).

Acute Rhinosinusitis (ARS)

Acute rhinosinusitis in children is described as the immediate onset of the symptoms up to 3 months, with symptom-free intervals. ARS may occur once or several times at a specific time frame. This usually describes as having episodes every year, with complete remission of symptoms taking place in between each episode (171).

Rhinosinusitis is commonly triggered by viral infections (common cold), which can be prolonged in time (post-viral). In a limited minority of patients, bacterial infection which causes acute bacterial rhinosinusitis (ABRS), may be developed post-viral ARS (171). The occurrence of chronicity in ARS is quite low, and the disease usually resolves itself (172). Symptoms last for less than 10 days in ARS. In acute post-viral rhinosinusitis, symptoms persist after 10 days yet resolve within 12 weeks. Purulent secretion, local pain, and fever may be present as a sign of ABRS (171).

The CT appearances of ARS show nonspecific peripheral mucosal thickening, air-fluid levels, and pneumatized secretions of the maxillary sinus (171).

Chronic Rhinosinusitis (CRS)

Chronic rhinosinusitis in children is defined as the persistence of the symptoms of ARS for more than 3 months regardless of standard medical management (171). This management includes saline nasal rinses, nasal sprays, antibiotics, and steroids (173).

A displaced uncinate process, concha bullosa, and nasal septal deviation have all been identified as risk factors that might cause CRS (174). However, a few research that support this assertion have linked mucosal thickening on CBCT with CRS (175) when it has been observed that incidental mucosal thickening seen in about one-third of the asymptomatic population (176). Allergic rhinitis is also known to influence CRS (177). CRS is usually bacterial rather than viral. The dental origin should be evaluated during the consideration of the etiology of CRS (171). The anatomical proximity of the paranasal sinuses and dental tissues can be responsible for odontogenic maxillary sinusitis (OMS). The most prevalent cause of OMS is tooth extraction-related OMS. Besides this, dental caries, root infections, radicular lesions, impacted teeth, and dentigerous cysts are the causative factors of the OMS (178).

The radiographic characteristic of inflammatory lesions can be the increased radiopaque thickness of the mucous membrane, which might be an indicator of secretion accumulation.

Additionally, CT demonstrates polypoid mucosal thickening of the maxillary sinus, and the bones around it may suffer from sclerosis (179).

Inflammatory patterns for stages of rhinosinusitis are divided as following:

Infundibular Pattern: This pattern develops from the impedance of drainage of the maxillary sinus ostium, and ethmoid infundibulum, that results in an opacified antrum, generally due to polyp or thickening of the mucosa.

Ostiomeatal Unit Pattern: This pattern is caused by a blockage in the ipsilateral middle meatus, that results in opacification of the ipsilateral maxillary sinus, frontal sinus, and anterior ethmoid air cells.

Spheno-Ethmoidal Recess Pattern: This pattern results in the obstruction of the sphenoethmoidal recess, resulting in sphenoid sinus opacification regardless of whether the posterior ethmoid air cells are involved.

Sinonasal Polyposis Pattern: Polyps are seen as a post-inflammatory complication of infective or allergic rhinosinusitis. Most polyps, which are commonly multiple, are located in the anterior ostiomeatal unit. From maxillary sinus via sinus ostium, a polyp can prolapse into the nasal cavity and named antrochoanal polyp. Antrochoanal polyps are determined as smooth, soft tissue masses with downward convexity (180).

Sporadic Pattern: This pattern is not related to blockage of mucociliary drainage and includes randomly located mucosal changes (181).

Meningitis, epidural abscess, subdural abscess, intracranial abscess, and perivascular spread of infection are among the complications of rhinosinusitis (182).

Retention Cysts and Polyps

Retention cysts and polyps are regarded as the common complications of rhinosinusitis, and they are usually asymptomatic (183).

Retention cysts can develop most commonly within the maxillary sinus as a result of obstruction of exocrine duct. They are commonly seen on the floor of the maxillary sinus and described as rounded, smooth, dome-shaped, relatively radiopaque shadows (184).

Polyps are accumulated fluid lesions in the mucosa, and they are originated from the ostiomeatal complex. Although it is known as a complication of chronic infection, the certain etiology of nasal polyps is not completely understood. On CT imaging, polyps, such as retention cysts, are seen as smooth, convex soft tissue masses (185).

Since the appearance of the retention cysts and the polyps are comparable, the CT and magnetic resonance (MR) images are hard to differentiate (184,185). Also, these cysts are frequently incidental findings on radiography, and they are often mistaken for serious sinus diseases or related to a dental etiology (179).

Mucoceles

Mucoceles can develop due to blockage of the sinus ostium or part of a sinus septation and contain mucous secretions and desquamated epithelium (179). While they can occur mainly in the frontal sinuses (%65), only %10 of cases involves the maxillary sinus (186). Remodeling of the bone and expansion are the features of a mucocele due to the pressure effect. If an infection occurs frequently in a mucocele, it becomes a pyocele. The CT findings of a mucocele show an enlarged, airless sinus cavity that is filled with an adequately homogenous opacification that is equal to the mucoid secretion (179,186).

Antrolith

Antroliths (antral stones), occur within the paranasal sinuses as calcified bodies and are seen as radiopaque masses of varying forms and sizes in CT examinations (187). The term rhinolith is used when they are detected inside the nasal passages (188). Accumulation of calcium salts leads to the formation of antroliths (189). Although the etiology of antroliths still remains unknown, factors such as long-standing infection, inadequate sinus drainage, and the presence of a foreign body are considered pathogens (190).

Fungal Infections

A variety of fungi, mostly *Aspergillus* affect the sinonasal cavity. Clinically, it presents like chronic sinusitis but with no response to antibiotic treatment or irrigation. The infection may cause the maxillary sinus to calcify and develop rhinoliths. Large rhinoliths are known as

fungal balls (191). However, allergic fungal rhinosinusitis may appear due to a hypersensitivity reaction to a fungal antigen that results in a fairly complete sinus opacification (180).

2.2.1.3.B. Malignant Diseases

Malignant diseases of the paranasal sinuses are a rare condition, however, that is discovered at a late stage with the symptoms due to enlargement of the tumor. Dentists play an important role in the detection of malignancy in the maxillary sinus. Management of an abnormality and/or malignancy in the maxillary sinus requires a multidisciplinary team approach that includes an oral and maxillofacial surgeon, an otorhinolaryngologist, and a plastic and reconstructive surgeon (192).

2.2.1.4. Imaging Techniques Used for the Visualization of the Maxillary Sinuses

2.2.1.4.A. Panoramic Radiographs

In dentistry, panoramic imaging has developed into a common and significant diagnostic tool since its foundation in the 1950s. On a single film, it shows the entire maxilla, mandible, temporomandibular joints (TMJs), and related structures (193). It is used as an initial viewing radiograph to evaluate the dentition and bone support, diagnose maxillary and mandibular fractures or pathologies, identify impacted teeth, and assess the osseous status of the TMJs (194). It also provides an adequate image of the maxillary sinus and its relationship with the posterior maxillary teeth bilaterally (195). Some pathologies may be seen as opacification or cloudiness in the maxillary sinus. However, it does not reveal radiolucent defects, and its limitations, such as distortion and blurry images, can be seen (196).

2.2.1.4.B. Intraoral Periapical Radiographs

The most widely used imaging method used in dentistry is intra-oral radiography, which includes bitewing, periapical, and occlusal radiographies. Occlusal and bitewing radiography, however, are not adequate for visualization of the sinus (197).

While periapical radiography provides a high resolution that allows for the observation of the periapical radiolucency and carious lesions, these radiolucencies should increase to a larger dimension that is noticeable or perforate the cortical bone to be obvious on it (198,199). Furthermore, periapical radiography has limitations due to the two-dimensional rendering of the images and the restricted anatomical field of view. Mainly, it hampers the appropriate detection in the area of the posterior maxilla due to the anatomical overlap (199,200).

2.2.1.4.C. Waters Radiography

Waters radiography is one of the most common extraoral imaging techniques used for the visualization of the paranasal sinuses. By utilizing different angles, it is possible to assess internal anatomy, pathologies of the sinuses, and foreign substances (201). However, additional imaging may be required due to its limitations in complicated cases (202). Therefore, low-dose 3D imaging techniques have been commonly preferred (203).

2.2.1.4.D. Ultrasonography

Mann first utilized ultrasonography to diagnose sinusitis in research that was published in 1975 (204). The efficacy of ultrasonography in the diagnosis of rhinosinusitis in either children or adults has only been slightly examined in the literature, and it revealed conflicting results (205-207).

2.2.1.4.E. Computed Tomography

By using computed tomography, inflammatory changes in the maxillary sinus mucosa can be visualized in 3D (208). It allows visualization of both soft and hard tissues of the facial bones. CT views of the maxillary sinus show the association between the sinus floor and the periapical abscess (209). Furthermore, with a high contrast resolution, it eliminates anatomical overlap in the examined area (210). Yet, the high radiation dose makes this imaging technique impractical for dental applications. Moreover, the appearance of metallic objects in the tooth's surroundings can make image analysis difficult (203).

2.2.1.4.F. Cone Beam Computed Tomography

Cone Beam Computed Tomography (CBCT) is a comparatively new imaging technique for diagnosis in dentistry. The high resolution of CBCT has enabled the detection of a wide variety of tumors, infections, cysts, congenital developmental abnormalities, and trauma related to maxillofacial structures (211). Compared with CT scans, it can be advocated as a dose-sparing technique (212). Also, it shows a high certainty in detecting apical periodontitis and thickenings of the mucosa in comparison with 2D imaging techniques (200,213). The application of CBCT has found a place in different specialties of dentistry, such as oral and maxillofacial surgery, endodontics, implantology, orthodontics, periodontics, and pediatric dentistry. The quality of the image and the accuracy of the diagnosis of the CBCT are impacted by the artifacts and the scattering caused by high-density structures such as metallic or radiopaque materials. Scattering can cause limitations in imaging the soft tissue. Therefore, CBCT is used mainly for hard tissue imaging surrounding the oral cavity.

2.2.1.4.G. Magnetic Resonance Imaging (MRI)

Magnetic Resonance Imaging (MRI) scan is an imaging technique using non-ionizing radiation. The primary applications in dentistry of MRI have compromised soft tissue lesion differentiation in the salivary glands, TMJ imaging, and tumor staging (198,214). Despite being a primary disadvantage of CT and CBCT technology, MRI scans are generally not affected by metallic artifacts. However, sinus evaluation with an MRI scan has been found difficult in comparison with other 3D techniques (214). In addition, different types of hard tissues cannot be differentiated (215).

2.3. Relevant Background Literature Review

Duman and Duman (2017) assessed the sinus pathologies of 72 patients, 36 of whom had cleft lip and palate. Examined pathologies with CBCT were chronic sinusitis, inflammatory mucosal changes, and retention cysts. Even though they observed more pathology in control group patients' sinuses, it was not statistically significant (216).

Burton et al. (1971) found that the number of children with clinical symptoms and radiographic findings was similar in 21 children with cleft lip and palate who were clinically and radiographically examined (19).

Rak et al. (1990) studied the MR images of 128 patients to establish the relevance of the thickenings of the sinus mucosa. They concluded that in asymptomatic patients, mucosal thickening of up to 3 mm is typical and has no clinical implications (217).

Kula et al. (2015) conducted a randomized, retrospective study of CBCT with 30 patients. They examined the sinus volumes and mucosal thickening of the maxillary sinus in 15 UCLP patients and compared them with non-cleft patients. As a result of their study, the percentage of mucosal thickening was found to be significantly higher in the UCLP group (218).

Ali et al. (2022) examined the paranasal sinus abnormalities in 1849 patients who had head CT scans. They revealed that the maxillary sinuses were the most affected (219).

Rege et al. (2012) evaluated maxillary sinus abnormalities in 1113 CBCT images. Diagnosed abnormalities were classified as mucosal thickening, retention cysts, and

opacification. They concluded that maxillary sinus abnormalities were highly prevalent, even though the patients were clinically asymptomatic (220).

Hsiao et al. (2019) examined the prevalence of maxillary sinus pathology in 821 asymptomatic patients. They evaluated the CBCT scans retrospectively and categorized the findings as; mucosal thickening larger than 3 mm, polypoidal mucosal thickening with subcategorizations, partial opacifications, complete opacifications, and others. They strongly emphasized the importance of the evaluation of the maxillary sinuses since some of the patients would require medical consultation before undergoing any dental surgeries (221).

3. MATERIALS and METHODS

3.1. Ethical Approval and Study Design

This study received ethical approval from Yeditepe University Ethical Committee of Non-Invasive Clinical Research (Date: 11/02/2022, Decision no: 41).

Written informed consent forms had been signed by the children's parents or their legal representatives before the evaluation of the CBCT images.

The study was based on a retrospective evaluation of CBCT images of patients with ages between 7 to 18, taken from February, 2014 to December, 2021 at Yeditepe University, Faculty of Dentistry.

3.2. Patient Selection

A power analysis was carried out using the G*Power (v3.1.9) program to determine the sample size for each group. The mucosal thickening volume values in the Kula et al. (218) published study (study group=7439.5±5422.0, control group=2895.4±2371.6) was used and the effect size (d) was calculated as 1.09. Therefore, it was determined that at least 15 patients should be included in each group in order to achieve 80% power at the α=0.05 level.

For the sampling, the CBCT images of 8-18 aged patients between the years 2014 and 2022 were retrieved from the archives of the Department of Oral and Maxillofacial Radiology at Yeditepe University, the Faculty of Dentistry. Four hundred and two scans were reviewed initially. The images were the diagnostic records collected for different indications. CBCT scans were not performed for the purpose of this study.

All scans were taken using the same imaging device (0.3 mm voxel size, 8.9 second scan time; i-CAT Imaging Science International, Inc. Hatfield, PA, USA) with a flat panel image detector. The number of slices in one volume is 327. The images were displayed using the i-CAT Vision software on the same computer and monitor.

All CBCT scans, which included the entire images of the bilateral maxillary sinuses of children between the ages of 7-18, were included in the study samples. Patients with syndromes (except for syndromes associated with cleft lip and palate) and those with severe head and facial trauma were excluded from the study. This study also excluded patients under the age of 7,

patients over 18, and patients who have unclear CBCT images. Based on these criteria, groups were matched according to gender and age. Then a total of 130 scans were considered eligible for this study **(Fig. 4)**.

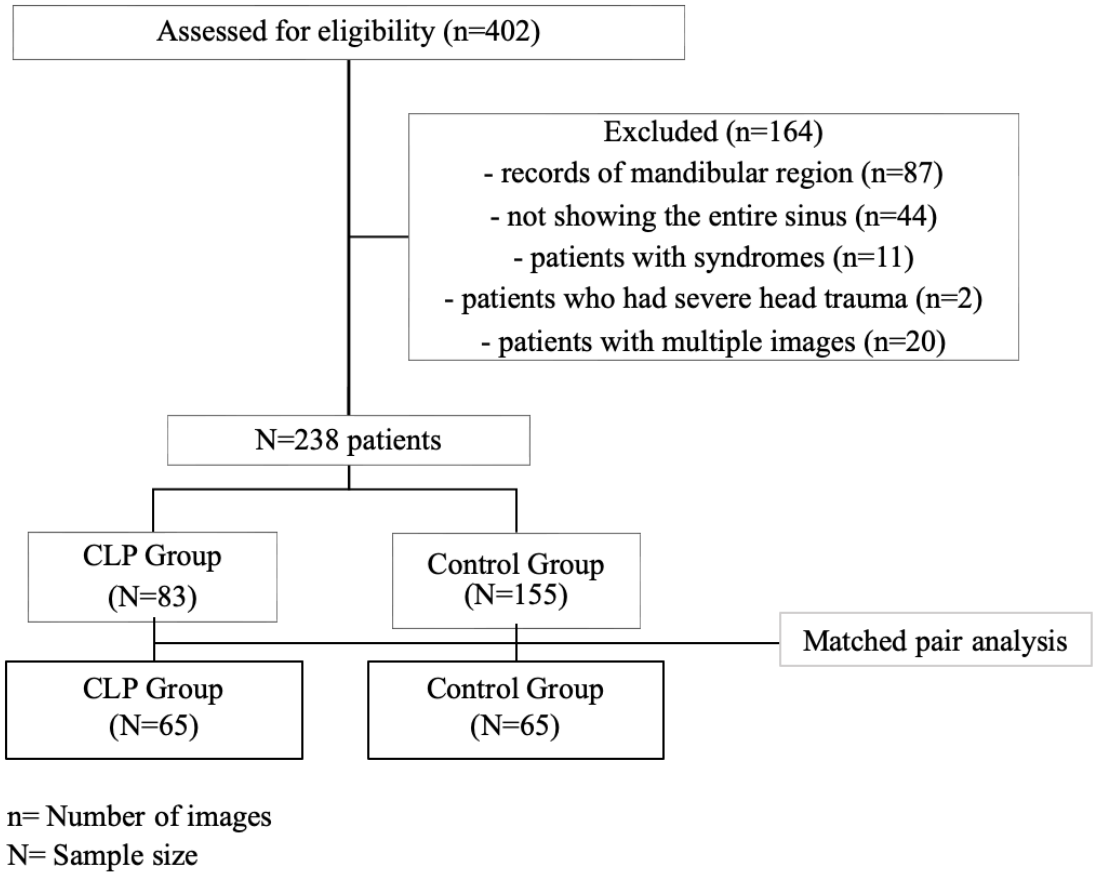

Fig. 4. The study sample's eligibility criteria process

3.3. Image Analysis

Among the remaining 238 patients, 83 were allocated to the CLP group and 155 to the control group. However, groups were matched by gender and age. Finally, 65 patients were in the CLP group and 65 patients were in the control group. After evaluating the coronal, sagittal, and axial views of the scans (Fig. 5), a yes/no scale was used to determine the presence or absence of sinus pathologies. Findings of the maxillary sinus were categorized into groups based on the level and pattern of sinus opacification. The groups were: (1) healthy, (2) mucosal thickening >3 mm, (3) polypoidal mucosal thickening, (4) partial

opacification, and (5) complete opacification (Fig. 6). Variations of polypoidal mucosal thickenings were subcategorized as small, large, and multiple. Partial and complete opacification were noted when the sinus cavity was filled to more than 50% or the opacification was high enough to block the ostium. The right and left sinuses of the patients in the CLP and control groups were recorded separately for pathologies. Also, the cleft side of the CLP patients was noted to identify the relationship with the side of the pathology. A Microsoft Excel spreadsheet was used to record the data (Fig. 7 & Fig. 8).

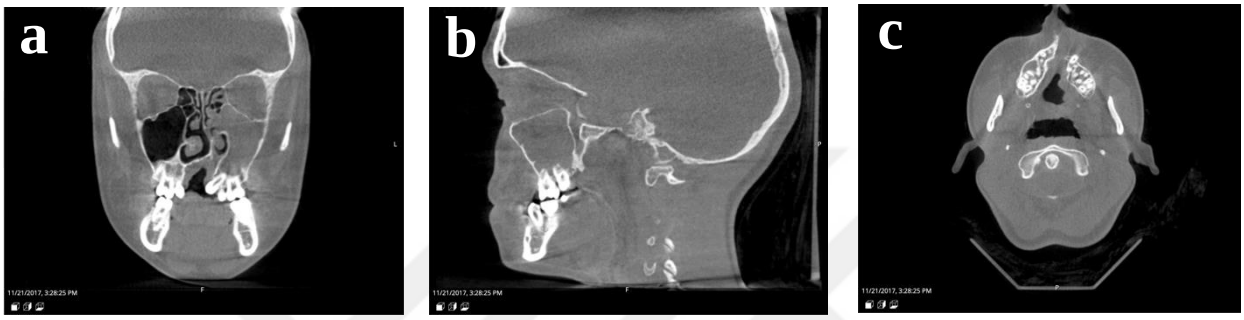

Fig. 5. CBCT images of the same patient obtained from (a) Coronal plane, (b) Sagittal plane, and (c) Axial Plane

3.4. Standardization and Reliability Analysis

The CBCT scans were analyzed twice by one observer with an interval of 2 weeks in order to ensure intra-examiner consistency. Ten percent of the data were calibrated with a boarded oral and maxillofacial radiologist. The inter-examiner reliability data, with a kappa coefficient of 0.75 indicating substantial agreement. The intra-examiner reliability data, with a kappa coefficient of 1 demonstrating almost perfect level of agreement.

3.5. Statistical Analysis

In this study, NCSS (Number Cruncher Statistical System) 2007 statistical software (Utah, USA) was used for the data analysis. In addition to descriptive statistics (mean, standard deviation, frequencies, and percentages), the Shapiro-Wilk normality test was used to confirm the normal distribution of the data. Study and control groups were compared using the independent t-test for the evaluation of the quantitative data, and by the chi-square test for the evaluation of the qualitative data. The inter-rater and intra-rater agreement was calculated using Kappa statistics. A p-value of <0.05 was considered significant.

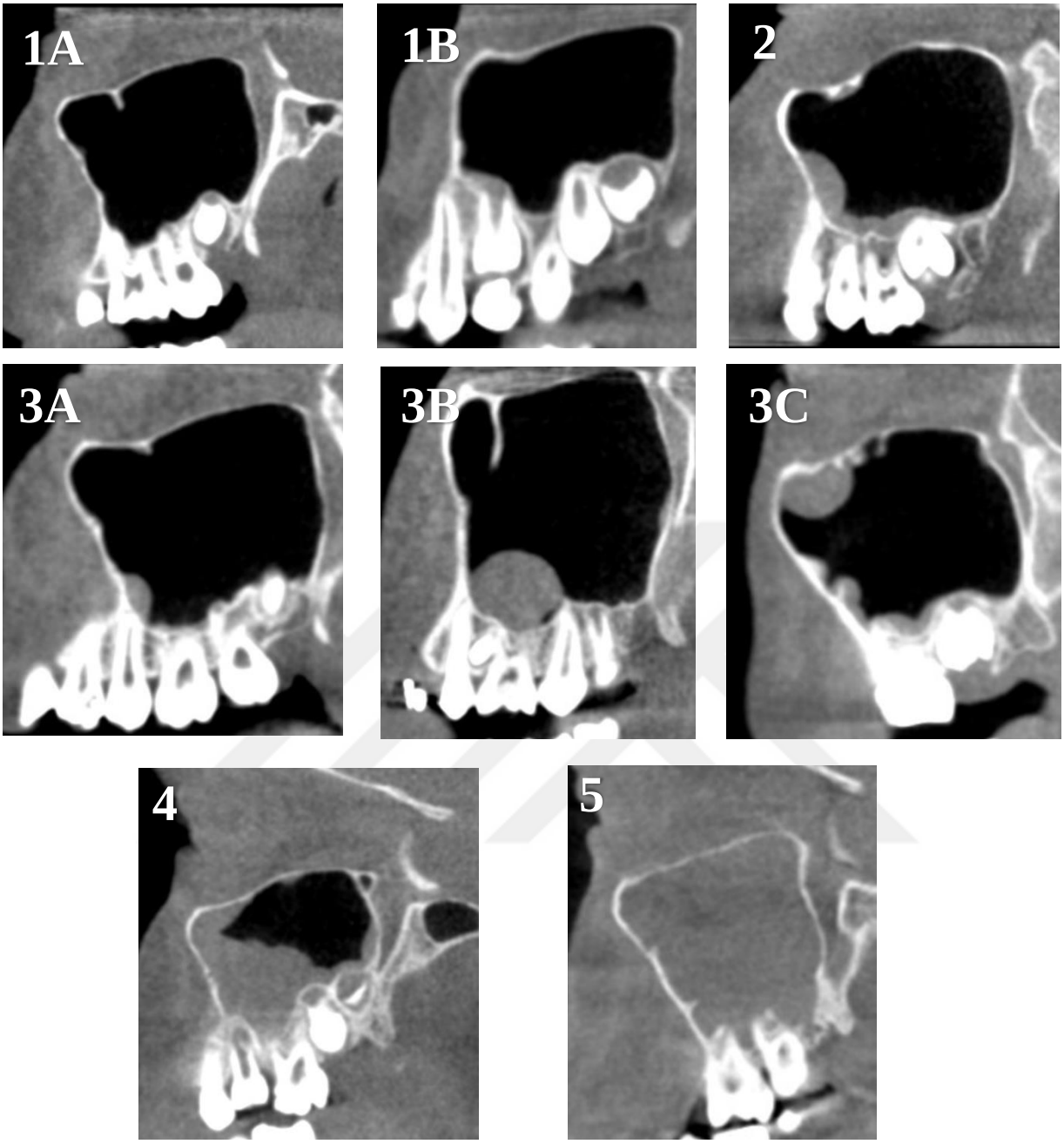

Fig.6. Categorization of maxillary sinus pathologies (1A: healthy sinus with no pathology, 1B: healthy sinus with mucosal thickening < 3 mm, 2: mucosal thickening > 3 mm, 3A: small polypoidal mucosal thickening, 3B: large polypoidal mucosal thickening, 3C: multiple polypoidal mucosal thickening, 4: partial opacification, and 5: total opacification)

	A	B	C	D	E	F	G	H	I	J	K	L
1	**Patient**	**Gender**	**Age**	**Cleft type**	**Cleft side**	**pathology**	**side of the path.**	**muco. thick.>3mm**	**polypoid**	**type of polypoid**	**partial**	**complete**
2	1	1	17	ULCLP	L	yes	L	0	L	L (9.06 mm)	0	0
3	2	1	16	B LCLP	RL	no	0	0	0	0	0	0
4	3	2	17	B LCLP	RL	yes	R	0	R	L (15.50 mm)	0	0
5	4	2	13	B LCLP	RL	yes	RL	L	R	S (3.82 mm)	0	0
6	5	1	10	ULCLP	L	yes	R	0	R	L (7.80 mm)	0	0
7	6	1	8	ULCLP	R	yes	L	0	L	S (3.75 mm)	0	0
8	7	2	13	ULCLP	R	yes	RL	RL	0	0	0	0
9	8	1	17	ULCLP	L	no	0	0	0	0	0	0
10	9	1	9	ULCLP	R	no	0	0	0	0	0	0
11	10	1	8	ULCLP	L	yes	RL	RL	0	0	0	0

Fig. 7. An example of an Excel spreadsheet of the CLP group

	A	B	C	D	E	F	G	H	I	J
1	**Patient**	**Gender**	**Age**	**pathology**	**side of path.**	**muco. thick.>3mm**	**polypoid**	**type of polypoid**	**partial**	**complete**
2	1	1	17	yes	L	0	L	L (5.45 mm)	0	0
3	2	1	11	no	0	0	0	0	0	0
4	3	2	14	yes	RL	0	R	L(5.69 mm)	L	0
5	4	1	13	yes	L	0	L	S (3.02 mm)	0	0
6	5	1	17	yes	L	L	0	0	0	0
7	6	2	13	no	0	0	0	0	0	0
8	7	1	14	no	0	0	0	0	0	0
9	8	1	8	no	0	0	0	0	0	0
10	9	2	14	no	0	0	0	0	0	0
11	10	2	8	no	0	0	0	0	0	0

Fig. 8. An example of an Excel spreadsheet of the control group

4. RESULTS

The total sample consisted of CBCT scans from 130 patients, including 58 (44.6%) females and 72 (55.4%) males. Among females, 29 were in the control group and 29 were in the CLP group. Among males, 36 were in the control group, and 36 were in the CLP group. Table 2 shows the gender and mean age distributions of the patients in both groups.

Table 2. Age and Gender Distribution of Subjects in the CLP and study groups

	CLP Group (n=65)		Control Group (n=65)	
Mean Age ± SD	12.43±3.13		12.43±3.13	
Min.	7		7	
Max.	18		18	
Gender				
Male	36	55.4%	36	55.4%
Female	29	44.6%	29	44.6%

In the cleft group, the distribution of the patients according to cleft type and the comparison of the number of UCLP sides according to the Pearson Chi-Square Test are shown in Table 3. The prevalence of the LUCLP was found statistically significantly higher than the RUCLP ($p < 0.05$).

Table 3. Cleft Type Distribution in the CLP Group

N=65		**n**	**%**	**p**
Cleft Type	**Bilateral**	22	16.9%	
	Unilateral	43	33.1%	**0.004**
	R	12	9.2%	
	L	31	23.8%	

Pearson Chi-Square Test

4.1.Patient-Based Assessments

The number and percentage of patients exhibiting each category of pathologies are given in Table 4. Of the 130 individuals with CBCT scans, 72 (55.4%) patients were determined as healthy, and the remaining 58 (44.6%) patients revealed some evidence of maxillary sinus pathology. Out of 58 patients with sinus pathologies, 22 patients had pathologies present in both sinuses and 36 patients had either left or right sinus pathologies.

Among 130 patients, polypoidal mucosal thickening (25.4%) was found as the most frequent sinus pathology, followed by mucosal thickening greater than 3 mm (19.2%), partial opacification (6.1%), and total opacification (1.6%).

In 25 patients with mucosal thickening greater than 3 mm, 6 (4.6%) patients had it in both sinuses. Whereas it was observed only in the right sinus of 12 (9.2%) patients and only in the left sinus of 7 (5.4%) patients.

Of the 33 patients who had polypoidal mucosal thickening in their sinuses, it was most frequently observed on the right (13.1%), left (10.0%), and bilateral (2.3%), respectively.

Partial opacification was assessed in 8 patients: 2 (1.5%) on the right sinus, 3 (2.3%) on the left sinus, and 3 (2.3%) bilaterally.

While total opacification was not observed bilaterally in any patient, it was assessed in two patients in the right (0.8%) and left (0.8%) sinuses separately.

4.1.1. Comparison of CLP and Control Groups

Maxillary sinus pathologies were assessed among 65 CLP patients and 65 matched-pair control patients. The comparison of the presence and absence of the pathologies according to Pearson Chi-Square Test and the comparison of the sides of the pathologies, and the comparison of the groups according to Fisher-Freeman-Halton Exact Test are shown in Table 5 and Figure 9.

Although the presence of maxillary sinus pathologies was found higher in the CLP group than the control group, the difference between the two groups was not found statistically significant ($p > 0.05$).

In the comparison of the side of the pathologies, there were no statistically significant differences between the two groups ($p > 0.05$).

Comparisons of the categories of maxillary sinus pathologies between the CLP and control groups revealed several differences. However, no statistically significant difference was observed in any category ($p > 0.05$).

Table 4. Number and Percentage of Patients Exhibiting Pathology

N=130		**n**	**%**
Pathology	**No**	72	55,4%
	Yes	58	44,6%
	R	22	16.9%
	L	14	10.8%
	RL	22	16.9%
Mucosal thickening >3 mm	**No**	105	80.8%
	Yes	25	19.2%
	R	12	9.2%
	L	7	5.4%
	RL	6	4.6%
Polypoidal mucosal thickening	**No**	97	74.6%
	Yes	33	25.4%
	R	17	13.1%
	L	13	10.0%
	RL	3	2.3%
Partial opacification	**No**	122	93.9%
	Yes	8	6.1%
	R	2	1.5%
	L	3	2.3%
	RL	3	2.3%
Total opacification	**No**	128	98.4%
	Yes	2	1.6%
	R	1	0.8%
	L	1	0.8%
	RL	0	0.0%

Table 5. Distribution of Patients Exhibiting Pathology Among CLP and Control Groups

N=130		CLP	Control	p
		n (%)	n (%)	
Pathology	**No**	33 (50.8%)	39 (60%)	[a]0.290
	Yes	32 (49.2%)	26 (40%)	
	R	10 (15.4%)	12 (18.5%)	[b]0.309
	L	7 (10.8%)	7 (10.8%)	
	RL	15 (23.1%)	7 (10.8%)	
Mucosal thickening >3 mm	**No**	48 (73.9%)	57 (87.7%)	[b]0.176
	Yes	17 (26.1%)	8 (12.3%)	
	R	8 (12.3%)	4 (6.2%)	
	L	4 (6.2%)	3 (4.6%)	
	RL	5 (7.7%)	1 (1.5%)	
Polypoidal mucosal thickening	**No**	48 (73.9%)	49 (75.3%)	[b]0.999
	Yes	17 (26.1%)	16 (24.7%)	
	R	8 (12.3%)	9 (13.8%)	
	L	7 (10.8%)	6 (9.2%)	
	RL	2 (3.1%)	1 (1.5%)	
Partial opacification	**No**	62 (95.4%)	60 (92.3%)	[b]0.638
	Yes	3 (4.6%)	5 (7.7%)	
	R	0 (0%)	2 (3.1%)	
	L	1 (1.5%)	2 (3.1%)	
	RL	2 (3.1%)	1 (1.5%)	
Total opacification	**No**	64 (98.5%)	64 (98.5%)	[b]0.999
	Yes	1 (1.5%)	1 (1.5%)	
	R	0 (0%)	1 (1.5%)	
	L	1 (1.5%)	0 (0%)	
	RL	0 (0%)	0 (0%)	

[a]Pearson Chi-Square Test
[b]Fisher-Freeman-Halton Exact Test

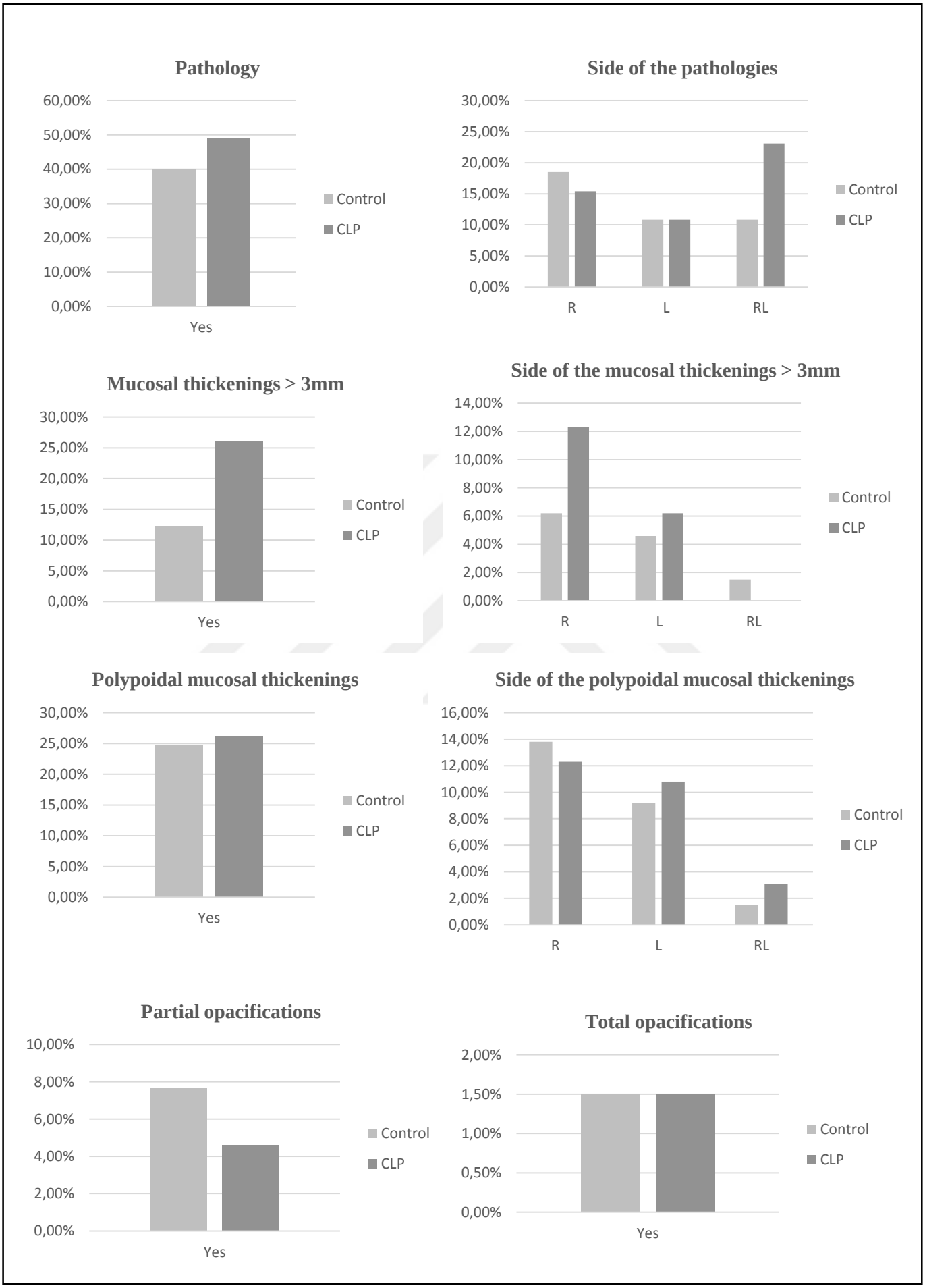

Fig. 9. The Distribution of the Percentages of Presence and Sides of Each Pathology in the Groups

4.1.2. Comparison of Presence of Pathologies Among the Cleft Types (UCLP and BCLP) in the CLP Group

The comparison of the presence and absence of the pathologies according to Pearson Chi-Square Test and the comparison of the sides of the pathologies among the cleft types according to Fisher-Freeman-Halton Exact Test are presented in Table 6.

In the comparison between the cleft types (UCLP and BCLP), neither the presence of MS pathologies or their sides nor the categories of MS pathologies have been found statistically significant ($p > 0.05$).

4.1.3. Comparison of Presence of Pathologies Among the Cleft Sides in the CLP Group

The comparison of the presence and absence of the pathologies according to Pearson Chi-Square Test and the comparison of the sides of the pathologies among the cleft sides according to Fisher-Freeman-Halton Exact Test are presented in Table 7.

Maxillary sinus pathologies were observed most frequently in bilateral CLP patients (59.1%). However, the difference was not found statistically significant ($p > 0.05$).

There was no statistically significant difference between the cleft side and the sides of the pathologies ($p > 0.05$). Also, there was no statistically significant difference between the clefting sides in terms of types of pathologies ($p > 0.05$).

4.2. Sinus-Based Assessments

4.2.1. Comparison of CLP Group and Control Group

The comparison of the presence and absence of the pathologies according to Pearson Chi-Square Test and the comparison of the sides of the pathologies, and the comparison of the groups according to Fisher-Freeman-Halton Exact Test are in presented in Table 8. In the CLP group, of the 130 sinuses (65 patients multiplied by 2), 45 of them were evaluated as pathological. In control group, of the 130 sinuses (65 patients multiplied by 2), 33 of them were evaluated as pathological.

Table 6. Distribution of CLP Patients Exhibiting Pathology Among Cleft Types

N=65		Unilateral CLP	Bilateral CLP	p
		n (%)	n (%)	
Pathology	**No**	24 (55.8%)	9 (40.9%)	[a]0.255
	Yes	19 (44.2%)	13 (59.1%)	
	R	4 (9.3%)	6 (27.3%)	[b]0.318
	L	5 (11.6%)	2 (9.1%)	
	RL	10 (23.3%)	5 (22.7%)	
Mucosal thickening >3 mm	**No**	34 (79.1%)	14 (63.7%)	[b]0.445
	Yes	9 (20.9%)	8 (36.3%)	
	R	5 (11.6%)	3 (13.6%)	
	L	2 (4.7%)	2 (9.1%)	
	RL	2 (4.7%)	3 (13.6%)	
Polypoidal mucosal thickening	**No**	32 (74.4%)	16 (72.7%)	[b]0.461
	Yes	11 (25.6%)	6 (27.2%)	
	R	4 (9.3%)	4 (18.2%)	
	L	6 (14%)	1 (4.5%)	
	RL	1 (2.3%)	1 (4.5%)	
Partial opacification	**No**	40 (93%)	22 (100%)	[b]0.695
	Yes	3 (7%)	0 (0%)	
	R	0 (0%)	0 (0%)	
	L	1 (2.3%)	0 (0%)	
	RL	2 (4.7%)	0 (0%)	
Total opacification	**No**	42 (97.7%)	22 (100%)	[b]0.999
	Yes	1 (2.3%)	0 (0%)	
	R	0 (0%)	0 (0%)	
	L	1 (2.3%)	0 (0%)	
	RL	0 (0%)	0 (0%)	

[a]Pearson Chi-Square Test
[b]Fisher-Freeman-Halton Exact Test

Despite the fact that the sinuses in the CLP group had a higher incidence of pathology than the sinuses in the control group, no statistical association was found ($p > 0.05$).

Comparing the number of sinuses with mucosal thickening greater than 3 mm in the CLP and control groups showed that the number of affected sinuses in the CLP group was significantly higher than that of the control group ($p < 0.05$).

However, there were no statistically significant differences between the number of sinuses with other categories of pathologies of CLP and control groups ($p > 0.05$).

Table 7. Distribution of CLP Patients Exhibiting Pathology Among Cleft Sides

N=65		R	L	RL	p
		n (%)	n (%)	n (%)	
Pathology	**No**	6 (%50)	18 (58.1%)	9 (40.9%)	[a]0.468
	Yes	6 (%50)	13 (41.9%)	13 (59.1%)	
	R	0 (0%)	4 (12.9%)	6 (27.3%)	[b]0.430
	L	2 (16.7%)	3 (9.7%)	2 (9.1%)	
	RL	4 (33.3%)	6 (19.4%)	5 (22.7%)	
Mucosal thickening >3 mm	**No**	10 (83.3%)	24 (77.4%)	14 (63.6%)	[b]0.797
	Yes	2 (16.7%)	7 (22.6%)	8 (36.4%)	
	R	2 (16.7%)	3 (9.7%)	3 (13.6%)	
	L	0 (0%)	2 (6.5%)	2 (9.1%)	
	RL	0 (0%)	2 (6.5%)	3 (13.6%)	
Polypoidal mucosal thickening	**No**	8 (66.7%)	24 (77.4%)	16 (72.7%)	[b]0.219
	Yes	4 (33.3%)	7 (22.6%)	6 (27.2%)	
	R	0 (0%)	4 (12.9%)	4 (18.2%)	
	L	3 (25%)	3 (9.7%)	1 (4.5%)	
	RL	1 (8.3%)	0 (0%)	1 (4.5%)	
Partial opacification	**No**	10 (83.3%)	30 (96.8%)	22 (100%)	[b]0.105
	Yes	2 (16.7%)	1 (3.2%)	0 (0%)	
	R	0 (0%)	0 (0%)	0 (0%)	
	L	1 (8.3%)	0 (0%)	0 (0%)	
	RL	1 (8.3%)	1 (3.2%)	0 (0%)	
Total opacification	**No**	12 (100%)	30 (96.8%)	22 (100%)	[b]0.999
	Yes	0 (0%)	1 (3.2%)	0 (0%)	
	R	0 (0%)	0 (0%)	0 (0%)	
	L	0 (0%)	1 (3.2%)	0 (0%)	
	RL	0 (0%)	0 (0%)	0 (0%)	

[a]Pearson Chi-Square Test
[b]Fisher-Freeman-Halton Exact Test

4.2.2. Comparison of Presence of Pathologies Among the Cleft Types (UCLP and BCLP) in the CLP Group

The comparison of the presence and absence of the pathologies according to Pearson Chi-Square Test and the comparison of the sides of the pathologies among the cleft types according to Fisher-Freeman-Halton Exact Test are presented in Table 9.

Despite the fact that maxillary sinus pathologies were found to be more frequent in the sinuses of the bilateral CLP group than in the sinuses of the unilateral CLP group, there was no statistically significant difference ($p > 0.05$).

When comparing the frequency of pathology based on the sinuses according to cleft types, no significant difference was found in any of the pathology groups ($p > 0.05$).

Table 8. Distribution of Sinuses Exhibiting Pathology Among CLP and Control Groups

N=260		CLP	Control	p
		n (%)	n (%)	
Pathology	**No**	85 (65.4%)	97 (74.6%)	[a]0.104
	Yes	45 (34.6%)	33 (25.4%)	
Mucosal thickening >3 mm	**No**	108 (83.1%)	121 (93.1%)	**[a]0.013***
	Yes	22 (16.9%)	9 (6.9%)	
Polypoidal mucosal thickening	**No**	111 (85.4%)	113 (86.9%)	[a]0.720
	Yes	19 (14.6%)	17 (13.1%)	
Type of polypoidal mucosal thickening	**Small**	3 (2.3%)	7 (5.4%)	[a]0.391
	Large	8 (6.2%)	5 (3.8%)	
	Multiple	8 (6.2%)	5 (3.8%)	
Partial opacification	**No**	125 (96.2%)	124 (95.4%)	[a]0.758
	Yes	5 (3.8%)	6 (4.6%)	
Total opacification	**No**	129 (99.2%)	129 (99.2%)	[c]0.999
	Yes	1 (0.8%)	1 (0.8%)	

[a]Pearson Chi-Square Test
[c]Fisher's Exact Test
***p<0.05**

Table 9. Distribution of Sinuses Exhibiting Pathology in CLP Group Among Cleft Types

N=260		Unilateral	Bilateral	p
		n (%)	n (%)	
Pathology	**No**	57 (66.3%)	28 (63.6%)	[a]0.764
	Yes	29 (33.7%)	16 (36.4%)	
Mucosal thickening >3 mm	**No**	75 (87.2%)	33 (75%)	[a]0.079
	Yes	11 (12.8%)	11 (25%)	
Polypoidal mucosal thickening	**No**	74 (86%)	37 (84.1%)	[a]0.765
	Yes	12 (14%)	7 (15.9%)	
Type of polypoidal mucosal thickening	**Small**	2 (2.3%)	1 (2.3%)	[b]0.834
	Large	6 (7%)	2 (4.5%)	
	Multiple	4 (4.7%)	4 (9.1%)	
Partial opacification	**No**	81 (94.2%)	44 (100%)	[c]0.166
	Yes	5 (5.8%)	0 (0%)	
Total opacification	**No**	85 (98.8%)	44 (100%)	[c]0.999
	Yes	1 (1.2%)	0 (0%)	

[a]Pearson Chi-Square Test
[b]Fisher-Freeman-Halton Exact Test
[c]Fisher's Exact Test

5. DISCUSSION

Congenital abnormalities affecting the craniofacial region are the fourth most prevalent birth anomaly in newborns. The most common among these abnormalities that concern the head and neck region is the cleft lip and palate (222). Oral clefts are a diverse group of non-fatal birth abnormalities that are known to have a multifactorial etiology, in that both genetic and environmental factors are involved in their formation (223).

Clefts can be classified as non-syndromic or syndromic. It is usually non-syndromic, as only 10% of infants with CLP have an associated syndrome (57). Patients with non-syndromic CLP were included in the present study.

Various anatomical abnormalities accompany CLP other than clefting. These variations may result in many problems, greatly impacting the ear, nose, and throat. Especially sinus diseases, mainly sinusitis, are frequently seen in CLP patients (10). Suffering from various impairments can negatively impact the quality of life. Understanding the impacts of cleft lip and/or palate on the overall health of affected individuals and families and also identifying their healthcare needs is critical for treatment planning and early referral in healthcare practices to improve the health outcomes and quality of life (QoL) of affected individuals (224). The management of patients with CLP needs a multidisciplinary approach. Pediatric dentists have important roles in maintaining oral hygiene and detecting dental anomalies and/or pathologies in CLP patients (225).

Since maxillary sinusitis is frequently observed in cleft lip and palate patients (19), it was aimed to evaluate and compare the presence and distribution of maxillary sinus pathologies in cleft lip and palate patients in this study regarding reducing the burden of cleft lip and palate on the individual when considering their QoL.

The most common imaging methods in dentistry are intraoral and panoramic radiographs, which provide two-dimensional (2D) imaging of oral and dental hard tissues. These 2D radiographies, however, are not capable of evaluating defects, anatomical variations and relationships in 3D. The CBCT imaging provides a three-dimensional view of the defect and structures by allowing the examination of structures in all three planes, including the maxillary sinus (226). There are many studies in the literature examining the maxillary sinuses of patients with cleft lip and palate (11,23,27,29) using different imaging techniques. However,

the volume of the maxillary sinus is the main focus of recent studies with CLP patients (6,21,28).

For these reasons, CBCT was used in this study to assess maxillary sinus pathologies in CLP patients. In order to carry out a comprehensive evaluation, the data was recorded and statistically analyzed in terms of patient-based and sinus-based findings.

There are many studies carried out in individuals with cleft lip and palate that question the incidence of maxillary sinusitis (10,11,19). However, imaging alone is not sufficient to diagnose the condition. Furthermore, in the previous literature the radiographic findings of the sinusitis were slightly related with the clinical status of the patients (219,227,228). For instance, ***Cha et al.*** (229) evaluated 500 CBCT scans of asymptomatic patients, 63% of whom had maxillary sinus pathologies. In addition, ***Flinn et al.*** (230) confirmed other studies with their prospective study that a high percentage of maxillary sinus abnormalities have been seen in patients without any clinical symptoms of airway problems.

In the literature review, it was determined that, previous studies included patients of a range of ages. While some research provided findings of a wide an age range (11, 220, 221), several focused-on patients in a particular age group (21, 218). This conflict arises from contrasting opinions on the effect of continued development of the maxillary sinus (220).

Suzuki et al. (11) studied patients ranging in age from 4 to 35 years; ***Kula et al.*** (218) worked with CLP patients aged 8 to 14 years; ***Rege et al.*** (220) included patients over 12 years of age; and ***Hsiao et al.*** (221) conducted their study with participants ranging in age from 8 to 90 years.

In order to evaluate the effect of occurrence of CLP on the maxillary sinus pathologies in a population with continuing growth and development, 7-18 age group was included in the present study.

In addition to these studies, some researchers compared cleft and age-matched non-cleft patients. ***de Rezende Barbosa et al.*** (21) compared age matched UCLP, BCLP, and non-CLP individuals ranging in age from 9 to 12 years old. Also, ***Kula et al.*** (218) designed a study with 15 UCLP patients and 15 sex- and age-matched non-cleft controls, aged 8 to 14 years. Lastly, ***Demirtas et al.*** (23) conducted research with cleft patients and age- and sex-matched controls to evaluate and compare the maxillary sinus volume of individuals.

Since children and adolescents with CLP were evaluated in this study, due to their incomplete sinus development, sex- and age-matched controls were chosen.

Furthermore, ***Kula et al.*** (218) and ***Vallo et al.*** (231) concluded different age groups that exhibited similar relative amounts of mucosal thickening. This outcome provided a pathway for the sex- and age-matched methodology which was followed in the present study.

Santos et al. (232) assessed the incidental findings on CBCT in CLP patients. They pointed out that beside the dentoalveolar complex, the highest rate of findings was in the sinuses. Another study, published by ***Cha et al.*** (229), evaluated the incidental findings in maxillofacial structure on CBCT in patients without a cleft and found that the most recurrent incidental findings were in the airway area. Also, they classified the sinus findings as sinusitis, retention cysts, and sinus polyps.

Ali et al. (219) categorized maxillary sinus pathological findings as maxillary antrum sinusitis, maxillary cysts, and maxillary polyps in their recent research.

Rosado et al. (233) conducted a study to evaluate the knowledge level of dental students for diagnosis and classified maxillary sinus findings as normal, mucosal thickenings > 3 mm, sinus polyp, antral pseudocyst, nonspecific opacification, periostitis, and antrolith in their recent research.

In this retrospective study, detected sinus pathologies were categorized the same as in the research published by ***Hsiao et al.*** (221). They were healthy, mucosal thickening > 3 mm, polypoidal mucosal thickening, partial opacification, and total opacification.

The literature has conflicting findings on the level of mucosal thickening that indicates a problem. While according to ***Patel et al.*** (234) and ***Lim et al.*** (235), significant mucosal thickening was greater than 2 mm, recent studies (210, 220, 221, 236) considered 3 mm as pathological. Also, previous studies (237, 238) have suggested assessments ranging from 4 to 6 mm.

Mucosal thickenings were evaluated, and 3 mm was considered as the reference measure for presence of pathology in this study. The mucosal thicknesses less than 3 mm were considered healthy.

In this study, the incidence of unilateral clefts on the left side was significantly higher than on the right side, agreeing with previous literature published by ***Derijcke et al.*** (47).

Kula et al. (218) examined 30 CBCT scans of 15 UCLP and 15 sex- and age-matched noncleft controls. They compared the percentage of mucosal thickening in the sinuses of patients and found that nearly three times more mucosal thickening occurs in the UCLP sample than in the control sample.

Santos et al. (232) evaluated 110 scans of various types of cleft patients. They assessed incidental findings using CBCT and resulted that only one patient had mucosal thickening among the study group. They mostly observed partial opacification of the mucosa. However, they did not mention the measurement of the thickening they took as reference.

Paknahad et al. (239) investigated anatomical variation impairments in cleft patients and compared them with a non-cleft control group. CBCT images of 40 UCLP, 14 BCLP, and 54 control patients were analyzed and assessed for quantitative and qualitative measures. The results showed a significantly higher incidence of mucosal thickening of the sinuses in the cleft groups than in the noncleft group.

In this study, only the mucosal thickening > 3 mm category showed a statistically significant difference. We found that thickenings were greater in cleft group patients than in age-matched controls, agreeing with a previous study (216) based on a Turkish population that demonstrated a significant difference in inflammatory mucosal change of the maxillary sinuses. This can be a result of a higher incidence of bilateral sinus pathologies in the CLP group than found in the non-cleft group. ***Jaffe et al.*** (19) also found that patients with a unilateral cleft lip and palate usually have sinusitis bilaterally, similar to our results.

Suzuki et al. (11) conducted a study to investigate maxillary sinus development and sinusitis in cleft lip and palate patients. Their results indicated that maxillary sinusitis is more common in cleft patients with developing maxillary sinuses. They discussed some etiological factors that would play a role in this prevalence. First, having a small maxilla can be a predisposing factor for a malpositioned or narrow sinus ostium. Additionally, congenital sinusitis can possibly be seen in cleft patients. Lastly, rhinosinusitis plays a huge role as an etiologic factor, which can happen through upper respiratory infections, regurgitation of saliva and food through the cleft, or an incompetent velopharynx that can irritate the nasal and paranasal sinus mucosa.

In this study, the anatomy of the maxillary sinuses of the patients wasn't investigated. The main focus was on examining the prevalence as well as the etiology of maxillary sinus pathologies.

Dental-related conditions can be associated with mucosal thickening of the maxillary sinus (240). ***Brüllmann et al.*** (241) examined the maxillary sinuses and posterior maxillary teeth of 204 patients using CBCT. They observed a correlation between decayed teeth, or periodontitis, in the posterior region and basal mucosal thickening.

In this study, dental caries, or apical pathologies in the posterior maxillary teeth of the patients were not evaluated. Since previous dental literature (242) has revealed a predisposition between being a cleft patient and having dental caries, the higher percentage of mucosal thickening in cleft patients may be linked to this result.

Duman and Duman (216) reported that retention cysts were statistically significantly higher in the CLP group patients than in control group patients, on the contrary, no significant differences between the CLP and control groups regarding polypoidal mucosal thickening were found in our study.

When comparing the total pathologies of the maxillary sinuses, ***Duman and Duman*** (216) found higher pathological findings in the control group without significant differences.

Erdur et al. (6) concluded in their study that having a lower volume of maxillary sinus in unilateral cleft patients than control patients can be a result of having greater pathologies in their maxillary sinuses. Even though the cleft group presented with higher pathological findings in our study, no statistically significant differences were found.

Some studies compared their results among cleft subgroups (19,232). ***Santos et al.*** (232) determined the prevalence of the incidental findings in maxillary sinuses among each cleft type group. According to their results, there is a positive correlation between cleft severity and the frequency of abnormalities.

Considering our results, the incidence of maxillary sinus pathologies was higher among unilateral cleft patients than bilateral cleft patients. However, no statistically significant difference was found in any parameter.

Previous studies in the literature have also compared their findings based on the cleft side (6,23,24,243,244). ***Nemţoi et al.*** (244) compared maxillary sinus volumes between cleft and non-cleft sides among 15 CLP patients. Their results showed no statistically significant difference, in contradiction with a recent study (23) that demonstrated a significant difference with a greater maxillary sinus volume on the cleft side.

In this study, maxillary sinus pathologies were also compared regarding the cleft sides among CLP group patients. No statistically significant difference was found in any parameter between the defect and non-defect sides.

Limitations of this study

- In this retrospective study, CBCT scans of the patients were evaluated without considering their detailed medical and dental histories. Additionally, a thorough clinical examination of each patient was not performed by the examiner in this study. It can be speculated that clinical conditions, medications, and/or manifestations of dental problems may play a role in the occurrence of maxillary sinus pathologies. However, since a long-term prospective study design would not be proper in terms of ethical aspects for the growing young patients who were referred for dental treatment needs, previous images already taken for various indications were used in this study.
- The lack of a sound method for the radiological classification of maxillary sinus pathology limited the analysis in this study.
- Different evaluation methods may result in different results. The lack of consensus on the level of mucosal thickening may limit the outcomes.
- Seasonal factors may play a role in the mucosal thickening of the maxillary sinuses due to changing temperature or allergic reactions. However, in this study, the possible effects of seasonal changes on the maxillary sinus pathologies were not considered.

6. CONCLUSIONS

In the present study, maxillary sinus pathologies in children and adolescents with cleft lip and palate were evaluated and compared with those of an age-matched control group using CBCT;

1. The incidence of unilateral clefts on the left side was significantly higher than on the right side ($p<0.05$).
2. The total number of maxillary sinus pathologies showed no statistically significant difference between cleft patients and non-cleft patients ($p>0.05$).
3. According to the patient-based results, no statistically significant differences were found between the CLP group patients and the control group patients in any parameters ($p>0.05$).
4. According to the sinus-based results, a significant difference was found only in the mucosal thickening greater than 3 mm category between the CLP and the control group patients ($p<0.05$).
5. In the CLP group of patients there were no statistically significant differences between the cleft types and cleft side in terms of either the total number of pathologies or the classification of pathologies ($p>0.05$).
6. CLP patients have a significantly higher incidence of having bilateral sinus mucosal thickenings compared to non-cleft patients.

In conclusion, CBCT plays a very important role in detecting incidental findings in the oral and maxillofacial region in patients referred to dentists. For children with CLP, it's absolutely vital to get an early diagnosis of maxillary sinusitis, which has a negative impact on quality of life. However, in addition to radiographic findings, clinical signs and symptoms must also be considered when diagnosing sinusitis in children. Therefore, a survey of sinusitis symptoms in children with CLP should be included in future CBCT research.

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8. APPENDICES

APPENDIX 1: Ethical Approval Form for Non-Invasive Clinical Research Committee

YEDİTEPE ÜNİVERSİTESİ
GİRİŞİMSEL OLMAYAN KLİNİK ARAŞTIRMALAR
ETİK KURULU

Versiyon No 2.0
13.02.2022

KARAR FORMU

06:25

ETİK KURUL BİLGİLERİ		
	Etik Kurulun Adı	Yeditepe Üniversitesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu
	Açık Adres	Yeditepe Üniversitesi Kayışdağı Kampüsü, Tıp-Mühendislik Binası, Sağlık Bilimleri Enstitüsü, İnönü Mah. Kayışdağı Cad. 326A, 26 Ağustos Yerleşimi 34755 Ataşehir, İstanbul
	İnternet Sayfası	http://goetik.yeditepe.edu.tr/
	Telefon	0216 578 00 00
	E-posta	goetik@yeditepe.edu.tr

DEĞERLENDİRİLEN BELGELER	
	Islak imzalı başvuru dosyası, CD'si ve elektronik başvuru ☒
	Araştırma başlığı ve araştırmacıların isimleri ☒
	Başvuru dilekçesi ☒
	Başvuru Formu- Araştırmanın; ☒
	• Niteliği ☒
	• Önemi ve özgün değeri ☒
	• Amaç ve hedefleri ☒
	• Yöntemi ☒
	• Yönetimi ☒
	• Yaygın etkisi ☒
	• Araştırma bütçesi (Mevcutsa) ☒
	• Süresi ve uygunluğu (Zaman cetveli) ☒
	• Kaynakları ☒
	Bilgilendirilmiş Gönüllü Olur Formu (yapılan araştırmaya özel olarak hazırlanmış) ☒
	Taahhütname-1 Araştırmanın yapılacağı kurumdan izin alma sorumluluğunun araştırmacılara ait olduğuna dair taahhüt ☒
	Taahhütname-2 Dünya Tıp Birliği Helsinki Bildirgesinin son versiyonunun ve Sağlık Bakanlığı'nın ilgili tüm kılavuzlarının okunmasına dair taahhüt ☒
	Taahhütname-3 Daha önce yapılmış etik kurul başvuruları mevcut olup olmadığına dair taahhüt ☒
	Taahhütname-4 Araştırma sırasında araştırma bütçesinde yer almayan ve gönüllünün kendisine veya Sosyal Güvenlik Kurumuna ek yük getirecek hiçbir işlem uygulanmayacağına dair taahhüt ☒
	Taahhütname-5 COVID-19 hastalarında tedavi yaklaşımları ve bilimsel araştırmalar genelgesi okunmasına dair taahhüt ☒
	Taahhütname-6 Milli Eğitim Bakanlığı Araştırma Uygulama İzinleri konulu yazının okunmasına dair taahhüt ☒
	Araştırmacıların her birisine ait özgeçmiş formu ☒
	Ek belgeler (Varsa kullanılan ölçek izinleri vb.) ☒

KARAR BİLGİLERİ		
	Başvuru Numarası	202201146
	Toplantı Tarihi	11.02.2022
	Toplantı Yeri	Çevirim içi (Google Meet)
	Karar No	41

Araştırmanın Başlığı: Dudak Damak Yarıklı Çocuk veGenç Hastalarda Maksiller Sinüs Patolojilerinin Konik Işınlı Bilgisayarlı Tomografi ile Retrospektif Olarak Değerlendirilmesi

Araştırmacılar: Dt.Ayşe Çelik, Prof.Dr. Senem Selvi Kuvvetli,Doç.Dr.Nilüfer Ersan

YEDİTEPE ÜNİVERSİTESİ
GİRİŞİMSEL OLMAYAN KLİNİK ARAŞTIRMALAR
ETİK KURULU

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☒**KABUL**	☐ **RET** ☐ *KAPSAM DIŞI (GİRİŞİMSEL)* ☐ *BİLİMSEL VE/VEYA ETİK KURALLARA AYKIRI* ☐ *BİR SORUMLU ARAŞTIRMACININ (TEZ ISE DANIŞMAN), BİR TOPLANTIYA **İKİ (2) ADETTEN FAZLA ÇALIŞMA BAŞVURUSUNDA** BULUNMASI* ☐ *KURUM İÇİ BAŞVURULARINDA **KURUMSAL E-POSTA HESABI** İLE GİRİŞ YAPILMAMIŞ OLMASI* ☐ *ŞARTLI KABULDE BELİRTİLEN REVİZYONLARIN ZAMANINDA VE/VEYA İSTENİLDİĞİ ŞEKİLDE YAPILMAMIŞ OLMASI*

Yeditepe Üniversitesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu adına
Prof.Dr.Didem Özdemir ÖZENEN
Başkan

Araştırmanın Başlığı	Dudak Damak Yarıklı Çocuk veGenç Hastalarda Maksiller Sinüs Patolojilerinin Konik Işınlı Bilgisayarlı Tomografi ile Retrospektif Olarak Değerlendirilmesi
Araştırmacılar	Dt.Ayşe Çelik, Prof.Dr. Senem Selvi Kuvvetli,Doç.Dr.Nilüfer Ersan

APPENDIX 2: Informed Consent Form

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DİŞ HEKİMLİĞİ FAKÜLTESİ VE DİŞ HASTANESİNDE
ÇOCUK HASTALARDA YAPILACAK OLAN
"Dudak Damak Yarıklı Çocuk ve Genç Hastalarda Maksiller Sinüs Patolojilerinin Konik Işınlı Bilgisayarlı Tomografi ile İncelenmesi"
DOKTORA TEZ ÇALIŞMASI İÇİN "EBEVEYN" BİLGİLENDİRİLMİŞ GÖNÜLLÜ OLUR FORMU ÖRNEĞİ

Araştırma Projesinin Adı: Dudak Damak Yarıklı Çocuk ve Genç Hastalarda Rastlantısal Bulguların ve Maksiller Sinüs Patolojilerinin Konik Işınlı Bilgisayarlı Tomografi ile İncelenmesi
Sorumlu Araştırmacının Adı: Prof. Dr. Senem Selvi Kuvvetli
Diğer Araştırmacıların Adı: Dt. Ayşe Çelik, Doç. Dr. Nilüfer Ersan
Destekleyici (varsa): -

Değerli Ebeveynler;

Çocuğunuzun, kliniğimizde yapılması planlanan "Dudak Damak Yarıklı Çocuk ve Genç Hastalarda Rastlantısal Bulguların ve Maksiller Sinüs Patolojilerinin Konik Işınlı Bilgisayarlı Tomografi ile İncelenmesi" isimli bir çalışmada yer alabilmesi için sizden izin istiyoruz. Çocuğunuzun bu çalışmaya davet edilmesinin nedeni, hastanemizde çocuğunuzdan çeşitli nedenlerle Konik Işınlı Bilgisayarlı Tomografi (KIBT) çekilmiş olmasıdır. Bu çalışma, bilimsel araştırma amacı ile yapılmaktadır ve katılım gönüllülük esasına dayalıdır. Çocuğunuzun çalışmaya katılması konusunda karar vermeden önce araştırma hakkında sizi bilgilendirmek istiyoruz. Çalışma hakkında tam olarak bilgi sahibi olduktan sonra ve sorularınız cevaplandıktan sonra eğer çocuğunuzun katılmasını isterseniz sizden bu formu imzalamanız istenecektir.

Çalışmanın amaçları ve dayanağı nelerdir?

Bu çalışmanın amacı, dudak damak yarıklı çocuk ve genç hastalarda rastlantısal bulguların ve maksiller sinüs patolojilerinin konik ışınlı bilgisayarlı tomografi ile incelenmesi ve dudak damak yarıklı olmayan bir grup çocukla karşılaştırılmasıdır. Dudak damak yarıklı hastalarda sık karşılaştığımız maksiller sinüzit hastalığının nedeni günümüzde hala tam olarak bilinmemektedir. Burun tıkanıklığı, baş ağrısı, koku almada azalma gibi kronik sinüzit şikayetlerinin nedeni araştırılırken, diş tedavileri için çekilen konik ışınlı bilgisayarlı tomografilerde sinüslerin incelenmesi ile bu hastalığın erken teşhisinin mümkün olup olmadığı da çalışmamızın amaçları arasında yer almaktadır.

Çocuğum bu çalışmaya katılmalı mı?

Çocuğunuzun bu çalışmada yer alıp almaması tamamen size bağlıdır. Eğer katılmasına izin verirseniz bu yazılı bilgilendirilmiş olur formu imzalanmak için size verilecektir. Şu anda bu formu imzalasanız bile istediğiniz herhangi bir zamanda çocuğunuzu çalışmadan çekebilirsiniz. Eğer katılmasını istemezseniz veya çalışmadan ayrılırsanız, doktorunuz tarafından çocuğunuz için en uygun tedavi planı uygulanacaktır. Aynı şekilde çalışmayı yürüten doktor çocuğunuzun çalışmaya devam etmesinin yararlı olmayacağına karar verebilir ve onu çalışma dışı bırakabilir.

Çocuğum bu çalışmaya katılırsa onu neler bekliyor?

Bu araştırma kapsamında çocuğunuza, herhangi bir girişim yapılmayacaktır. Daha önceden hastanemizde çekilen, çocuğunuza ait konik ışınlı bilgisayarlı tomografi görüntülerinin incelenmesi için onayınız istenmektedir.

Çalışmanın riskleri ve rahatsızlıkları nelerdir, çocuğumun görebileceği olası bir zarar durumunda ne yapılacak?

Çocuğunuza yeni bir girişim yapılmayacağı için çalışmamız risk teşkil etmemekte ve çocuğunuzun görebileceği olası bir zarar durumu bulunmamaktadır.

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Çocuğumun bu çalışmada yer almasının yararları nelerdir?

Planlanan çalışmanın amaçları doğrultusunda, elde edilen veriler ve sonuçların bilimsel katkı sağlayacağı düşünülmektedir.

Çocuğumun bu çalışmaya katılmasının maliyeti nedir?

Çalışmaya katılmakla parasal yük altına girmeyeceksiniz ve size de herhangi bir ödeme yapılmayacaktır.

Çocuğumun kişisel bilgileri nasıl kullanılacak?

Sorumlu araştırmacı ve diğer araştırmacılar çocuğunuz ile ilgili kişisel bilgileri, araştırmayı ve istatiksel analizleri yürütmek için kullanacaktır ancak çocuğunuzun kimlik bilgileri gizli tutulacaktır. Yalnızca gereği halinde, çocuğunuz ile ilgili bilgileri etik kurullar ya da resmi makamlar inceleyebilir. Çalışmanın sonunda, sonuçlar hakkında bilgi istemeye hakkınız vardır. Çalışma sonuçları tıbbi literatürde yayınlanabilecektir ancak çocuğunuzun kimliği açıklanmayacaktır.

Daha fazla bilgi, yardım ve iletişim için kime başvurabilirim?

Çalışma ile ilgili bir sorununuz olduğunda ya da çalışma ile ilgili ek bilgiye gereksiniminiz olduğunuzda aşağıdaki kişi ile lütfen iletişime geçiniz.

ADI : Ayşe Çelik
GÖREVİ : Araştırma Yürütücüsü

Yeditepe Üniversitesi Diş Hekimliği Fakültesi Çocuk Diş Hekimliği Anabilim dalında, Dt. Ayşe Çelik tarafından tıbbi bir araştırma yapılacağı belirtilerek bu araştırma ile ilgili yukarıdaki bilgiler bana aktarıldı ve ilgili metni okudum.

Çocuğumun araştırmaya katılması konusunda zorlayıcı bir davranışla karşılaşmış değilim. Eğer çocuğumun çalışmaya katılmasını reddedersem, bu durumun çocuğumun tıbbi bakımına ve hekim ile olan ilişkime herhangi bir zarar getirmeyeceğini de biliyorum. Çalışmanın yürütülmesi sırasında herhangi bir neden göstermeden çocuğumu araştırmadan çekebilirim.

Araştırma için yapılacak harcamalarla ilgili herhangi bir parasal sorumluluk altına girmiyorum. Bana da bir ödeme yapılmayacaktır.

Bana yapılan tüm açıklamaları ayrıntılarıyla anlamış bulunmaktayım. Bu koşullarla, çocuğumun söz konusu klinik araştırmaya katılmasını gönüllülük içerisinde kabul ediyorum.

İmzalı bu form kağıdının bir kopyası bana verilecektir.

Veli Tarih:
Adı Soyadı:
İmza:

Araştırmacı Tarih:
Adı Soyadı:
Tel:
İmza:

Şahit Tarih:
Adı Soyadı:
Tel:
İmza: