Title
Maxilla Component in Craniofacial Microsomia: A CBCT Retrospective Study of Craniofacial Skeleton

Author
Chen, Shih-Chin chin

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A thesis submitted in partial satisfaction of the

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in Oral Biology

by

Shih-Chin Chen

2022

ABSTRACT OF THE THESIS

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A CBCT Retrospective Study of Craniofacial Skeleton

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Shih-Chin Chen

Master of Science in Oral Biology

University of California, Los Angeles, 2022

Professor Benjamin M. Wu, Chair

Introduction:

Craniofacial microsomia (CFM) is the second most common craniofacial congenital defect after cleft lip and palate. It is a congenital deformity characterized by hypoplasia of derivatives from the first and second pharyngeal arches. Clinically, patients who have CFM usually express the phenotype of facial asymmetry. The condition has a wide spectrum of involvement and expresses in a variety of clinical features which may affect patients' zygoma, orbit, trigeminal nerve, facial nerve, mastication muscles, facial muscles, external ear, maxilla, and mandible. It is essential to reconstruct maxilla-mandibular symmetry to achieve better facial skeletal harmony. Correction asymmetry and occlusion of CFM patients involves orthodontic treatment combined with orthognathic surgery to correct most of the asymmetry. Orthognathic surgery is either just in the

mandible or involves bi-jaws surgery. The asymmetry expression becomes more obvious where it meets the lowest part of the skull. Previous studies show significant relapse when surgery was limited to the mandible with longitudinal follow-up. Patients look asymmetrical again after long-term follow-up. Previous studies also identify the reason for the relapse as a larger amount of growth in the non-affected side. However, a significant amount of dentoalveolar compensation is found after mandibular surgery. The dentoalveolar compensation is accomplished by dental extrusion, which is the most unstable type of tooth movement. This movement has a higher chance of relapse. During the past ten years, the surgical methods to correct facial asymmetry in CFM patients has tended to involve surgery on both jaws; however, optimal correction techniques remain unclear. Previous articles related to CFM patients focus on analyzing mandible asymmetry, and not much attention has been paid to the maxilla. Growth is one of the reasons for relapse after surgical intervention, and not many articles include long-term follow-up results. Nevertheless, after high levels of dental alveolar compensation, the risk of relapse is significant and might be another reason for the relapse observed in long-term follow-up patients. This study addresses these gaps in the research and investigates the extent to which the maxilla contributes to the asymmetry that can affect the treatment result and long-term stability of the treatment.

This study is based on cone beam computed tomography (CBCT) images of CFM patients and the normal population. It evaluates the pattern of maxillary asymmetry in three dimensions—anteroposterior, transverse, and vertical.

Methods: This is a retrospective study. Initial CBCTs of patients with severe CFM (14 patients), mild CFM (16 patients), and the control group (16 patients) before orthodontic

treatment were compared using Dolphin image 11.95 software. Asymmetry indices were calculated from linear measurements obtained from dentoskeletal landmarks to three reference planes (coronal, axial, midsagittal). Additionally, angular measurements were obtained from each landmark to the axial plane.

Results: In the vertical direction of linear measurements in patients with craniofacial microsomia, the non-affected side is longer than the affected side ($p<0.05$). This difference is not statistically significant if the landmarks are higher than the orbital rim. All the lines connected by the same landmarks on both sides have the same canting direction trend and are canted upward to the affected sides. However, in patients with a severe condition of craniofacial microsomia, the line connects both sides of the condyles and is canted up in the opposite direction toward the non-affected side. There is no statistically significant difference for the maxilla landmarks in the anteroposterior direction. For the skeletal landmarks of the mandible angle (Ag, Go, Gop), the affected side is more forward than the non-affected side in the anteroposterior position. In the transverse direction, the affected side is wider than the non-affected side in the maxilla. Landmarks at the anterior part of the skull all showed statistically significant differences ($P<0.05$). The landmarks in the mandible all showed the same result between the severe and the control groups. For the angular measurements, all lines connected both sides of landmarks canted up toward the affected side and showed statistical significance except the condyle canted up toward the non-affected side. The severe group (type IIb, type III according to Pruzansky's classification) showed significant differences in its asymmetry index in the vertical and transverse directions. If the patient needs early surgical intervention, the direction of the deformity and simultaneous bi-jaw surgery should be considered.

The thesis of Shih-Chin Chen is approved.

Renate Lux

Min Lee

Benjamin M. Wu, Committee Chair

University of California, Los Angeles

2022

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INTRODUCTION

a) Craniofacial Microsomia

Craniofacial microsomia (CFM) is the second most common craniofacial congenital defect after cleft lip and palate. It is also known as hemifacial microsomia (HFM), with a wide range of expression and alteration clinically. It is also diagnosed as Goldenhar syndrome or oculo-auriculo-vertebral spectrum (1). CFM is a congenital deformity characterized by hypoplasia of derivatives from the first and second pharyngeal arches, both of which originate from neural crest cells. Structures derived from the first and second pharyngeal arches can be affected. Clinically, CFM patients usually exhibit heterogeneous phenotypes of facial asymmetry (2). Patients' zygoma, orbit, trigeminal nerve, facial nerve mastication muscles, facial muscles, external ear, maxilla, mandible, and neck may be affected (3). The condition primarily involves the lower face and midface. Several theories have been proposed for the etiology of CFM, but there is currently no consensus. One of the most commonly accepted hypotheses is reported by Poswillo (4), who claimed that the cause of CFM is stapedial artery disruption causing hemorrhaging during embryologic formation, with pathological changes in the development of the first and the second branchial arches. The phenotypic variation in CFM may reflect the degree of vascular disruption (1). Although it is mostly presented unilaterally in its clinical expression, 10% of prevalence occurs bilaterally (5). The prevalence of CFM ranges from 1 in 3500 to 1 in 5600 in live births (6). In a study by Caron et al.(1906) involving 755 patients with CFM, the male-to-female ratio and right-to-left ratio were both 1.2:1 (2).

The most common categorization used in CFM is Pruzansky's classification (7), which recognizes three types. Type I means the ramus shape is normal but the affected side is smaller than the non-affected side. In type II, the condyle, ramus, and sigmoid notch are still identifiable but grossly distorted in size and shape. Moreover, type II classification has two modifications. In type IIa, the mandibular ramus is short and has an abnormal shape, with the glenoid fossa in a satisfactory position. In type IIb, the temporomandibular joint is abnormally placed inferiorly, medially, and anteriorly. Type III classification in CFM means the ramus or condyle is absent. Previous articles focus primarily on the mandible, where facial asymmetry is more obvious and easier to see. Figure 1 shows that the mandible is the most obvious part of asymmetry, but the maxilla also contributes.

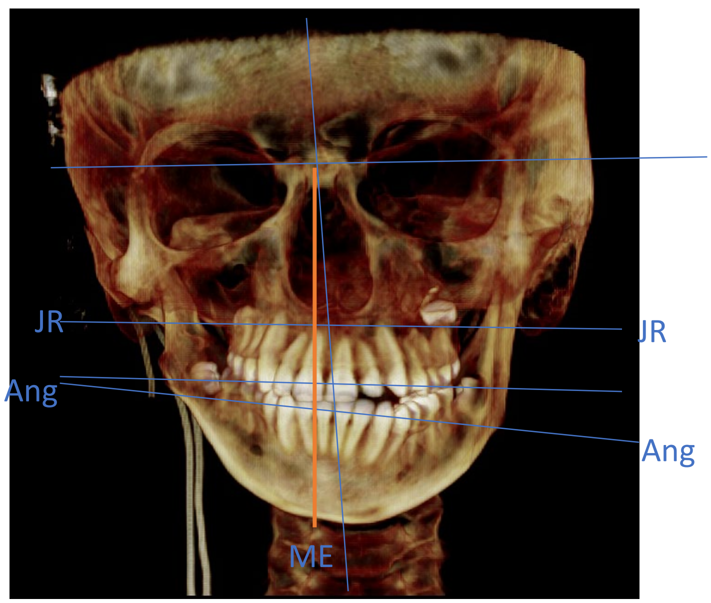

Fig 1. From the upper third of the skull to the lower third of the skull, the mandible is the most obvious part of the asymmetry.

b) Treatment

To achieve better facial skeletal harmony, it is crucial to reconstruct maxilla-mandibular symmetry. Addressing correction asymmetry and occlusion in CFM patients involves orthodontic treatment combined with orthognathic surgery to correct most of the asymmetry. Orthognathic surgery is either in the mandible only or involves the upper and lower jaws. A longitudinal follow-up study by Huisinga-Fischer et. al. (2003) considered eight patients with hemifacial microsomia three years after undergoing a mandible distraction osteogenesis procedure. The results showed that the relapse progress three years after distraction compared to 15 weeks after distraction. The authors concluded that this was due to normal growth on the non-affected side and reduced growth on the affected side (8). However, this raises the question of why there is reduced growth on the affected side. Meazzini et al. (2005) followed up with eight patients for more than five years after the patients had undergone mandible distraction osteotomy. The patients they recruited started treatment at young age. They found that patients gradually returned to asymmetry and 77% of the correction they obtained from distraction disappear (9).

In the past ten years, many articles have focused on two-jaw surgery in CFM patients. Sant'Anna et al. (2015) looked at the treatment of eight patients (mean age 13.2-year-old) with LeFort I osteotomy and mandible distraction osteogenesis. The intermaxillary fixation was applied during distraction (10). Mehrotra et al. (2017) reported that seven adult patients (mean age 22.14-year-old) were treated with the same methods as those reported in Sant'Anna et al. (2015) (11). All recent articles are case studies without long-term follow-up reports (10-14). The treatment results all improve facial harmony and symmetry. For correction of asymmetry and occlusal canting, the surgery can involve either an osteotomy or a distraction osteogenesis surgical procedure. The decision to perform a distraction osteogenesis procedure depends on the amount of movement. If a large amount of movement is necessary, distraction osteogenesis will be preferred because distraction can gradually increase soft tissue volume and increase the superior amount of bone length. However, multiple factors contribute to facial asymmetry; bone, soft tissue, muscle, and nerves can all contribute to the unbalanced facial appearance. The final results are not always aesthetically perfect. Therefore, the optimal correction techniques for facial asymmetry in CFM patients remain unclear.

c) Previous Studies

Previous studies (Trahar et al. (2003), Chow et al. (2008)) published by the University of California at Los Angeles (UCLA) School of Dentistry's Section of Orthodontics involved CFM patients treated with mandible distraction osteogenesis surgery. Six of these were diagnosed with hemifacial microsomia. The patients' mean age was 9.5 years old before the distraction osteogenesis surgery. Four of these patients were followed up for more than two years and analyzed with posteroanterior cephalograms and 45 degrees cephalograms. The ramus height showed a significant difference between treatment and control side throughout treatment (Fig.2). The mandibular length, on the treatment side, increased 6.64mm from the distraction (T1: pre-OP to T2: end of distraction). The maxillary height data indicate a favorable change, increasing 3.1mm on the treated side and 1.2mm on the control side. However, a general decline two years after distraction was observed. For the chin point, all patients demonstrated immediate improvement in chin position toward the skeletal midline; however, three months after distraction, the menton point appeared to be moving away from the midline over time (15).

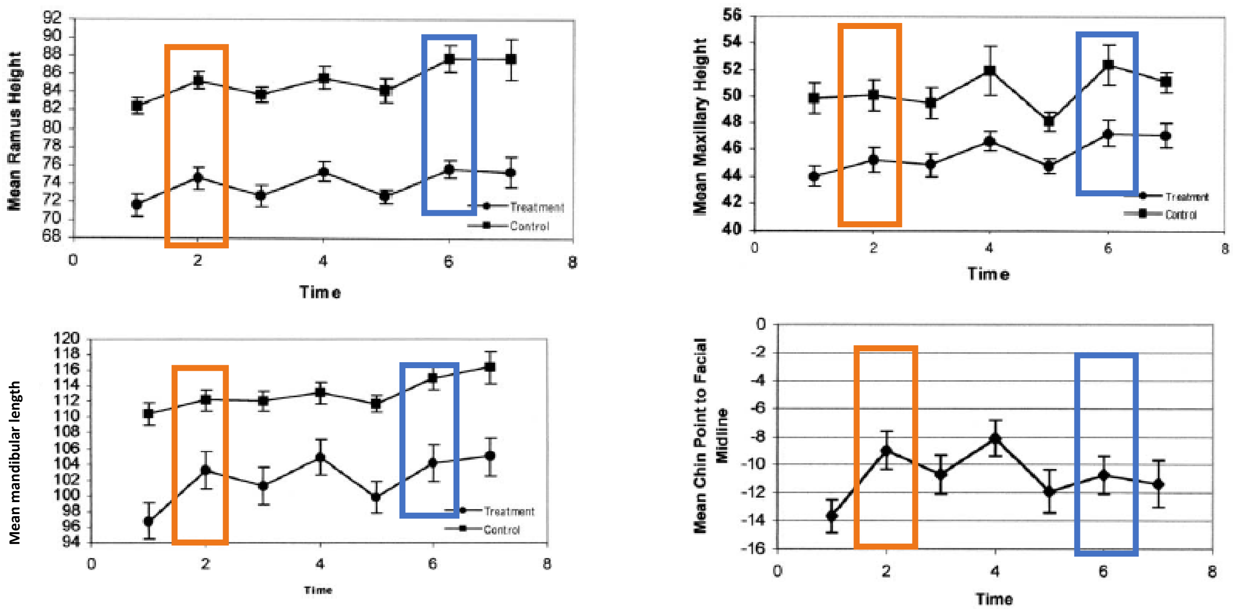

Fig. 2 After mandible distraction osteogenesis, ramus height, maxillary height, mandibular length all has significant improvement. T1: pre-op; T2: after distraction; T3: After removal of distractor; T4: 3 months after removal of distractor; T5: 6 months after removal of distractor; T6: 12 months after removal of distractor; T7: 24 months after removal of distractor (From Trahar et. al., 2003, AJODO)

After six months of follow-up for these CFM patients, the difference between the affected side and the non-affected side of the mandibular ramus height decreased. However, with another five years of follow-up, the difference increased again, although both sides showed some amount of growth. It can also be seen from the chin point deviation that the menton point fluctuated toward and away from the skeletal midline from T1 to T7 (24 months after the removal of the distractor). Ultimately, the deviation was greater than the original position (Fig.3). For occlusal height and maxillary height, compared to pre-treatment and six months after distraction, the difference was smaller in both areas compared to the initial measurements, even when no surgery had been performed on the maxilla. However, the mean difference at five years after distraction was the greatest, suggesting that the non-affected side grew more than the distracted side or a relapse occurred. Nevertheless, for the occlusal height, the discrepancy after five years of distraction was similar to the initial position, with minor long-term improvement. However, two years after distraction, the difference between the treatment and control groups is a minimum implied short-term improvement from distraction. The maxilla difference increased, but the occlusal height difference did not increase much. This situation occurs because the occlusal change is mainly due to dentoalveolar compensation in interocclusal space created by unilateral mandibular distraction. Chow et al. (2008) reported that for mandible ramus height and chin point, after five years of follow-up, the discrepancy became larger due to the greater inherent growth potential of the unaffected side. Hence, more overcorrection than initially believed is needed to offset the persistent asymmetry in growing hemifacial microsomia patients who undergo unilateral distraction osteogenesis. (16)

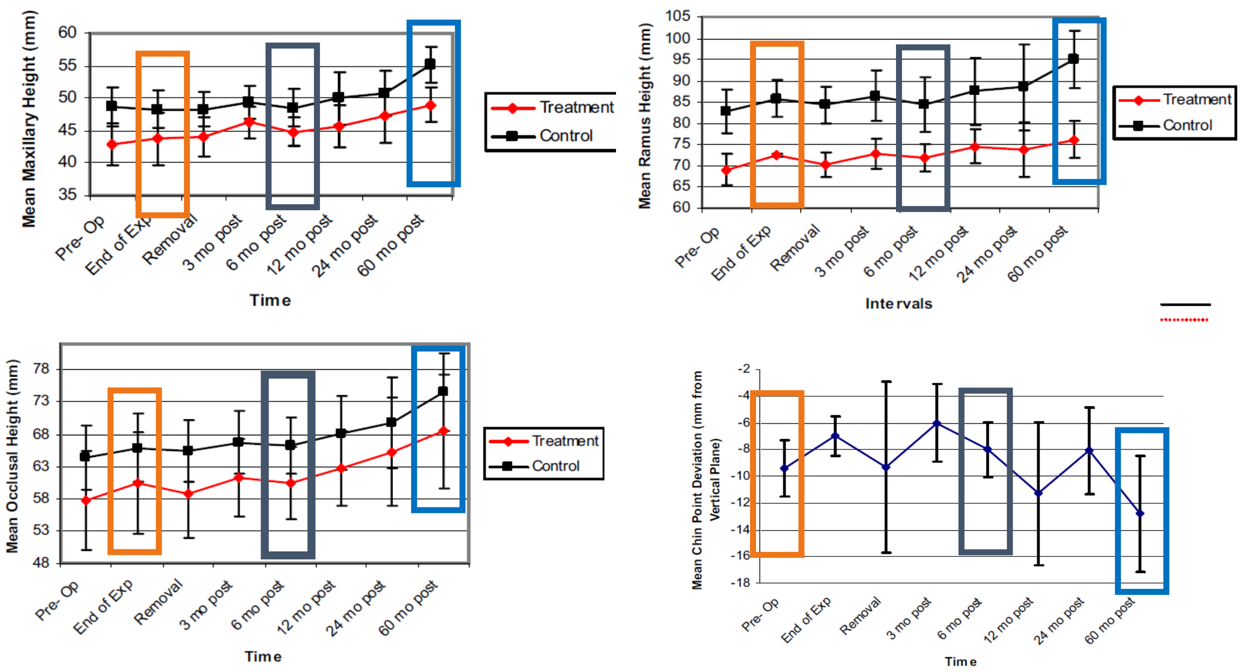

Fig. 3 For mandible ramus height and chin point, after five years of follow up, the discrepancy became larger, because of the greater inherent growth potential of the unaffected side. (From Chow et. al., 2008, AJODO)

Longer-term follow-up is available for cases more than 12 years after distraction (UCLA Orthodontic resident, Peter Joo-Hak Lee's clinical study). After patients' pubertal growth, the asymmetry worsens (Fig.4). This situation may have arisen because the patients were treated surgically only in the mandible without maxilla surgery. After distraction osteogenesis in the mandible, the maxillary dentoalveolar portion requires dental compensation to fulfill better occlusion. However, after an extended period, the relapse of dentoalveolar may occur.

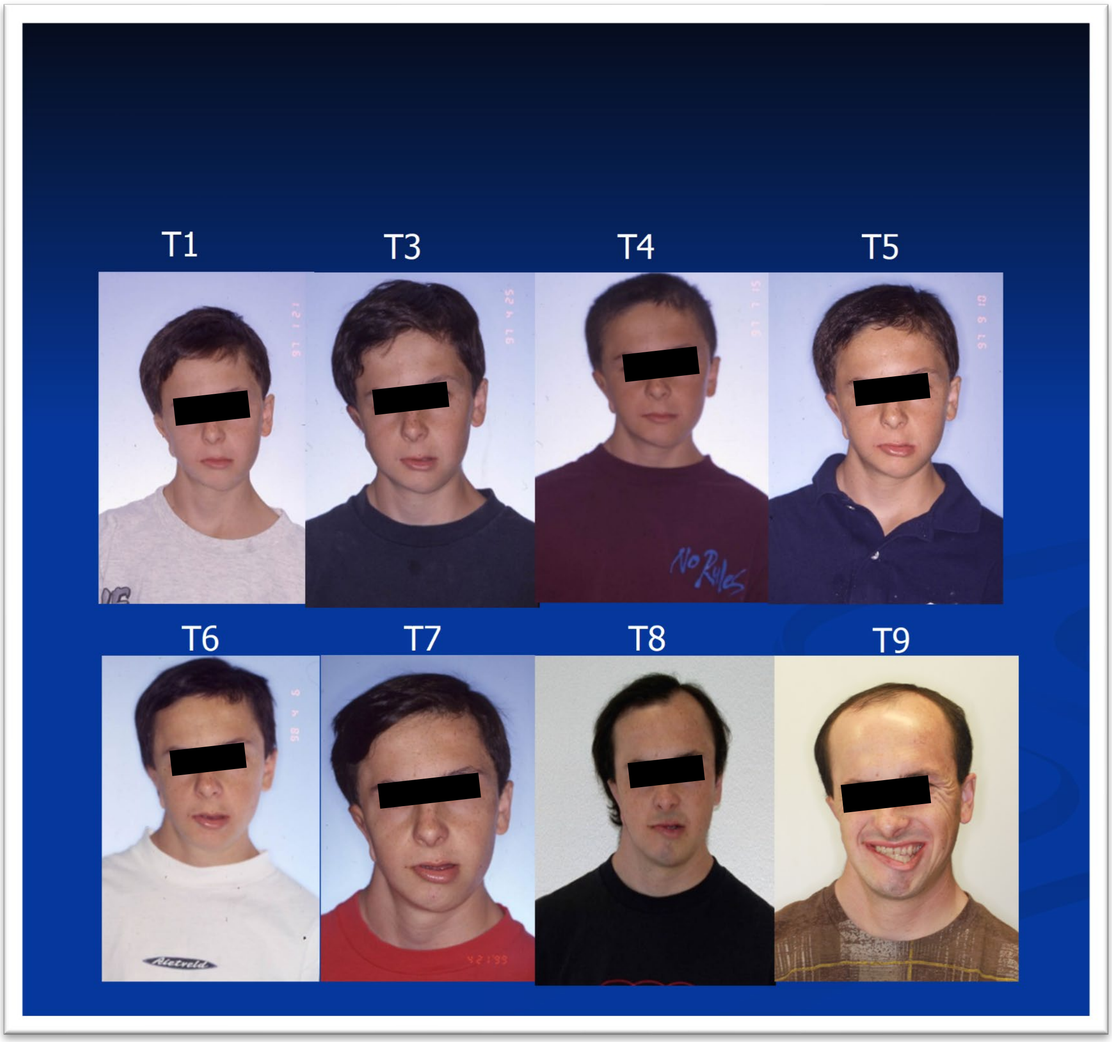

Fig. 4 Follow up for more than 12 years after distraction. After patients' pubertal growth, the asymmetry became worse. (UCLA Orthodontic resident, Peter Joo-Hak Lee's clinical study)

When only mandible distraction osteogenesis was performed without involving surgery in the maxilla, there was a vertical gap in between the maxilla and the mandible because the ramus becomes longer on the affected side. This vertical gap is eventually filled by dentoalveolar change (Fig.5). However, the stability of this kind of orthodontic tooth movement (extrusion), tends to have a higher chance of relapse (17-19). Therefore, the maxilla might contribute to the asymmetry, especially in a specific direction (i.e., anteroposteriorly, transversely, or vertically.) This raises the question of whether the surgery in the maxilla should be performed at the same time as the mandible surgery in cases with severe deficiency to reduce the chance of this kind of relapse. However, few articles discuss this topic.

Fig. 5 After mandible distraction osteogenesis, the vertical gap showed up on the distraction side. After awhile, the gap fill up by dental-alveolar compensation. (Figure from Trahar et al., 2003, AJODO)

Within the past ten years there have been several articles describing CFM patients who have undergone surgery on two jaws simultaneously (10, 11, 13, 14, 20). Most of these articles are case studies without long-term follow-up, in which distraction osteogenesis in the mandible and LeFort I surgery in the maxilla were implemented at the same time. By performing the distraction osteogenesis, soft tissue volume can be gradually increased and a superior bone length can be achieved. However, the final results for this kind of treatment are not always aesthetically perfect due to the many factors that contribute to maxilla-mandibular asymmetry. The optimal correction techniques remain unclear.

Previous studies of CFM patients have focused more on mandible asymmetry. With increasing use of CBCT in diagnosis, some studies have used CBCT measurements for analyzing facial asymmetry. For example, Chen et al. (2020) analyzed the mandibles of patients with CFM and found distinct mandibular body and length asymmetries in the affected sides (21). Before the development of three-dimensional analysis, skeletal asymmetry in individuals with hemifacial microsomia was evaluated using posteroanterior (PA) cephalograms and panoramic radiographs. The overlap of structures made it difficult to evaluate deeper structures and the occlusal relationship. Moreover, panoramic radiographs are often distorted, making it difficult to analyze asymmetry of the mandible and maxilla. Diagnosis with CBCT has higher diagnosis quality (22). Previous studies involving patients with severe asymmetry without a craniofacial syndrome tend to put the emphasis on mandible analysis (22-24). Most studies related to CFM patients focus on analyzing mandible asymmetry too (6, 21), but few discuss the proportion of maxilla that contributes to the craniofacial asymmetry among these patients. Nevertheless, after a high level of dental alveolar compensation, the relapse might be significant and thus be another reason for relapse in long-term follow-up patients. Moreover, it is uncertain whether the asymmetry of the maxilla has enough significance to affect the treatment result and long-term stability of the treatment. Hence, this study evaluates the pattern of maxillary asymmetry in the dimensions of anteroposterior, transverse, and vertical, based on CBCT images of CFM patients and a control population of patients without CFM.

Overall Objectives and Specific Aims

Objective: The goal of this study is to give clinicians insight into deciding the treatment for asymmetry correction in CFM patients. The maxilla should always be a variable to be taken into consideration.

Specific Aim:

This retrospective study is based on analyzing CBCT images of CFM patients and a control population without CFM to evaluate the pattern of maxillary asymmetry in the three dimensions of anteroposterior, transverse, and vertical.

DESIGN AND METHODOLOGY

- **Sampling and Interventions**

This retrospective study was performed at UCLA with approval by the ethics committee (IRB number 21-000144). It was conducted by obtaining CFM patients' initial CBCT before orthodontic treatment at the UCLA orthodontic clinic. We recruited 30 patients with CFM and 16 for the control group.

- Inclusion criteria: patients with CFM diagnosed in the UCLA craniofacial center from 2010 to 2018, with CBCT images available before the orthodontic treatment.
- Exclusion criteria: patients who received previous orthodontic treatment or orthognathic surgery.

The experimental group contained 30 patients, 14 female and 16 male. The patients' mean age was 11.8 ±3.5 years old. The experimental group was further divided into two subgroups: a mild group (16 patients, type I and type IIa in Pruzansky's classification) and a severe group (14 patients, type IIb and type III in Pruzansky's classification) (25). The rationale for dividing into two subgroups was to differentiate whether the deformity involved the condyle and glenoid fossa.

- **<u>Data Collection</u>**

  - ***CBCT Analysis***

All patients had CBCT images taken (5G; NewTom, Verona, Italy; 18x3x16cm field of view; 14-bit grayscale, standard voxel size 0.3mm; configuration of the CBCT included 18 seconds scan time, 3.6 seconds emission time, with 110kV). Dolphin image version 11.95 was used for image processing, linear measurements, and angular measurements on CBCT.

All three-dimensional digital image diagnosis data went through an orientation process, which involved adjusting the head position on the software images. However, just as the results of asymmetry analysis based on different head positions differ when traditional 2D cephalometry is used, orientation also significantly influences the results obtained using 3D digital imaging data, such as in CBCT. Lin et al. (2025) reported Frankfort horizontal and lateral semicircular canal planes are the landmark-oriented reference planes in the axial plane (26). In the present study, the plane of the lateral semicircular canal was chosen because, according to Pelo (2009), the semicircular canals are usually parallel with the ground for functional reasons. Consequently, the segment linking the two canals will be parallel to the ground. Using this plane in patients with severe asymmetry will make the results more steady, reproducible, detectable, and closer to the patient's anatomy (27). Except for the lateral semicircular canals on both sides (Fig. 6), the third landmark is the nasion point to make an axial plane. This plane is used as the reference plane for measuring the vertical dimensions of the anatomic structure.

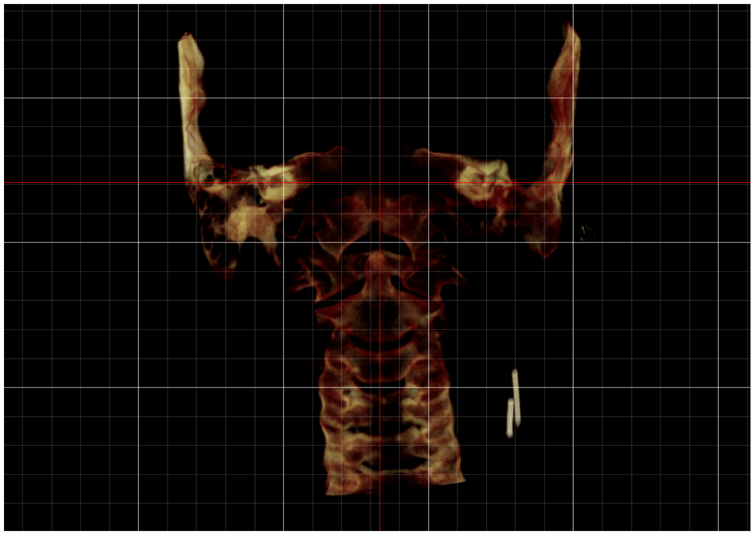

Fig. 6 Lateral semicircular canals on both sides of a CFM patient.

The midsagittal plane for this study is the vertical plane passing through the superior point of Crista Galli and a midpoint between the two anterior clinoid processes, perpendicular to the axial plane (Fig. 7). This midsagittal plane is the reference plane for measuring the transverse dimensions of the anatomic structure. The coronal plane is the one perpendicular to the axial and midsagittal plane and passes through the median (midline) point of the posterior margin of the foramen magnum (Fig. 8). This plane is the reference plane for measuring the anteroposterior dimensions of the maxilla and mandible.

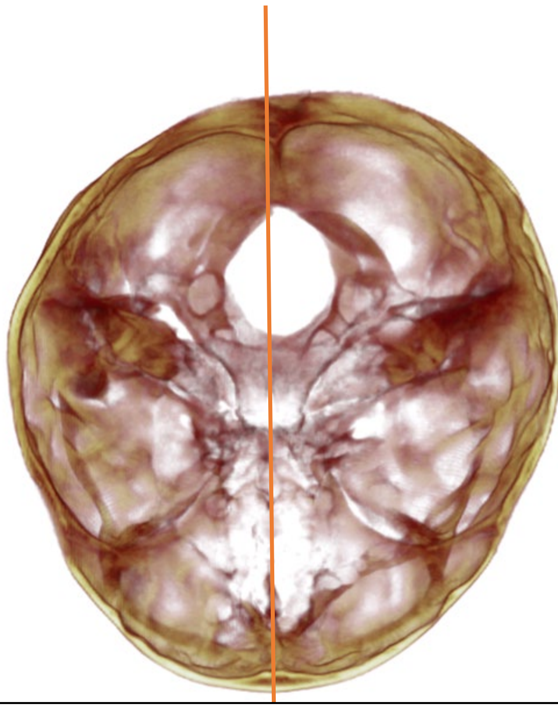

Fig. 7 Midsagittal plane: The vertical plane passing through the superior point of Crista Galli and another midpoint between the two anterior clinoid processes and perpendicular to the axial plane.

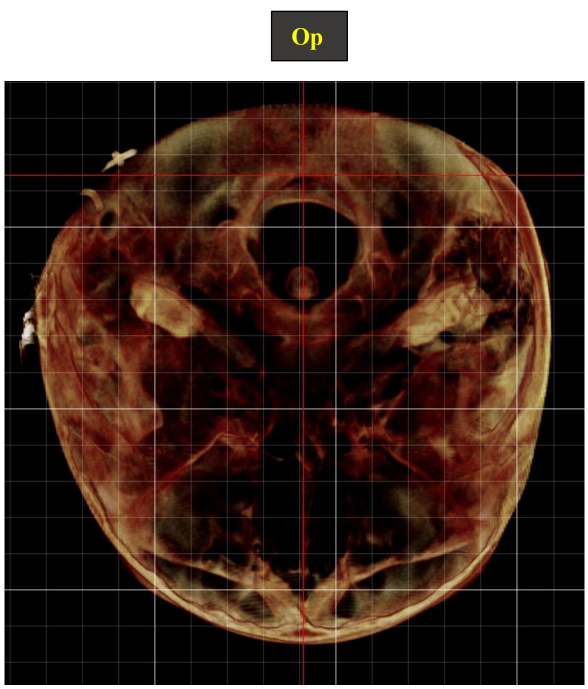

Fig. 8 Coronal plane: The plane perpendicular to the axial and midsagittal plane and passing through the median point of the posterior margin of the foramen magnum.

- **Measurements and Statistics**

Linear measurements are measured from the landmarks to the three reference planes (coronal, axial, midsagittal) and represent the position of the landmarks in the anteroposterior, vertical, and transverse direction. A “+” sign indicates that the landmarks are below the axial plane and forward of the coronal plane. For the dental part in the maxilla, landmarks include the maxillary canine cusp tip (**U3**) and the mesiobuccal and mesiopalatal cusp tip of the maxillary first molar (**U6B** and **U6P**). If there is no permanent canine, but there are primary canines, we measured directly from the primary canines. For the skeletal part, measurements are from the alveolar bone of the maxillary first molar (**U6a**) and alveolar bone of the maxillary canine (**U3a**), which is at the prominent point on the buccal side to the reference planes. For the posterior part of the maxilla, measurements are obtained from the junction of the internal pterygoid plate and palatal bone to the reference planes (pterygoid palatal point, the lowest point of the junction of the internal pterygoid plate and palatal bone (**PP**)) (Fig. 9). For the nasomaxillary complex, landmarks include the jugal points (where the outer surface of the maxillary tuberosity intersects with the zygoma buttress (**Jr**)), the center of the zygoma (the most lateral point of the outward curvature of the zygoma when viewed from the top (**Zy**)), the orbitale (the point at the lowest border of the infraorbital rim (**Or**)), the frontal process of the maxilla (the outer surface of the frontal process of the maxilla at the intersection of frontal and nasal bone (**FPM**)), the frontozygomatic suture (the most medial and anterior point of frontozygomatic suture (**Fz**)) to the three reference planes. And the anterior nasal spine (ANS) to the sagittal plane. (Table 1.)

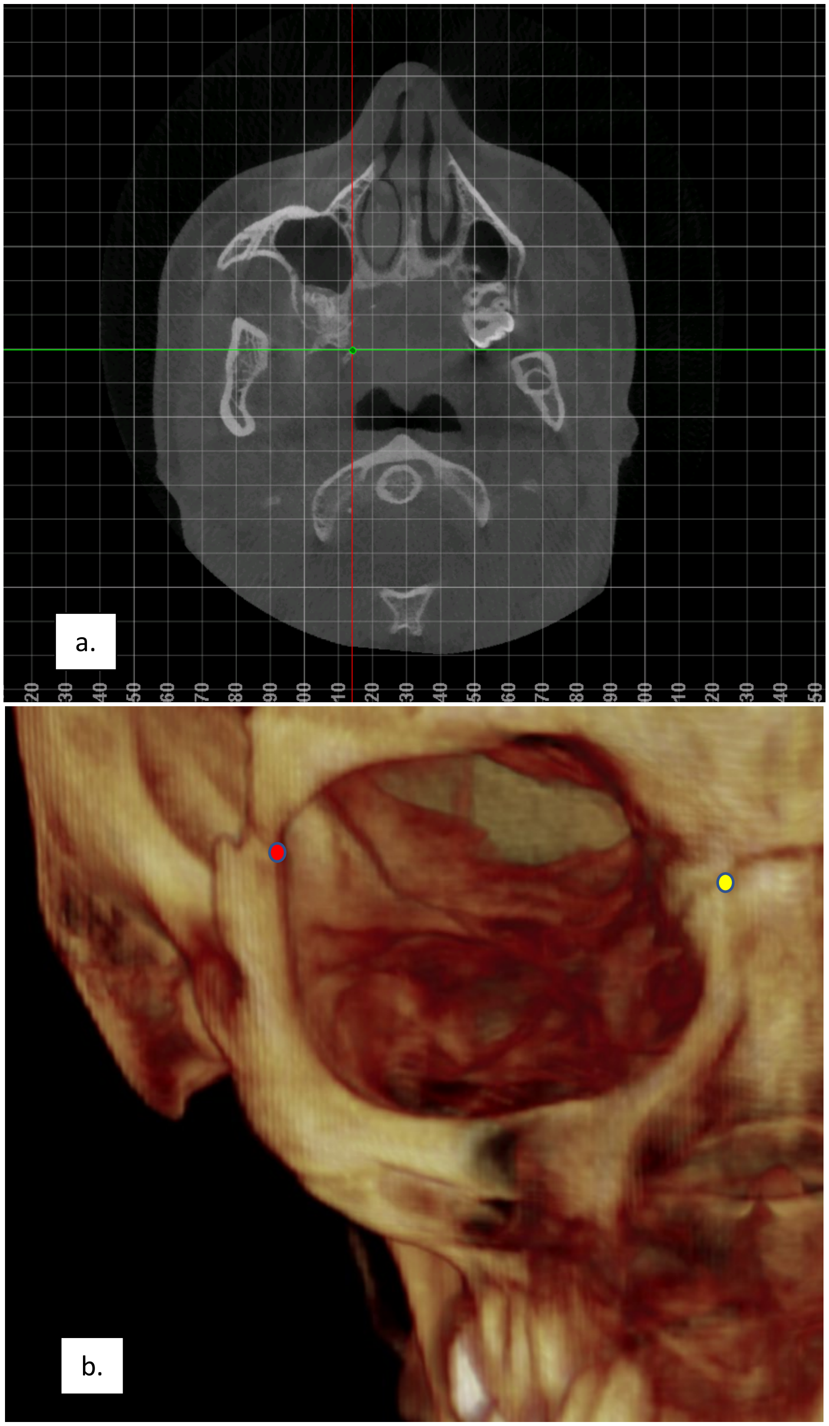

Fig. 9 a. Pterygoid palatal point (the lowest point of the junction of the internal pterygoid plate and the palatal bone (**PP**)). **b**. Yellow point: the frontal process of the maxilla (the outer surface of the frontal process of the maxilla at the intersection of frontal and nasal bone (**FPM**)). Red point: the frontozygomatic suture (the most medial and anterior point of frontozygomatic suture (**Fz**)).

	Abbreviation	Landmarks		Interpretation
Dental	**U3**	Maxillary canine (or primary canine) cusp tip		
	U6B	Maxillary first molar mesiobuccal cusp tip		
	U6P	Maxillary first molar mesiopalatal cusp tip		
Skeletal	**U3a**	Alveolar bone of maxillary canine (or primary canine)		Anterior part of maxilla
	U6a	Alveolar bone of maxillary first molar		
	PP	Junction of internal pterygoid plate and palatal bone		Posterior part of maxilla
	Jr	Jugal process: the outer surface of the maxillary tuberosity intersects with the zygoma buttress	To coronal plane, midsagittal plane, axial plane	
	Zy	The most lateral point of the outward curvature of zygoma, viewed from the top		Nasomaxillary complex
	Or	The point at the lowest border of the infraorbital rim		
	FPM	Intersection of the frontal process of the maxilla, frontal bone and nasal bone		
	Fz	The most medial and anterior point of		

		frontozygomatic suture		
	ANS	Anterior nasal spine	To midsagittal plane	Maxillary midline deviation

Table. 1 Landmarks of linear measurements of the maxilla and the nasomaxillary complex: landmarks U3, U6(B), U6(P), U3(a), U6(a), PP, Jr, Zy, Or, FPM, Fz to three reference planes and ANS to the midsagittal plane.

	Abbreviation	Landmarks		Interpretation
Dental	**L3**	Mandibular canine (or primary canine) cusp tip		
	L6B	Mesiobuccal cusp tip of mandibular first molar		
	L6L	Mesiolingual cups tip of mandibular first molar		
Skeletal	**L3a**	Alveolar bone of mandibular canine (or primary canine)		
	L6a	Alveolar bone of mandibular first molar		
	Ag	Antegonion point (the highest point of the antegonial notch)	To coronal plane, midsagittal plane, axial plane	
	Go	Gonion point (the most posterior, inferior point of the mandibular angle)		
	Gop	Posterior gonion point (the most posterior point passing through the tangent line to the posterior border of the ramus)		
	Cd	Condyle head (condylion: the most superior and posterior point of the condyle head)		

	Me	Menton (the lowest point on the symphysis of the mandible)	To midsagittal plane	Mandibular midline deviation

Table. 2 Landmarks of linear measurements of the mandible: landmarks L3, L6b, L6l, L3a, L6a, Ag, Go, Gop, Cd to three reference planes and Me to the midsagittal plane.

For the linear measurements of the mandible, the dental part includes the mandibular canine (or primary canine) cusp tip (**L3**) and mandibular first molar mesiobuccal and mesiolingual cusp tips (**L6B, L6L**). For the skeletal part, measurements are from the alveolar bone of the mandibular first molar (L6a) and canine (L3a), which is also at the prominent point on the buccal side to the reference planes. For the mandible ramus and body, measurements are obtained from landmarks including the antegonion point (the highest point of the antegonial notch (**Ag**)), the gonion point (the most posterior, inferior point of the mandibular angle (**Go**)), the posterior gonion point (the most posterior point passing through the tangent line to the posterior border of the ramus (**Gop**)), and the condyle head (the most superior and posterior point of the condyle head (**Cd**)) to the three reference planes and the menton (the lowest point on the symphysis of the mandible (**Me**)) to the sagittal plane. (Table 2.)

Angular measurements are measurements of the angulation between a line and the axial plane for evaluating canting in the roll axis. For the dental part, they include canines and buccal and palatal (lingual) cusp of first molars for occlusal cant evaluation. Skeletal measurements include measurements from the alveolar bone of the first molars and canines, the jugal point, the orbitale, the antegonion point, and the condylion point.

Statistical analysis was conducted using the SPSS statistical analysis software (version 26; IBM, Armonk, NY). Four investigators (S.C., G.M., K.D., and N.K.) conducted the measurements in this research. To assess intra-observer variability and reproducibility, patient measurements were taken twice by the same investigator with an interval of 14 days using the intraclass correlation coefficient (ICC). To assess inter-examiner variability and reproducibility, patients were measured twice by all investigators using the interclass correlation coefficient (ICC). The asymmetry index modified from Habets (1988) was used for all linear measurements (28) (29). The asymmetry index is the value of the non-affected side minus the affected side divided by the non-affected side. For the control group, the asymmetry index is the absolute value of the right side minus the left side divided by the mean value of both sides. By using the asymmetry index, the study compared the asymmetry between the CFM and control groups. The Kruskal-Wallis test (non-parametric test) was used to compare the asymmetry index and angular measurements between each subtype group of CFM patients and the control group.

- **Asymmetry Index:**

Exp group (non-affected-affected)/(non-affected side)

Control group |(R-L)/((R+L)/2)|

RESULTS

Patient Characteristics

This study included 46 subjects (22 female and 24 male) with a mean age of 14.3 ± 5.3 years (females 13.3 ± 4.7 and males 15.2 ± 5.7.) There were 14 patients in the severe experimental group (8 female and 6 male), with a mean age of 11.2 ± 3.2 years. The mild experimental group contained 16 patients (6 female and 10 male), with a mean age of 12.3 ± 3.7 years. The control group had 16 patients (8 female and 8 male), with a mean age of 19.2 ± 4.9 years.

Method Reliability

Values of interclass correlation coefficient and intraclass correlation coefficient less than 0.5 indicate poor reliability; values between 0.5 and 0.75 indicate moderate reliability; values between 0.75 and 0.9 indicate good reliability; values greater than 0.90 indicate excellent reliability (30). In this research, the interclass correlation coefficient for the agreement between examiners showed a relatively high agreement (Pearson correlation coefficients ≥ 0.902) and the same for intra-examiner reliability, which showed excellent reliability (Pearson correlation coefficients ≥ 0.999).

Linear Measurements Results

The Shapiro-Wilk test was used to test the results' normality, which revealed that not all measurements follow the normal distribution. Hence, the Kruskal-Wallis test was used to compare the asymmetry index and angular measurements between each subtype group of craniofacial microsomia and control group patients. Furthermore, the Mann-Whitney U test was used for between-group comparisons.

Comparing the severe and control groups in the vertical direction reveals that the non-affected side is longer than the affected side. Notably, there is no significant difference for the landmarks in the upper face higher than the orbit. The other noteworthy finding is that the lines formed by both sides of the landmarks are skewed upward toward the affected side. However, the line formed by the condyle is going in the opposite direction for all the cases in the severe group, skewing upward toward the non-affected side. This observation indicates that the condyle on the affected side is shorter than on the non-affected side. The results are described in greater detail in the following paragraphs.

For the linear measurements of the vertical direction in the maxilla, the asymmetry index is significantly different ($P<0.05$) between the three groups based on the Kruskal-Wallis test, except for the landmark frontozygomatic suture (Fz). The asymmetry index of the severe group at the landmarks maxillary canine (U3), mesiobuccal cusp tip of maxillary first molar (U6(B)), and pterygoid palatal point (PP) is larger than in the mild group and has statistical significance. For the same landmarks, there is a statistically significant difference between the mild and control groups. There are also statistically significant differences between the severe and control groups at these landmarks. The mean value of these landmarks is larger in the severe than the mild group, and the mild group's mean value is in turn larger than that of the control group.

The differences in the asymmetry index between the severe, mild, and control groups at landmark mesiopalatal cusp tip of upper first molar (U6(P)) and landmark alveolar bone of maxillary canine (U3(a)) are statistically significant ($P<0.05$) under the Kruskal-Wallis test. The same index for the severe group at landmarks U6(P) and U3(a) is larger than for the mild group at landmark U6(P) but has no statistical significance according to the Mann-Whitney U test. There are statistically significant differences between the mild and control groups for the same two landmarks, with the former group having the greater mean value. As for the severe and control groups, the mean values also have statistical significance, with the former's mean value being greater. The asymmetry indices of the severe group are larger than the mild group at landmarks jugal process (Jr), zygoma (Zy), and orbitale (Or), and these differences have statistical significance. However, the asymmetry indices of the mild group at the same landmarks are larger than the control group without a statistically significant difference. The severe group has a larger mean value than the control group at the same landmarks, and the difference is statistically significant. The differences in the asymmetry index between the severe, mild, and control groups at the frontal process of the maxilla (FPM) landmark are also statistically significant ($P<0.05$). Nevertheless, for the vertical position of the variable FPM, there is no decreasing trend from the severe to the mild to the control groups. Moreover, there is no statistically significant difference in the asymmetry index between the severe, mild, and the control group at the frontozygomatic suture (Fz) landmark. (Fig.10, 11, 12)

For the linear measurement of the vertical direction in the mandible, there is a statistically significant difference ($P<0.05$) in the asymmetry index between the severe, mild, and control groups at landmarks mandibular canine cusp tip (L3), alveolar bone of mandibular canine (L3(a)), mesiobuccal cusp tip of first mandibular molar (L6(MB)), antegonion (Ag), and condylion (Cd). The asymmetry index of the severe group at landmarks L3 and L3(a) is larger than in the mild group, which is, in turn, larger than that of the control group. The difference is statistically significant ($P<0.05$) for all three comparisons: between the severe and mild groups, the mild and control groups, and the severe and control groups. For landmark L6(B), the severe group's mean value is greater than that of the mild group, and the mild group's mean value is greater than that of the control group. However, only the difference between the mild and control groups is statistically significant. For landmark Ag, the mean values also decrease from the severe to the mild group and from the mild to the control group. The differences between the severe and mild groups and between the severe and control groups are statistically significant. The asymmetry index of the severe group at landmark Cd is smaller than that of the mild group, which, in turn, is smaller than that of the control group. However, only the differences between the severe and mild group and the severe and control group are statistically significant. (Fig. 13, 14, 15)

	Group						K-W test
Variables	Severe		Mild		Control		P-value
Vertical (Asymmetry Index)	Mean±SD	P-value[a]	Mean±SD	P-value[b]	Mean±SD	P-value[c]	(Kruskal-Wallis test)
Maxilla Landmarks		severe vs mild		Mild vs control		Severe vs control	
U3	0.070±0.036	0.031*	0.035±0.042	0.005*	0.001±0.017	<0.001*	<0.001*
U6(B)	0.105±0.063	0.011*	0.043±0.042	0.001*	0.001±0.017	<0.001*	<0.001*
U6(P)	0.082±0.069	0.081	0.034±0.037	0.008*	0.002±0.017	0.005*	0.003*
U3(a)	0.071±0.050	0.262	0.043±0.062	0.024*	0.002±0.018	<0.001*	0.001*
U6(a)	0.121±0.079	0.006*	0.044±0.051	0.019*	0.002±0.025	<0.001*	<0.001*
PP	0.174±0.122	0.020*	0.095±0.063	<0.001*	-0.003±0.012	<0.001*	<0.001*
JR	0.151±0.114	0.005*	0.042±0.058	0.122	0.018±0.015	0.001*	0.001*
Zy	0.197±0.210	0.046*	0.080±0.164	0.258	0.010±0.055	0.001*	0.003*
Or	0.144±0.172	0.028*	0.045±0.084	0.546	0.031±0.021	0.001*	0.006*
FPM	1.094±0.959	0.001*	0.014±0.577	0.014*	0.436±0.244	0.070	0.001*
Fz	3.808±9.575	0.637	-0.076±2.078	0.678	0.428±0.310	0.728	0.835
Mandible landmarks		severe vs mild		Mild vs control		Severe vs control	
L3	0.062±0.075	0.022*	0.027±0.025	0.038*	0.010±0.006	0.001*	0.002*
L6(B)	0.085±0.080	0.157	0.045±0.039	0.032*	0.015±0.014	0.053	0.039*

L6(L)	0.072±0.073	0.096	0.027±0.031	0.274	0.012±0.009	0.056	0.085
L3(a)	0.056±0.067	0.025*	0.029±0.027	0.029*	0.010±0.009	0.002*	0.002*
L6(a)	0.071±0.070	0.211	0.045±0.049	0.214	0.015±0.012	0.056	0.107
Ag	0.154±0.135	0.022*	0.056±0.067	0.122	0.023±0.013	0.001*	0.002*
Go	0.129±0.168	0.067	0.034±0.106	0.407	0.032±0.021	0.074	0.097
Gop	0.125±0.193	0.101	0.034±0.120	0.181	0.033±0.031	0.044*	0.079
Cd	-1.724±2.596	<0.001*	-0.044±0.358	0.076	0.136±0.089	<0.001*	<0.001*

Table 3. The asymmetry index and statistical analysis of maxilla and mandible landmarks in the vertical position using the Kruskal-Wallis test and further analysis using the Mann-Whitney test

a: Compare the severe and the mild groups using the Mann-Whitney test

b: Compare the mild and the control groups using the Mann-Whitney test

c: Compare the severe and the control groups using the Mann-Whitney test

d: Compare the severe, mild, and control groups using the Kruskal-Wallis test

*statistically significant for $P<0.05$

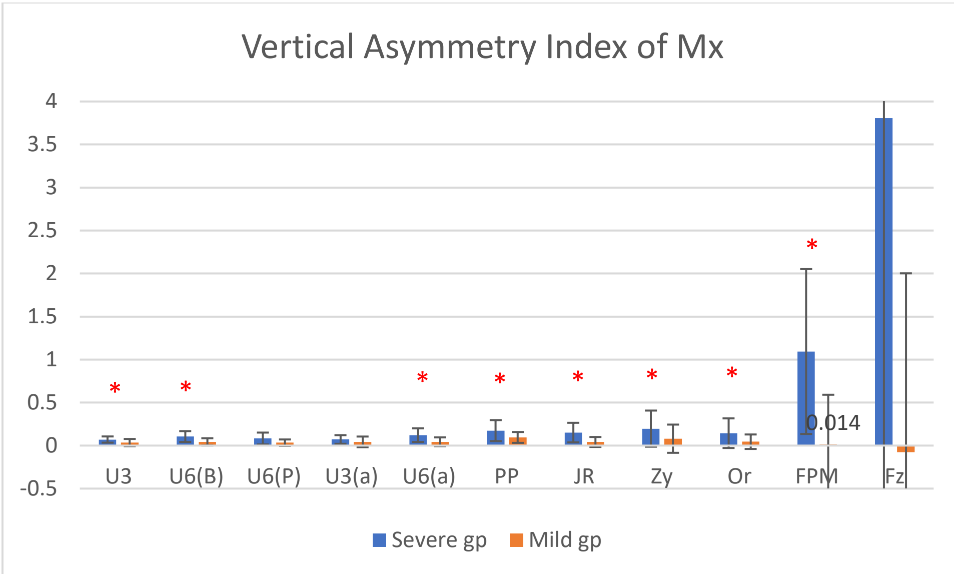

Fig.10 Comparison of asymmetry index of severe and mild groups in vertical position of maxilla. U3, U6B, U(a), PP, JR, Zy, Or, FPM shows statistical significance (P<0.05) using Mann-Whitney test. Difference between non-affected and affected sides is larger in severe group than mild group.

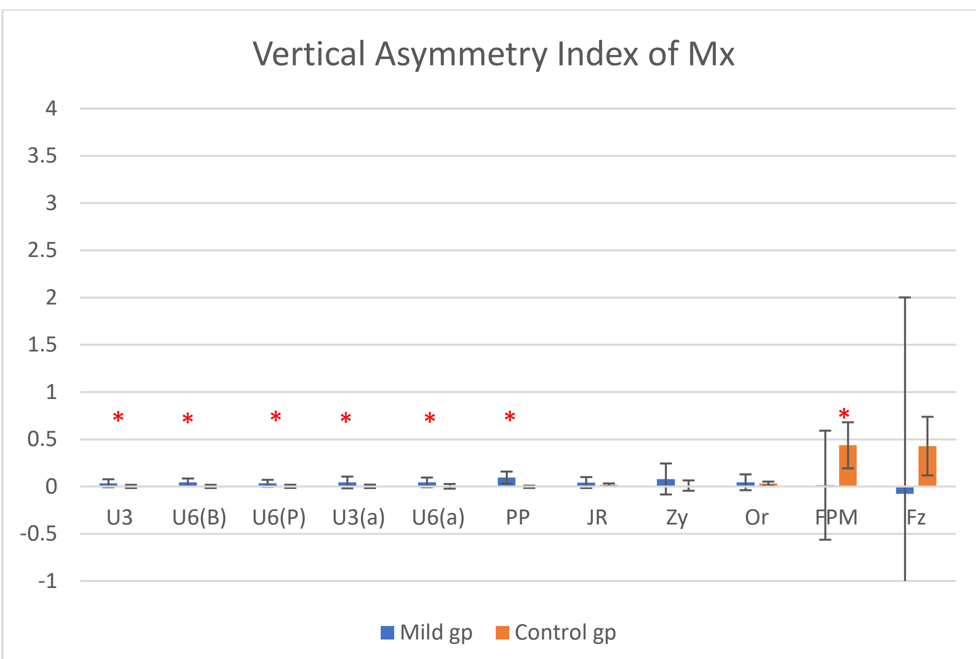

Fig.11 Comparison of asymmetry index of mild and control groups in vertical position of maxilla. U3, U6B, U6P, U3a, U6a, PP, FPM, Fz show statistical significance (P<0.05) using Mann-Whitney test.

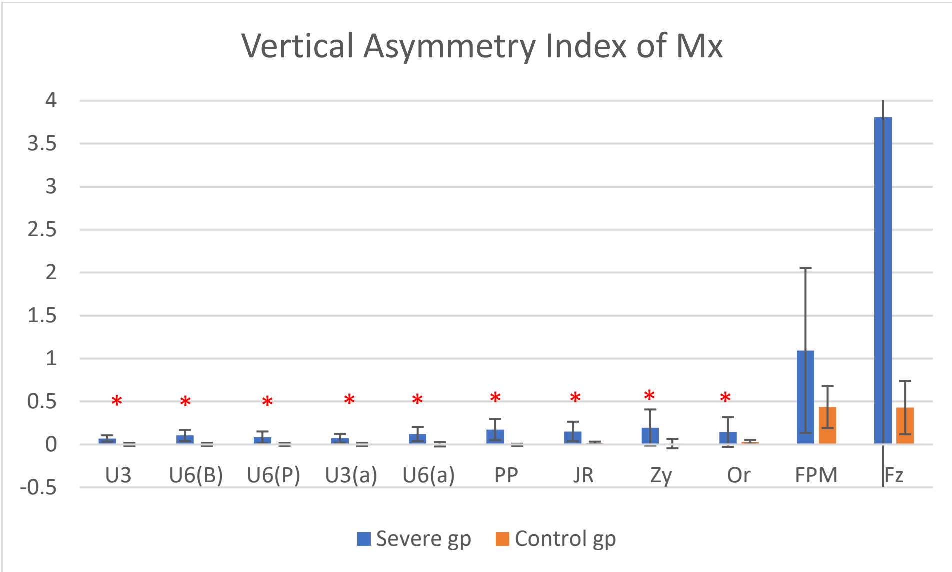

Fig.12 Comparison of asymmetry index of severe and control groups in vertical position of maxilla. U3, U6B, U6P, U3a, U6a, PP, JR, Zy, Or show statistical significance ($P<0.05$) using Mann-Whitney test. Difference between non-affected and affected sides is larger in severe group than in control group.

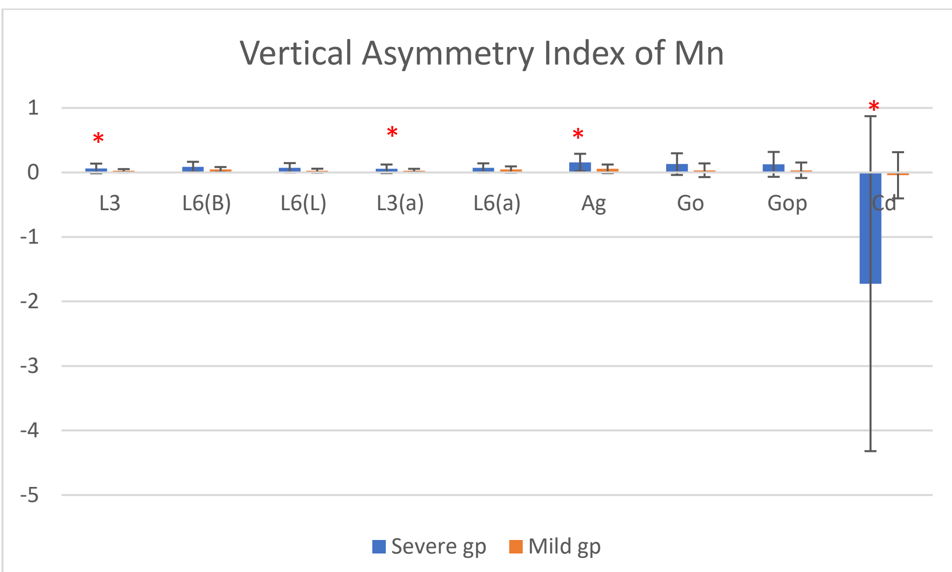

Fig.13 Comparison of asymmetry index of severe and mild groups in vertical position of mandible. L3, L3a, Ag, Cd show statistical significance ($P<0.05$) using Mann-Whitney test. Difference between non-affected side and affected side is larger in severe group than control group.

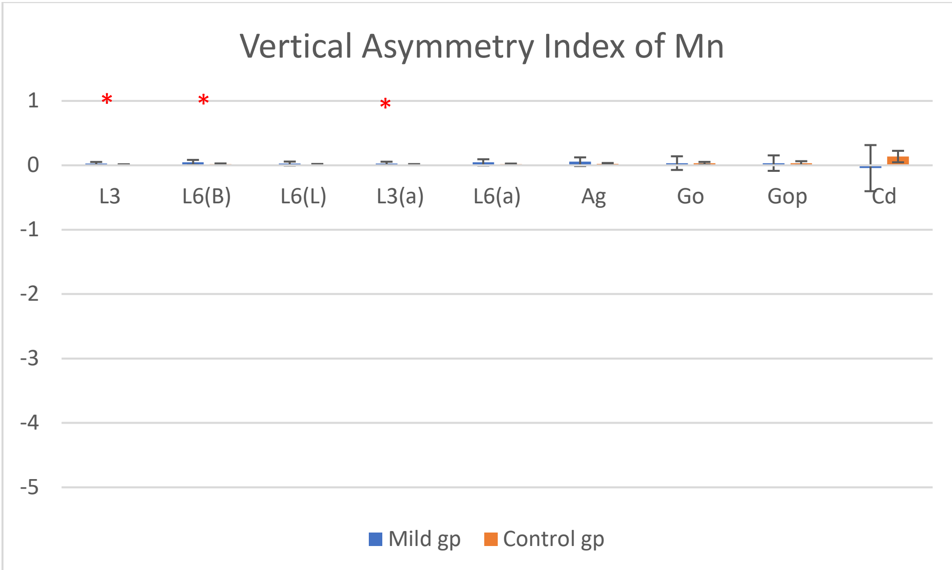

Fig.14 Comparison of asymmetry index of mild and control groups in vertical position of mandible. L3, L6B, L3(a) show statistical significance (P<0.05) using Mann-Whitney test.

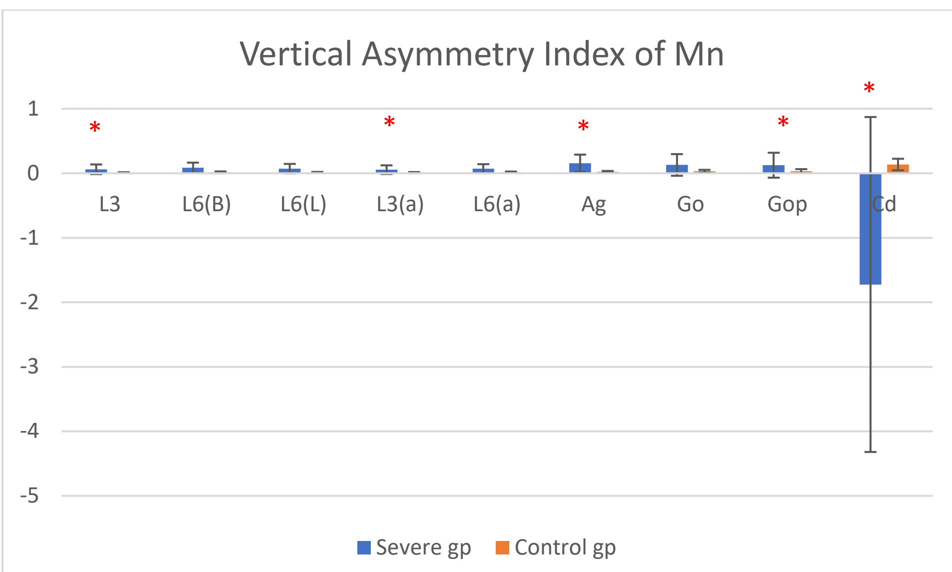

Fig.15 Comparison of asymmetry index of severe and control groups in vertical position of mandible. L3, L3(a), Ag, Gop, Cd show statistical significance (P<0.05) using Mann-Whitney test. Difference between non-affected and affected sides is larger in severe group than control group.

For the anteroposterior direction, the higher part of nasomaxillary complex showed significant differences at landmarks Or, FPM, and Fz, but the data in different groups lack consistency in the maxilla. The dentoalveolar area does not show significant asymmetry in the maxilla. The mandible part shows that the affected side is much more forward than the non-affected side at the lower molar and posterior part of the mandible. The details are discussed further in the following paragraphs.

For the linear measurements of the anteroposterior in the maxilla, the difference of the asymmetry index between the severe, mild and control groups at landmarks Or, FPM, and Fz are statistically significant ($P<0.05$). However, there is no decreasing or increasing trend from the severe to the mild or control groups. Moreover, there is no statistically significant difference in the asymmetry index between the severe, mild, and control groups at other landmarks in the maxilla. (Fig.16, 17, 18)

For the linear measurements of the anteroposterior in the mandible, the differences in the asymmetry index between the severe, mild, and control groups at landmark mesiobuccal cusp tip of lower first molar (L6(B)), alveolar bone of first mandibular molar (L6(a)), antegonion (Ag), gonion (Go), posterior gonion (Gop) are statistically significant ($P<0.05$) using the Kruskal-Wallis test. For landmark L6(B), the asymmetry index increases from the severe to the mild group and from the mild to the control group, while only the difference between the severe and control groups is statistically significant using the Mann-Whitney U test. For landmarks antegonion point (Ag), gonion (Go), and posterior gonion (Gop), the mean value of the asymmetry index increases from the severe to the mild group and from the mild to the control group. The differences between each group are statistically significant using the Mann-Whitney U test, except for the difference between the mild and control groups on landmark Ag. (Fig.19, 20, 21)

	Group						K-W test
Variables	Severe		Mild		Control		P-value
Anteroposterior (Index)	Mean±SD	P-value[a]	Mean±SD	P-value[b]	Mean±SD	P-value[c]	(Kruskal-Wallis test)
Maxilla landmarks		severe vs mild		Mild vs control		Severe vs control	
U3	-0.021±0.034	0.177	-0.005±0.018	0.821	0.002±0.015	0.114	0.236
U6(B)	-0.006±0.049	0.967	-0.009±0.026	0.522	0.0003±0.014	0.560	0.774
U6(P)	-0.003±0.059	0.901	-0.010±0.025	0.214	0.0003±0.019	0.755	0.598
U3(a)	-0.020±0.031	0.031*	0.0007±0.018	0.429	0.005±0.011	0.056	0.053
U6(a)	-0.007±0.052	0.835	-0.007±0.016	0.624	0.0006±0.012	0.618	0.838
PP	-0.021±0.085	0.506	-0.003±0.028	0.706	0.002±0.011	0.212	0.495
JR	-0.016±0.068	0.561	-0.002±0.024	0.806	0.0004±0.025	0.533	0.774
Zy	0.008±0.043	0.170	-0.009±0.041	0.970	0.001±0.197	0.183	0.300
Or	0.002±0.027	0.618	-0.004±0.017	0.002*	0.011±0.006	0.262	0.026*
FPM	-0.002±0.014	0.739	-0.004±0.006	<0.001*	0.102±0.334	0.014*	0.001*
Fz	0.009±0.031	0.257	-0.006±0.024	0.004*	0.017±0.017	0.580	0.036*

Mandible landmarks		severe vs mild		Mild vs control		Severe vs control	
L3	-0.004±0.031	0.170	0.005±0.028	0.792	0.011±0.012	0.016*	0.083
L6(B)	-0.014±0.052	0.100	0.005±0.029	0.090	0.081±0.250	0.001*	0.005*
L6(L)	-0.010±0.052	0.338	0.006±0.027	0.109	0.017±0.013	0.030*	0.065
L3(a)	-0.009±0.036	0.339	-0.00001±0.019	0.046*	0.011±0.006	0.051	0.057
L6(a)	-0.015±0.056	0.124	0.008±0.037	0.152	0.021±0.025	0.007*	0.020*
Ag	-0.137±0.188	0.025*	-0.002±0.088	0.175	0.037±0.034	0.001*	0.002*
Go	-0.199±0.209	0.022*	-0.045±0.085	0.002*	0.034±0.028	<0.001*	<0.001*
Gop	-0.166±0.200	0.014*	-0.032±0.092	0.004*	0.041±0.027	<0.001*	<0.001*
Cd	0.012±0.182	0.280	-0.010±0.095	0.243	0.040±0.038	0.803	0.417

Table 4. The asymmetry index and statistical analysis of maxilla and mandible landmarks in the anteroposterior position using the Kruskal-Wallis test and further analysis with the Mann-Whitney test

a: Compare the severe and mild groups using the Mann-Whitney test

b: Compare the mild and control groups using the Mann-Whitney test

c: Compare the severe and control groups using the Mann-Whitney test

d: Compare the severe, mild, and control groups using the Kruskal-Wallis test

*statistically significant for P<0.05

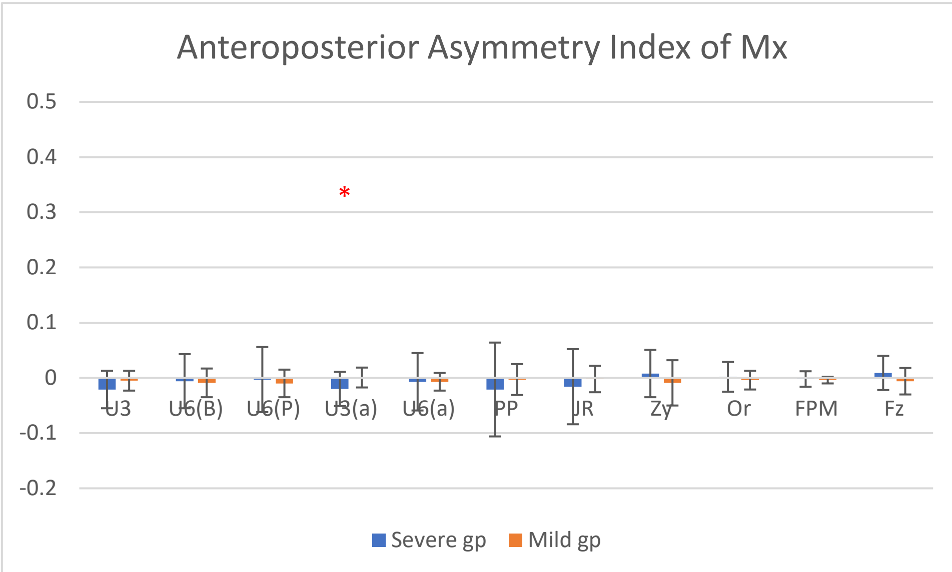

Fig.16 Comparison of asymmetry index of severe and mild groups in anteroposterior position of maxilla. U3(a) shows statistical significance (P<0.05) using Mann-Whitney test.

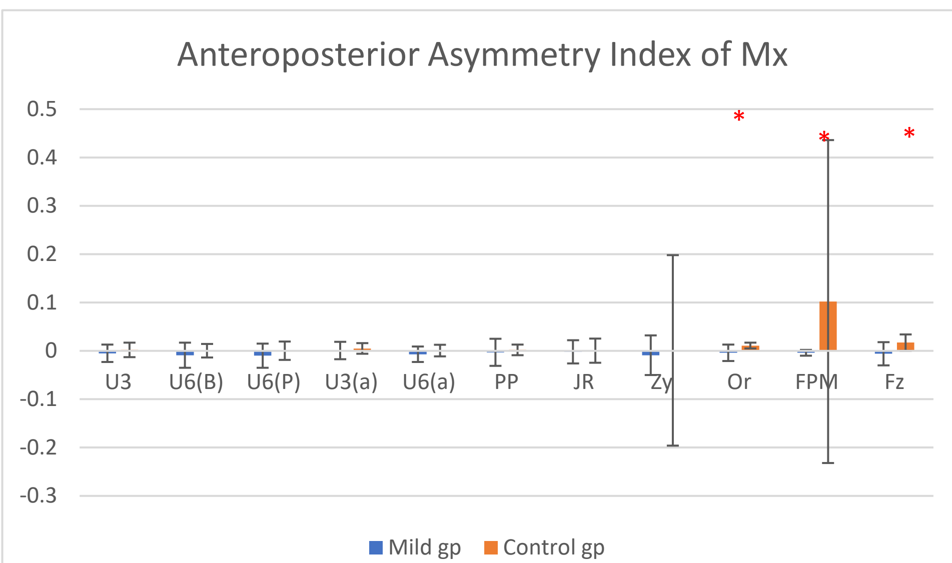

Fig.17 Ccomparison of asymmetry index of mild and control groups in anteroposterior position of maxilla. Or, FPM, Fz show statistical significance (P<0.05) using Mann-Whitney test.

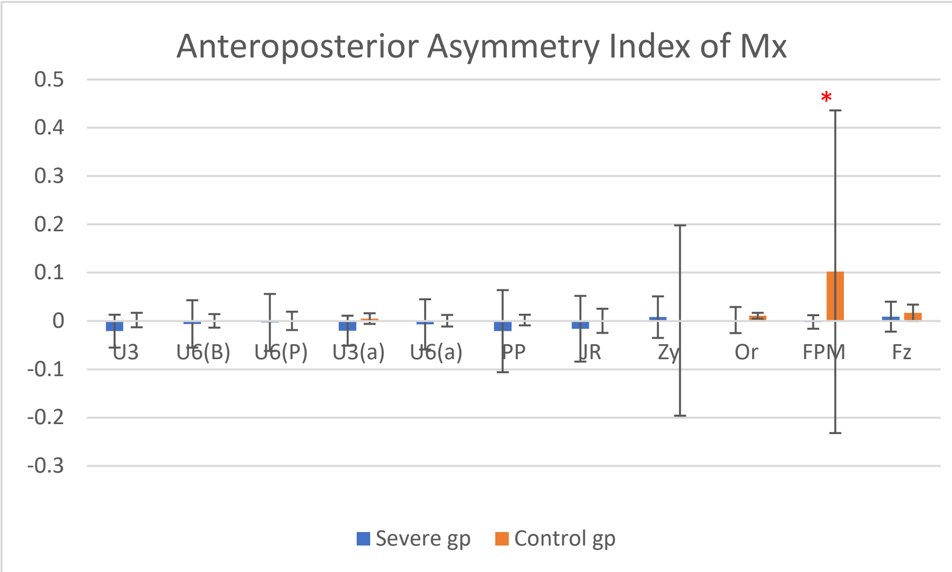

Fig.18 Comparison of asymmetry index of severe and control groups in anteroposterior position of maxilla. FPM shows statistical significance (P<0.05) using Mann-Whitney test.

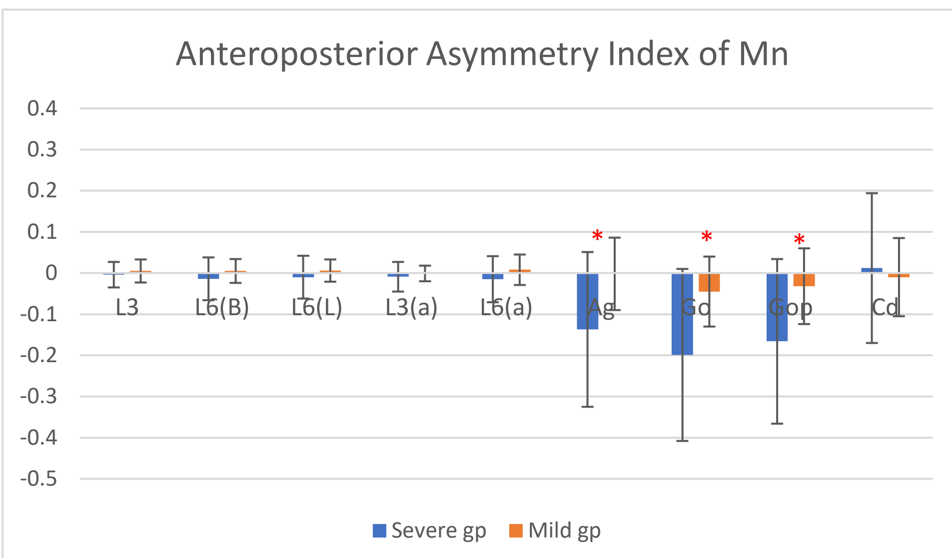

Fig.19 Comparison of asymmetry index of severe and mild groups in anteroposterior position of mandible. Ag, Go, Gop show statistical significance (P<0.05) using Mann-Whitney test.

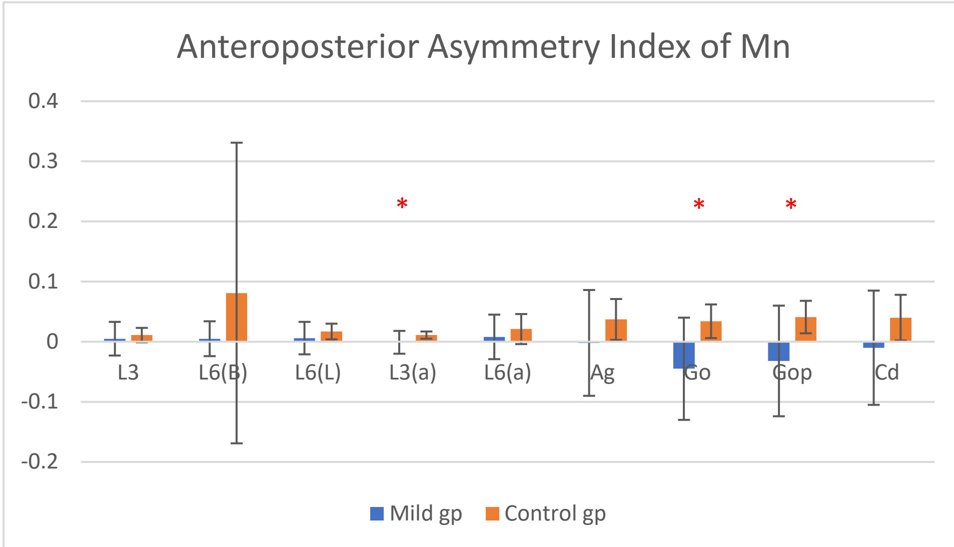

Fig.20 Comparison of asymmetry index of mild and control groups in anteroposterior position of mandible. L3(a), Go, Gop show statistical significance (P<0.05) using Mann-Whitney test.

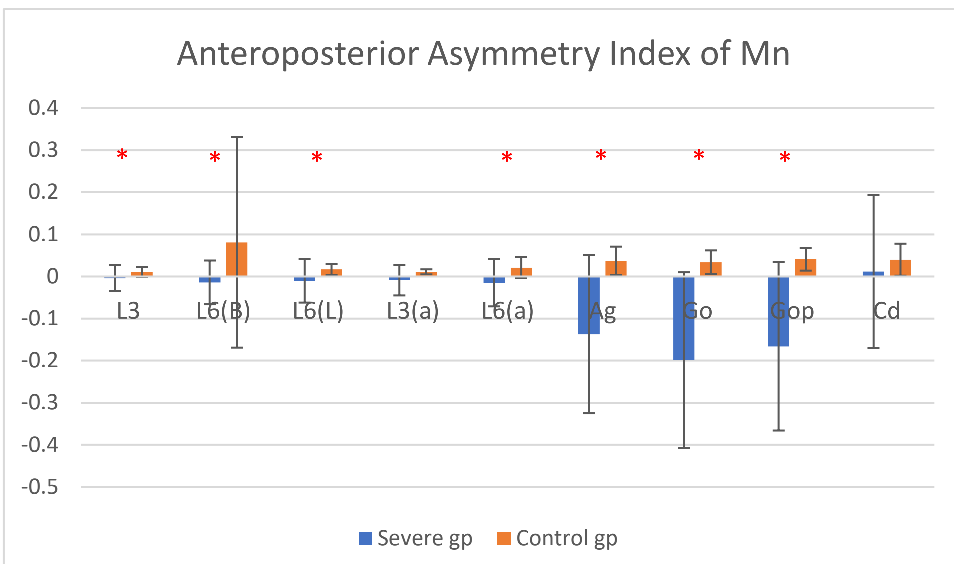

Fig.21 Comparison of asymmetry index of severe and control groups in anteroposterior position of mandible. L3(a), L6B, L6L, L6(a), Ag, Go, Gop show statistical significance (P<0.05) using Mann-Whitney test.

For linear measurements transversely in the maxilla, only the landmarks closer to the anterior part of the skull show significant asymmetry in the severe group. The differences in the asymmetry index between the severe, mild, and control groups at landmark maxillary canine (U3), mesiopalatal cusp tip of upper first molar (U6(P)), alveolar bone of maxillary canine (U3(a)), and frontoprocess of the maxilla (FPM) are statistically significant ($P<0.05$). The asymmetry indices of the severe group are smaller than in the mild group, which are in turn smaller than in the control group. The asymmetry indices of the mild group at these landmarks (U3, U6(P), U3(a), FPM) are smaller than those of the control group, but the differences are not statistically significant. The asymmetry indices of the severe group at the same landmarks are smaller than in the mild and control groups with statistical significance ($P<0.05$). The differences in the asymmetry index between the severe, mild, and control groups at landmarks orbitale (Or) and frontozygomatic suture (Fz) are statistically significant. The asymmetry indices of the severe group at these two landmarks (Or, Fz) are smaller than in the mild group, but the difference is not statistically significant. However, the asymmetry indices of the mild group at landmarks Or, Fz are smaller than in the control group with statistical significance; the asymmetry indices of the severe group at the same landmarks are smaller than in the control group, at a statistically significant level.

Landmark zygoma point (Zy) is the only point at which the differences in the asymmetry indices are statistically significant between all three groups. The mean value of Zy is smaller than in the mild group, which has a value smaller than in the control group.

There is no statistically significant difference between the severe, mild, and control groups at landmarks mesiobuccal cusp tip of maxillary first molar (U6(B)), jugal process (Jr), and internal pterygoid plate and palatal bone (PP). (Fig. 22, 23, 24)

Compared to the cranial base, the mandible skews to the affected side. The asymmetry indices of all landmarks in the mandible in the transverse direction show statistically significant differences. For the linear measurements transversely in the mandible, the differences in the asymmetry index between the severe, mild, and control groups at landmark mesiolingual cusp tip of lower first molar (L6(L)), landmark mesiobuccal cusp tip of lower first molar (L6(B)), alveolar bone of lower first molar(L6(a)), gonion point (Go), and posterior gonion point (Gop) are statistically significant ($P<0.05$) using the Kruskal-Wallis test. Using the Mann-Whitney U test, although the asymmetry index of the severe group at these landmarks is smaller than in the mild group, the differences are not statistically significant. However, the asymmetry indices of the mild group at these landmarks are smaller than in the control group, and the asymmetry indices of the severe group at the same landmarks are also smaller than in the control group, both with statistical significance using the Mann-Whitney U test. The differences in the asymmetry index between the severe, mild, and control groups at landmark lower canine (L3), alveolar bone of lower canine (L3(a), and antegonion point (Ag) show statistical significance. The asymmetry indices of the severe group at these landmarks are smaller than in the mild group, which has a smaller index than the control group, and the differences between these groups are statistically significant. Nevertheless, for the transverse position of the variable condylion (Cd), there is no increasing trend from the severe group to the mild to the control group. The deviation of the anterior nasal spine (ANS) and menton (Me) points from the sagittal plane is statistically significant between the severe, mild, and control groups. The severe group has the most deviation. (Fig. 25, 26, 27)

	Group						K-W test
Variables	Severe		Mild		Control		P-value
Transverse (Index)	Mean±SD	P-value[a]	Mean±SD	P-value[b]	Mean±SD	P-value[c]	(Kruskal-Wallis test)
Maxilla landmarks		severe vs mild		Mild vs control		Severe vs control	
U3	-15.14±39.23	0.003*	-0.27±0.45	0.083	0.005±0.169	<0.001*	<0.001*
U6(B)	-0.368±0.469	0.105	-0.086±0.247	0.910	0.029±0.0963	0.036*	0.099
U6(P)	-0.654±0.807	0.042*	-0.148±0.300	0.429	0.032±0.143	0.005*	0.016*
U3(a)	-1.668±2.118	0.002*	-0.106±0.193	0.142	0.009±0.124	<0.001*	<0.001*
U6(a)	-0.349±0.415	0.067	-0.065±0.186	0.910	0.024±0.084	0.010*	0.039*
PP	-0.269±0.341	0.212	-0.094±0.196	0.821	0.101±0.091	0.124	0.278
JR	-0.228±0.318	0.081	-0.049±0.159	0.910	0.023±0.077	0.034*	0.083
Zy	-0.072±0.0734	0.020*	-0.016±0.501	0.002*	0.037±0.030	<0.001*	<0.001*
Or	-0.122±0.161	0.105	-0.013±0.064	0.001*	0.073±0.056	<0.001*	<0.001*
FPM	-0.275±0.583	0.022*	0.147±0.280	0.132	0.277±0.241	0.001*	0.002*
Fz	-0.017±0.046	0.120	0.013±0.040	0.035*	0.040±0.028	<0.001*	0.002*
ANS	3.9±3.34	0.110	1.819±1.657	0.015*	0.669±0.685	0.002*	0.003*

Mandible landmarks		severe vs mild		Mild vs control		Severe vs control	
L3	- 5.994±0.026	0.017*	- 4.159±15.09	0.002*	0.188±0.215	<0.001*	<0.001*
L6(B)	-0.381±0.542	0.405	-0.181±0.317	0.007*	0.087±0.088	<0.001*	<0.001*
L6(L)	-0.658±1.042	0.441	-0.286±0.494	0.001*	0.114±0.125	<0.001*	<0.001*
L3(a)	-6.457±15.703	0.006*	-4.310±15.259	0.004*	0.159±0.156	<0.001*	<0.001*
L6(a)	-0.401±0.562	0.228	-0.178±0.313	0.002*	0.090±0.091	<0.001*	<0.001*
Ag	-0.370±0.201	0.004*	-0.125±0.193	<0.001*	0.059±0.050	<0.001*	<0.001*
Go	-0.148±0.170	0.244	-0.099±0.143	<0.001*	0.072±0.052	<0.001*	<0.001*
Gop	-0.110±0.147	0.480	-0.078±0.126	<0.001*	0.058±0.004	<0.001*	<0.001*
Cd	0.145±0.135	0.001*	-0.026±0.063	0.001	0.004±0.033	0.061	<0.001*
Me	14.850±8.663	0.001*	4.556±4.504	0.048*	1.338±1.242	<0.001*	<0.001*

Table 5. The asymmetry index and statistical analysis of maxilla and mandible landmarks in the transverse position using the Kruskal-Wallis test and further analysis with the Mann-Whitney test

a: Compare the severe and mild groups using the Mann-Whitney test

b: Compare the mild and control groups using the Mann-Whitney test

c: Compare the severe and control groups using the Mann-Whitney test

d: Compare the severe, mild, and control groups using the Kruskal-Wallis test

*statistically significant for P<0.05

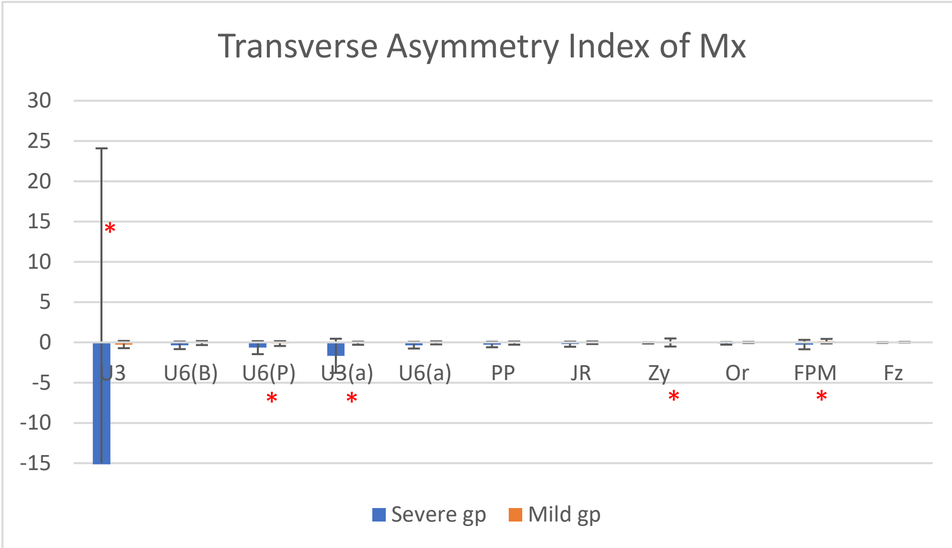

Fig.22 Comparison of asymmetry index of the severe and mild groups in transverse position of maxilla. U3, U6P, U3(a),Zy, FPM show statistical significance (P<0.05) using Mann-Whitney test.

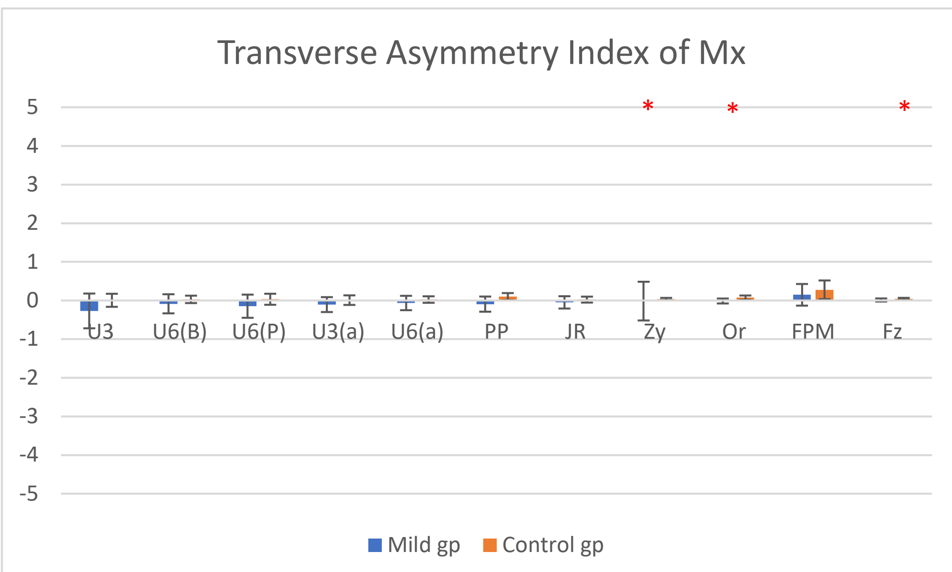

Fig.23 Comparison of asymmetry index of mild and control groups in transverse position of maxilla. Zy, Or, Fz show statistical significance (P<0.05) using Mann-Whitney test.

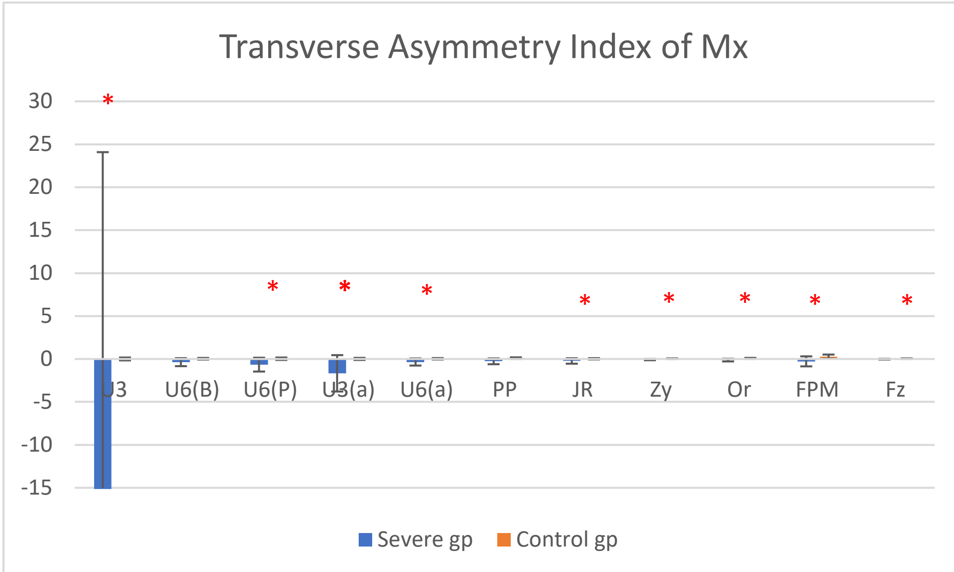

Fig.24 Comparison of asymmetry index of severe and control groups in transverse position of maxilla. U3, U6P, U3(a), U6(a), Jr, Zy, Or, FPM, Fz show statistical significance (P<0.05) using Mann-Whitney test.

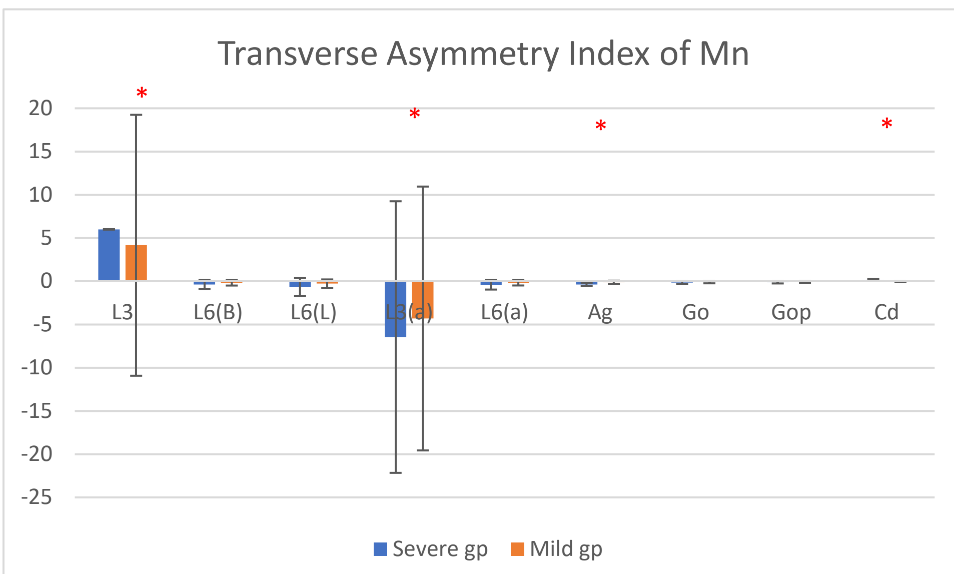

Fig.25 Comparison of asymmetry index of severe and mild groups in transverse position of mandible. L3, L3(a), Ag, Cd show statistical significance (P<0.05) using Mann-Whitney test. Difference between affected side and non-affected side is larger in severe group than mild group.

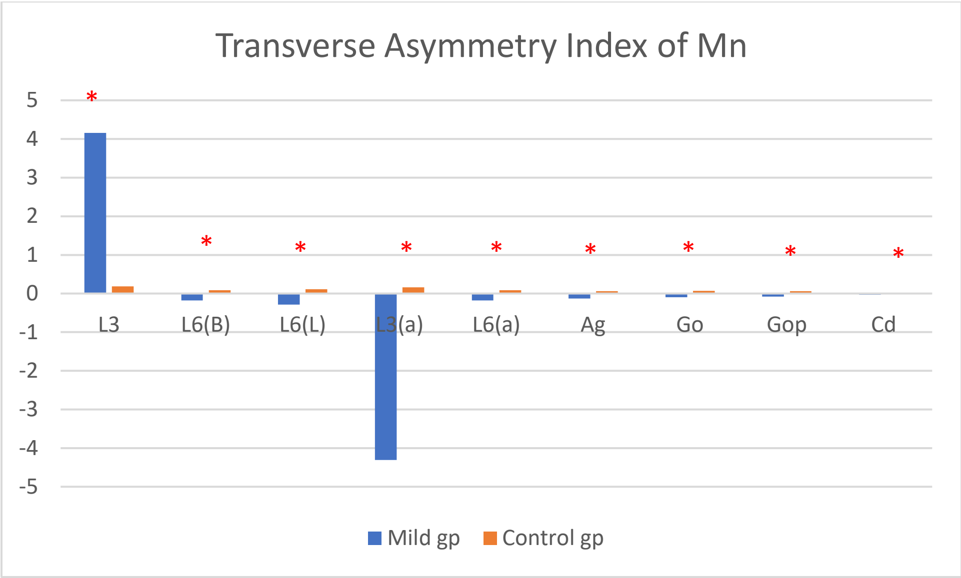

Fig.26 Comparison of asymmetry index of mild and control groups in transverse position of mandible. L3, L6(B), L6L, L3(a), L6(a), Ag, Go, Gop, Cd show statistical significance (P<0.05) using Mann-Whitney test.

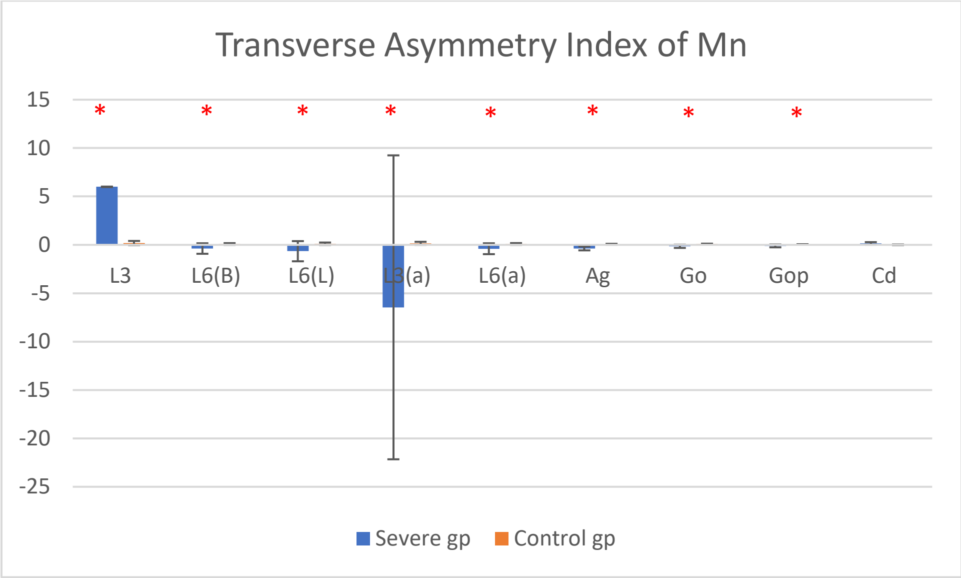

Fig.27 Comparison of asymmetry index of severe and control groups in transverse position of mandible. L3, L6B, L6L, L3(a), L6(a), Ag, Go, Gop show statistical significance (P<0.05) using Mann-Whitney test.

Angular measurement results

For the angular measurement in the maxilla, the coronal angulation measurements between the line from the affected to the non-affected side (or the left and right side in the control group) and the axial plane between the severe, mild, and the control groups at landmark upper canine (U3 to U3) and mesiobuccal cusp of upper first molar (U6B to U6B), mesiopalatal cusp of upper first molar (U6P to U6P), alveolar bone of upper first molar (U6a to U6a), jugal process (Jr to Jr), orbitale (Or to Or), lower canine (L3 to L3), mesiobuccal cusp of lower first molar (L6B to L6B), mesiolingual cusp of lower first molar (L6L to L6L), alveolar bone of L6 (L6a to L6a), alveolar bone of L3 (L3a to L3a), and antegonion point (Ag to Ag) all show statistical significance ($P<0.05$) between the severe, mild, and control groups. The angular measurement of the severe group at these landmarks is larger than that of the mild group, which is larger than that of the control group, and these differences are statistically significant. The angular measurements between the severe, mild, and control groups at landmark alveolar bone of upper canine (U3a to U3a) have statistically significant differences between the severe, mild, and control groups. The angular measurements of the mild group are larger than in the control group, and the angular measurements of the severe group are also larger than in the control group, at statistically significant levels. However, although the angular measurements of the severe group at these landmarks are larger than in the mild group, the difference is not statistically significant. In contrast, the angular measurements between the severe, mild, and control groups at landmark condylion (Cd to Cd) show statistically significant differences between the severe, mild, and control groups. The angular measurements of the severe group at this landmark are smaller than in the mild and control groups, with statistical significance. However, the angular measurement of the mild group at this landmark is smaller than in the control group, with no statistical significance (P=0.375). (Fig. 28, 29, 30)

	Group						K-W test
Variables	Severe		Mild		Control		P-value[d]
Angular measurements	Mean±SD	P-value[a] severe vs mild	Mean±SD	P-value[b] mild vs control	Mean±SD	P-value[c] severe vs control	(Kruskal-Wallis test)
U3 to U3	9.65± 4.177	.010*	5.19± 5.029	.000*	0.06± 1.924	.000*	0.000*
U6B to U6B	7.98± 3.974	.002*	2.90± 2.643	.003*	0.24± 1.380	.000*	0.000*
U6P to U6P	9.33±5.394	.004*	3.07±3.081	.002*	0.01±1.850	.000*	0.000*
U6a to U6a	7.43±4.490	.003*	2.70±2.520	.004*	0.25±1.526	.000*	0.000*
U3a to U3a	8.18±5.102	.051	4.78±5.040	.001*	0.31±2.040	.000*	0.000*
Jr to Jr	7.050±5.587	.009*	2.200±2.136	.001*	0.269±1.1802	.000*	0.000*
Or to Or	3.614±3.375	.015*	1.381±1.673	.001*	0.275±0.847	.000*	0.000*
L3 to L3	11.800±10.705	.008*	4.475±3.351	.001*	0.444±1.966	.000*	0.000*
L6B to L6B	9.66±4.668	.001*	3.47±2.603	.000*	0.06±1.570	.000*	0.000*
L6L to L6L	11.44±6.067	.001*	3.29±2.155	.001*	0.10±1.730	.000*	0.000*
L6a to L6a	8.27±3.912	.006*	3.58±2.905	.001*	0.37±1.436	.000*	0.000*
L3a to L3a	11.700±8.948	.003*	4.919±3.792	.002*	1.456±3.001	.000*	0.000*
Ag to Ag	8.764±7.457	.008*	2.963±3.542	.003*	0.125±1.425	.000*	0.000*
Cd to Cd	-5.086±3.189	0.000*	-0.394±1.470	.375	0.156±0.668	.000*	0.000*

Table 6. The angular measurements and statistical analysis of maxilla and mandible landmarks using the Kruskal-Wallis test and further analysis using the Mann-Whitney test

a: Compare the severe and mild groups using the Mann-Whitney test

b: Compare the mild and control groups using the Mann-Whitney test

c: Compare the severe and control groups using the Mann-Whitney test

d: Compare the severe, mild, and control groups using the Kruskal-Wallis test

*statistically significant for P<0.05

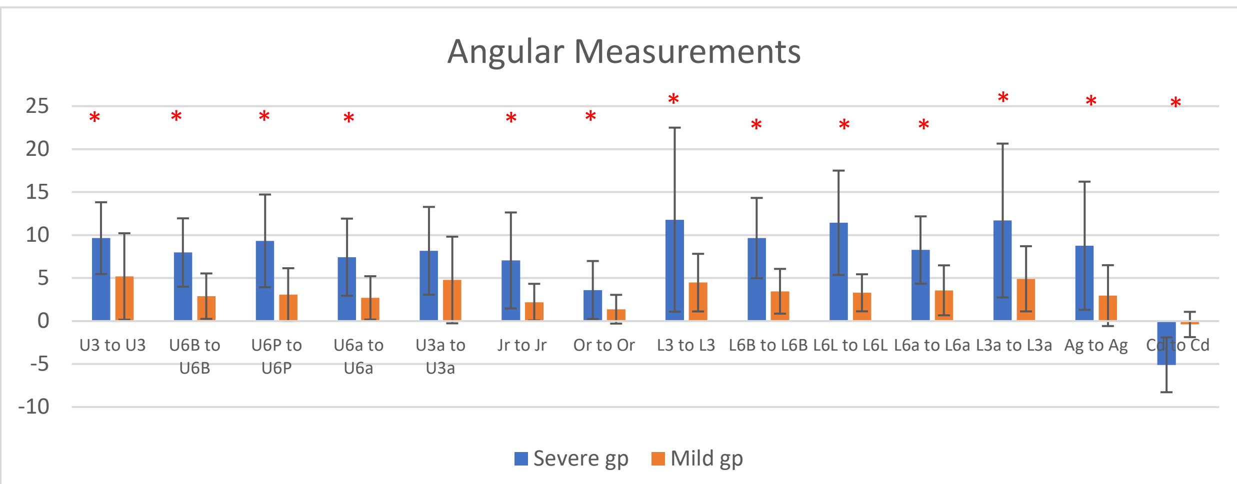

Fig.28 Comparison of angular measurements of severe and mild groups. All landmarks except U3(a) to U3(a) show statistical significance (P<0.05) using Mann-Whitney test. Difference between non-affected and affected side is larger in severe group than mild group.

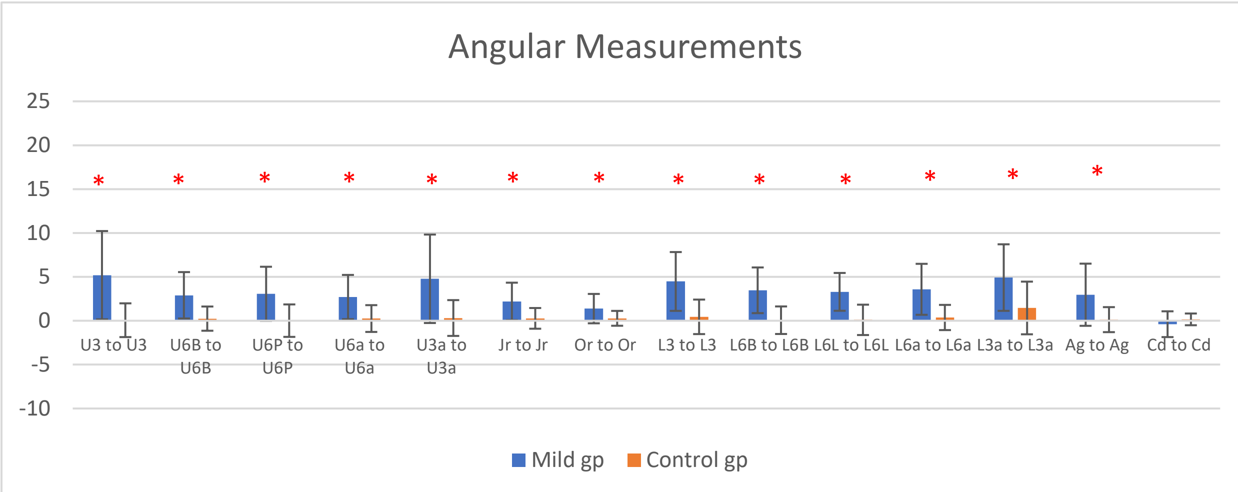

Fig.29 Comparison of angular measurements of mild and control groups. All landmarks except Cd to Cd show statistical significance ($P<0.05$) using Mann-Whitney test. Difference between non-affected and affected side is larger in mild group than control group.

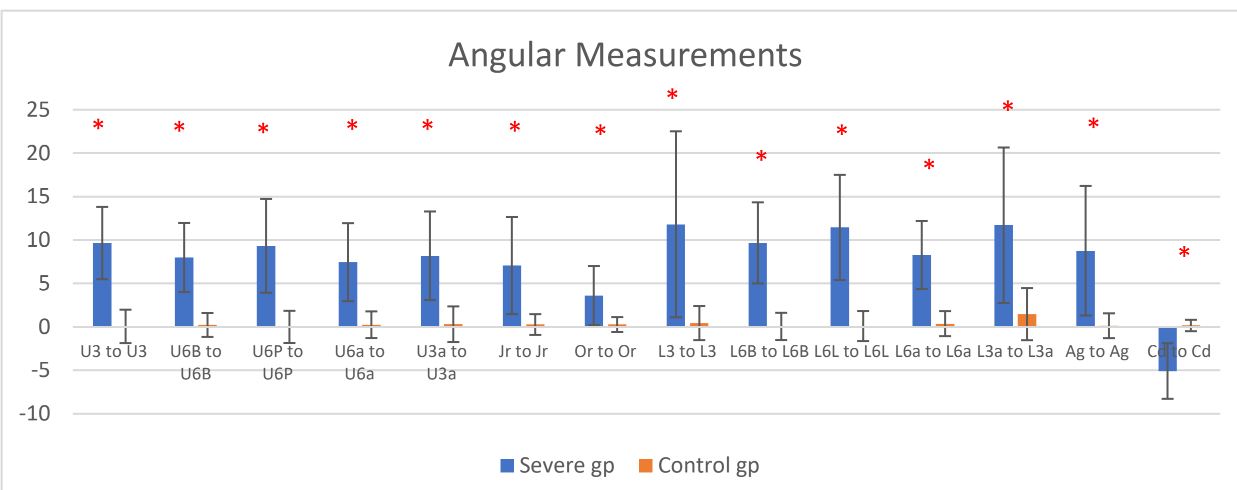

Fig.30 Comparison of angular measurements of severe and control groups. All landmarks show statistical significance ($P<0.05$) using Mann-Whitney test. Difference between non-affected and affected side is larger in severe group than control group.

Discussion

Craniofacial microsomia affects patients' facial anatomic structures derived from the first and second branchial arches. The characteristics of the deformities mainly involve the mandible and the ear (31). Clinically, the severity of asymmetry progressively increases from the upper third to the lower third of the whole face or skull among patients with craniofacial microsomia (32). Therefore, among all the deformities related to craniofacial microsomia, mandible deformity is the primary component contributing to facial asymmetry (33). Even Pruzansky's classification—the most commonly used classification of craniofacial microsomia—only focuses on mandible deformity. Consequently, in the past, surgical treatment has mainly emphasized correcting the asymmetric mandible or lengthening the morphology to reconstruct the function and facial appearance by early intervention mandibular distraction osteogenesis or later mandible osteotomy surgery (8, 9, 15, 16, 33, 34). However, in the longitudinal studies, the surgical results relapse after long-term follow-up (8, 9, 15, 16, 33-35). Even the severity of asymmetry turned out to be the same as the original severity of asymmetry in the previous case report (Chow et al. (2008)) (16). Nevertheless, there is debate about the advantages and disadvantages of early intervention treatment involving merely mandible distraction osteogenesis alone. While the early intervention of mandible distraction has psychosocial benefits for children with severe craniofacial microsomia, it may lessen the movement of the future orthognathic surgery due to enhanced bone generation. In contrast, due to the multiple surgeries involved (distraction and future orthognathic surgery) and the prolonged orthodontic treatment time, patients might feel treatment-fatigued, and repeated surgeries will cause scarring (36).

Moreover, Steinbacker et al. (2018) mentioned that after the mandible early distraction procedure, there will be dentoalveolar compensation, which may counteract the ideal presurgical orthodontic decompensation (36). Even with early mandible distraction intervention, future orthognathic surgery to correct the remaining or relapse asymmetry cannot be avoided (35, 37). Hence, early mandible distraction osteogenesis during childhood should be evaluated thoroughly by the family, the patient, the surgeon, and the related treatment doctors. In recent decades, many published articles discussed the treatment of craniofacial microsomia patients involving mandible distraction osteogenesis combined with maxilla surgery (osteotomy or distraction procedure) (10, 11, 38-40). However, there are currently no long-term follow-up studies.

Most previous studies discuss the morphology of the mandible of CFM patients due to the mandible representing a larger proportion of asymmetrical facial patterns. Ahiko et al. (2015) presented a study analyzing the mandible morphology of CFM patients. They measured the linear and angular measurements of the landmarks in the mandibles of CFM patients using PA and a frontal two-dimensional cephalogram. They concluded that the ramus and mandibular body length are smaller on the affected than the unaffected side. The more severe the deformity, the smaller the SNB and the larger the ANB, gonial angle, and mandibular plane (31). Kim et al. (2018) analyzed the mandibular functional units using three-dimensional reconstructed CBCT images. They found that the condyle unit was the major contributor to the deformity and that the lengths of the mandibular body and ramus were significantly shorter on the affected side (21, 41). However, few studies have focused on the maxilla morphology of CFM patients.

Xi Xu et al. (2020) segmented CT of the CFM patients' maxilla evaluating bone volume, sinus volume, and linear measurements of the maxilla in three directions between CFM patients with different severity. They found that the bone volume was decreased on the affected side (Pruzansky's class II and III patients). The linear measurements were increasingly aggravated from class I to IIb, and class III was unique. The severity of maxillary deficiency was not entirely consistent with mandibular deformity (42). Wink et al. (2014) also segmented CT to analyze different severity in CFM patients according to Pruzansky's classification. They found no statistically significant difference between the affected and non-affected sides for bone volume in the midface. Linear measurement ratio measurements showed no statistically significant difference (43). The similarity between these two studies and the present study is that we all analyzed CFM patients with CT three-dimensional images instead of traditional two-dimensional images; but these two studies (Xi Xu et al. (2020), Wink et al. (2014)) proceeded with three-dimensional image segmentation. They both considered bone volume and sinus volume for maxilla asymmetry. However, the volume of the maxillary sinus might be affected by various factors, including sinus pneumatization. Therefore, it might not reflect the real asymmetry proportion. Xi Xu et al. (2020) used the dentition part stands for posterior and the anterior part of the maxilla. In contrast, we used the skeletal landmarks in the maxilla, which measure the skeletal part of the maxilla more accurately. Both studies (Xi Xu et al. (2020), Wink et al. (2014)) compare the affected sides to the non-affected sides, whereas the present study recruited a control group and used the asymmetric index to compare the affected and non-affected sides and also compare to the normal population.

The vertical landmarks asymmetry indices between the affected and non-affected sides of the maxilla show statistical significance when the landmark is below the orbital point. The length in the non-affected side of the patient with severe deformity is longer than the affected side in the vertical direction, which shows statistical significance compared to the mild and control groups. This data indicates that the asymmetry trend canted up toward the affected side. However, U6P and U3a do not show a significant difference, suggesting dental compensation over the U6 palatal side. Noh et al. (2021) claims that when the occlusal plane canted up to the chin deviated side in asymmetry patients, posterior teeth buccal tipping occurs on the deviated side and palatal tipping on the non-deviated side (44, 45). Hence, the difference between the two sides of the palatal cusp is reduced. Fig. 31 shows that when there is dental compensation, the length difference is smaller for the orange line than the blue line. Therefore, the palatal cusp does not show significant difference, but the buccal cusp does. The accuracy decreases on the CBCT images when the bone is thinner (close to voxel size). It tends to become less detectable and is indistinguishable from the adjacent anatomy. Distinguishing the alveolar bone thickness is less accurate than distinguishing the height of the alveolar bone. Moreover, the alveolar bone thickness is harder to detect than the mandibular alveolar bone thickness because it is thinner than the mandible (46-48). The maxillary canine alveolar bone thickness is even thinner than the maxillary molar buccal alveolar bone thickness (49). The alveolar landmark measurements in this study measure the most prominent part at the buccal side of the alveolar bone. The accuracy of detecting bone thickness affects the identification of U3a. Among the mild group, the vertical asymmetric indices that show statistical significance are associated with maxillary landmarks below the nasomaxillary complex

(Jr, Zy, Or). The changes of the nasomaxillary complex in the mild group are not as drastic as observed for the anatomy below the nasomaxillary complex in the severe group (Table 3). The Fz and FPM have significantly large asymmetry indices exceeding 100%. Because many landmarks on both sides are above the axial reference plane and the non-affected side is much closer to the reference plane (close to 0), it turns out to be a large asymmetry index value (a negative sign indicates a value above the reference plane). The asymmetry index does not show consistency for Fz and FPM because they are too close to the reference plane, and it will overestimate the asymmetry (linear measurements are less than 1mm) (50). However, it indicates that the higher landmarks are not consistent and does not show a trend of asymmetry.

The asymmetry index of landmarks between the affected and non-affected sides of the mandible in the vertical direction shows statistical significance on L3, L3a, L6B, Ag, and Cd. The affected side L3, L3a is extruded 4.3mm more than the non-affected side (the asymmetry index shows 6.21% and 5.59%, respectively) in the severe group, which shows statistical significance compared to the mild and control groups. The L3 of the mild group also shows a statistically significant difference compared to the control group. The Ag in the severe group in the vertical position on the affected side is 10.64mm higher than on the non-affected side (asymmetry index shows 15.38%), which has statistical significance compared to the mild and the control groups. The vertical position of the L6 mesiobuccal or mesiolingual cusp tip is also affected by its position transversely and anteroposteriorly. Kim et al. (2019) found the L6 on the asymmetric side tipped lingually for patients with severe asymmetry (50). The present study found that the asymmetry indices of the lingual cusp tip of L6 and L6a do not have statistically significant differences in all three groups and nor does L6B in the severe group. This observation suggests that L6 exhibits dental compensation when the skeletal discrepancy is severe enough. For the Go and Gop, although the landmarks for the affected side are higher than the non-affected side in all groups, there are no significant differences in the asymmetry index in the vertical direction. Ko et al. (2017) utilized 3D craniofacial images and constructed to compare the craniofacial forms between CFM patients who did and who did not undergo distraction osteogenesis. They analyzed Pruzansky's classification II patients, where the gonion point on the affected side is higher than on the non-affected side. Although in the present study the asymmetry index does not show a statistically significant difference for the landmarks Go and Gop, Ko et al. (2017)'s study involved a different Pruzansky's classification group of CFM patients and a different reference plane definition (37). It is noteworthy that the condylion (Cd) canted up to the opposite direction, showing statistically significant differences in the severe group compared to the mild and control groups, indicating that the ramus length is shorter on the affected side. This result is in agreement with previous studies (21, 37).

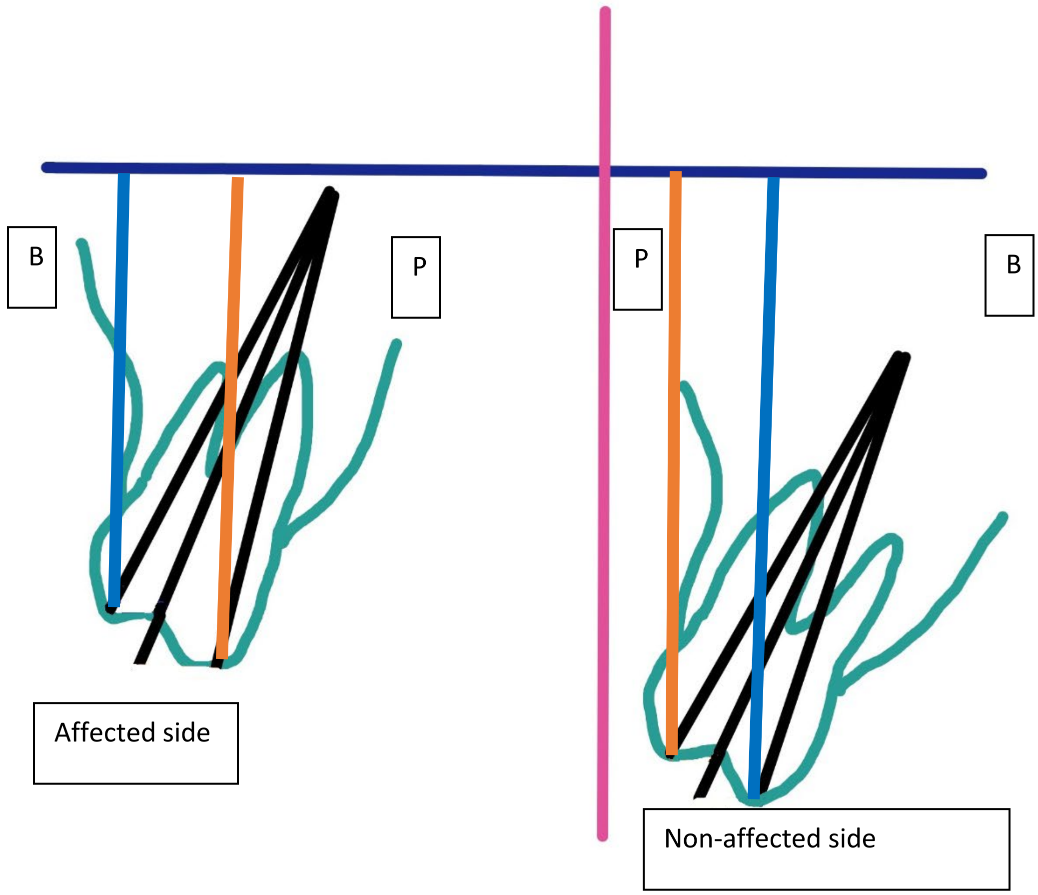

Fig.31 When there is dental compensation, the length difference between the orange line is smaller than the length difference of the blue line. Therefore, the palatal cusp does not show a significant difference between the affected and non-affected sides, but the buccal cusp does.

For the asymmetry index of anteroposterior direction in the maxilla, landmarks Or, FPM, and Fz have statistically significant differences, but the other maxillary landmarks do not. The lengths on the affected and non-affected sides in the coronal direction are similar, but these differences are not consistent between the three groups. In the mandible, L6B, L6a, Ag, Go, and Gop show statistically significant differences in the asymmetry index. L6 in the severe group shows statistical significance compared to the control group, which indicates that the L6 position on the affected side is in the forward position (Table 4). L6 is the tooth with a variable position, possibly due to having early space loss, which leads to a forward-tipping movement, rotations, or severe buccal or lingual version dental compensation. Therefore, L6L might not show a similar result due to this variability. In the severe group, the asymmetry index of Ag shows statistical significance compared to the mild and control groups, which suggests Ag is forward on the affected side if the CFM is severe enough. For Go and Gop, the asymmetry index shows statistical significance among all three groups. The Go and Gop are forward on the affected side if patients have CFM (21, 37, 51). Although the anteroposterior difference at Go and Gop is very significant, the vertical height does not show a significant difference over the gonion region. The reason for this is that when the skull is viewed from the front, the gonion area appears to have a higher position because, in severe asymmetry cases, the human eye interprets the anteroposterior difference as the vertical difference at the gonion position (Fig.31).

The asymmetry index in the transverse direction shows statistically significant differences in U3, U6, and the nasomaxillary complex of the maxilla. The asymmetry index of U3 and U3a in the severe group is negative and has a statistically significant difference compared to the mild and control groups. This data suggests that the affected side is wider than the non-affected side (Table 5). In the severe group of U3, the absolute value is larger than 1, and this is because the non-affected landmark of one of the cases (case code #106) is almost on the reference plane. The non-affected sides in other cases are also closer to the midsagittal plane. Therefore, the absolute value is larger than 1 because of the small denominator. U6P shows the same result as U3. The severe group has a statistically significant difference compared to the mild and control groups, and the affected side is wider than the non-affected side. Landmarks Zy, Or, FPM, and Fz show statistically significant differences in the asymmetry index between the severe and control groups. Zy in the severe group shows statistical significance between the mild and control groups. Although FPM, Fz, and Or also show a statistically significant difference, the asymmetry index has positive and negative signs, indicating that the differences do not indicate which side is wider.

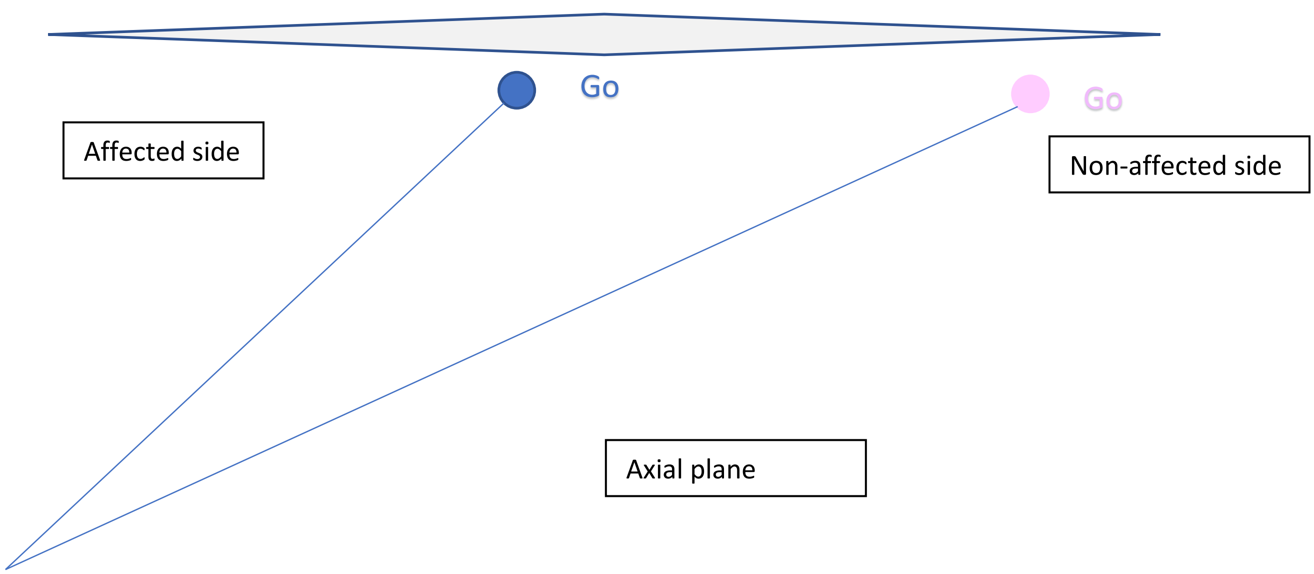

Fig. 32 The gonion area appears to be a higher position due to the human eye interpreting the anteroposterior difference as the vertical difference at the gonion position in severe asymmetry cases.

The asymmetry indices of all the landmarks in the transverse direction of the mandible show statistically significant differences, and the asymmetry index has a negative value, which gradually increases from the severe group to the mild and control groups. To be more specific, the asymmetry index of L3 and L3a show negative signs, and they have statistically significant differences in the severe groups compared to the mild and control groups. This data indicates that the affected side is wider than the non-affected side. L6L, L6B, and L6a show statistically significant differences between the severe and control groups and the mild and control groups. These observations suggest that the affected side is wider than the non-affected side in patients with CFM, even in the mild group. Furthermore, the L6 landmarks do not show statistical significance, but the L3 landmarks do when the CFM is severe enough, which indicates that dental compensation is significant while the CFM is in a severe condition. For the skeletal part, the severe and mild groups of Ag, Go, and Gop show statistically significant differences in the asymmetry index compared to the control groups. The value also shows a gradual increase in negative signs in the asymmetry index from the severe to the control group, which indicates that the affected side is wider than the non-affected side. The landmark Ag has a statistically significant difference between the severe and mild groups. Because the gonial angle is less prominent on the affected than the non-affected side, the width difference is reduced for landmarks Go and Gop. Even though the asymmetry index of landmark Cd has a statistically significant difference between the three groups, it has both negative and positive signs in the asymmetry index for the same group and does not show consistency. This data reflects the fact that there is more variety in the condyle morphology between the severe, mild, and control groups. In short, in the transverse direction, the affected side is wider than the non-affected side in CFM patients compared to the control group in the dental and skeletal parts. However, it does not show consistency in the condyle part.

For the angular measurements to the axial plane, all the maxillary and mandibular landmarks show statistically significant differences between the three groups except the angular measurement of U3a on both sides to the axial plane between the severe and mild groups and the Cd on both sides to the axial plane between the mild and control groups. The results indicate that the affected side is higher than the non-affected side in the vertical direction for dental and skeletal aspects. All the anatomy structures are canted up toward the affected side except the condyle, which is in the opposite direction (Table 6). The reason for the results of the angular measurements being different from the asymmetry index is that even with the same linear distance (Fig. 32 vertical distance from A to D equals to the vertical distance from B to C), when the two sides of the landmarks are closer to the midline (point B and point C are closer to the midline), the angulation from the landmarks to the reference plane will be larger. That is, the angular measurements will exaggerate the judgment of the severity of canting. U3a does not show a statistically significant difference in its asymmetry index between the severe and mild groups because the alveolar bone is thinner over U3a, and the accuracy is decreased on the CBCT images (closer to voxel size). The result of the angular measurements of Cd coincides with the result of the asymmetry index of Cd (i.e., the angular measurement of the severe group has a statistically significant difference compared to the mild and control groups), showing that the position is higher on the non-affected side.

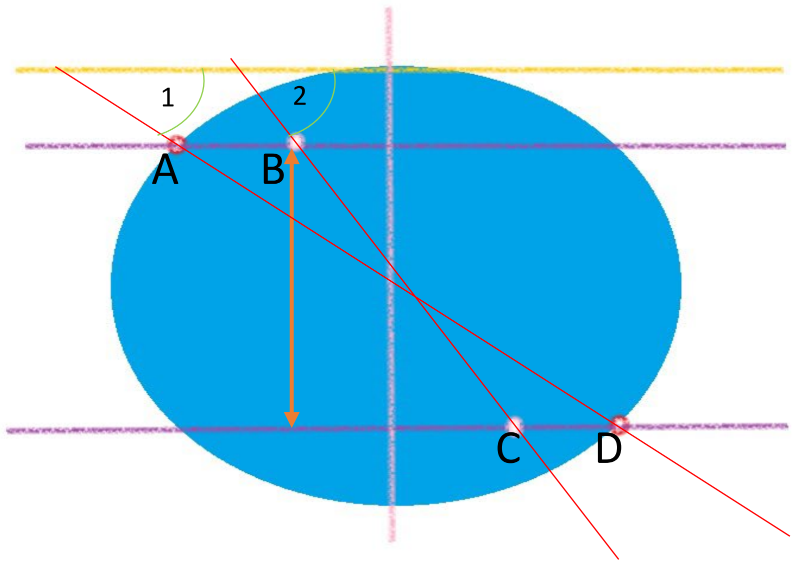

Fig. 33 The vertical distance perpendicular to the horizontal reference line from B to C is the same distance as A to D. If the two sides of the landmarks are closer to the midline e.g., B and C are closer to the midline), the angulation from the two sides' landmarks to the reference plane will be larger (i.e., angle #2 is larger than #1). The angular measurements will exaggerate the judgment of the severity of canting.

The mean age of the control group in this study was 19.2 ± 4.9 years, which is older than the mean age of the mild and severe groups (Mean age 12.3 ± 3.7 and 11.2 ± 3.2 years old). This discrepancy represents a limitation in this study (40, 52). With the growth potential during adolescence, the length, morphology, and maturity of skeletal characteristics might affect the results. In cases where there are no permanent molars or canines, the former were excluded from the samples, and the primary deciduous canines or permanent maxillary first premolars were measured instead. Nevertheless, the space distribution in the dentition would affect the tooth position directly (e.g., mesial tipping, tooth rotation, extrusion, or blocking out of the dentition.) It is difficult to control the consistency of tooth position. Although the G power analysis was performed to determine the sample size, not all the measurements followed the normal distribution in the normality test. Therefore, the Kruskal-Wallis test and Mann-Whitney U test were used. If a larger sample size can be recruited in the future, the results will tend to be closer to the normal distribution (53). Previous research mainly involves case studies with limited CFM patient sample sizes (sample sizes in previous research are less than 75 cases) (54). There were limited cases in the present study because of the low incidence of hemifacial microsomia, which ranges from 1/3500 to 1/5600 cases in newborn babies (25). The asymmetry index rose to higher than 1 due to the landmark on the non-affected side being almost on the reference plane (i.e., distance from the reference plane to the landmark is <1mm), which makes the denominator of the asymmetry index larger than 1. This leads to an overestimation of the asymmetry index. Defining a reference plane further away from the landmark being studied would prevent this overestimation.

The strength of this study is its use of three-dimensional image evaluation using CBCT images and three planes of measurement, which is practical and easy to access in our daily clinical practice. Before the development of 3D analysis, the skeletal evaluation of patients with skeletal asymmetry or craniofacial microsomia was analyzed using posteroanterior cephalograms and other two-dimensional images. The overlapping structures shown in the two-dimensional images limit the analysis and make it more challenging. Moreover, the two-dimensional images sometimes include distortion, making the examination even more difficult. This study analyzed the asymmetry of CFM patients with CBCT, which offers higher quality and a more accurate analysis compared to studies using two-dimensional images (22, 55, 56). The definition of the reference planes is crucial in cases involving asymmetry or craniofacial deformity. This is exemplified when defining the axial plane because the vertical measurements will be impacted by its orientation. Furthermore, this orientation is critical because the midsagittal plane is defined as being perpendicular to the axial plane. Lin et al. (2015) analyzed 30 patients with a facial deformity and found that Frankfort planes and lateral semicircular canal planes were reliable for the orientation of three-dimensional skull images (26). However, the interpretation of vertical measurements and the severity of asymmetry (such as the severity of menton shifted from the sagittal plane) will be different if different reference planes are chosen. In this study, the lateral semicircular canal was chosen because it is parallel to the floor, which is closer to the patients' head position. For the definition of the midsagittal plane, Damstra et al. (2012) used a three-dimensional morphometric method rather than a conventional two-dimensional method to define an optimal midsagittal plane for asymmetry patients. The authors suggested that internal structures of the skull may be irrelevant to visible facial symmetry (55). In the present study, we used the plane of the midpoint of the anterior clinoid process and the Crista Galli perpendicular to the defined axial plane. Therefore, the chosen reference plane was far from the relevant visible facial asymmetry. This study used the asymmetry index by turning the linear measurements into a percentage to remove the factor of variation in skull size. The denominator of the asymmetry index is simply the ratio of the normal side, and the affected side was not included in the denominator, which can reduce the impact of the affected side in the asymmetry index ratio. This study included severe and mild CFM patient groups. By grouping the patients in this manner, it was possible to evaluate whether there was a statistically significant difference between the different severity groups (25). Although the primary purpose of this study was the study of the maxilla, the mandible was measured simultaneously as a reference.

This study found that the skeletal and dental portion of landmarks below the orbital level on the affected side is in a higher position in the vertical direction for patients with CFM. In the anteroposterior direction, the landmarks' positions on the two sides of the maxilla do not show statistically significant differences. The anteroposterior position of the landmarks Go, Gop, and Ag on the affected sides is more forward than on the non-affected side, which implies that the mandible body is shorter on the affected side. The transverse direction on the affected side is wider than the non-affected side of the maxilla for CFM patients. L3, Go, Gop, and Ag show the same result. The landmarks closer to the anterior surface of the skull show a statistically significant difference. The landmarks of menton (Mn) and anterior nasal spine (ANS) also deviated to the affected side, which shows a statistically significant difference. While the upper and lower dental midlines were shifted toward the side of the chin deviation, the affected side was wider because the maxillary and mandibular arches were both shifted transversely to the affected side relative to the skull base. This observation corroborates the results of Noh et al.'s (2021) study, which also showed similar results in a population of asymmetric patients (44). Therefore, for the surgical correction of the maxilla and mandible, the surgical movement direction should be planned in roll movement, transverse shift for maxilla and the mandible but not that much of the yaw movement in the maxilla. For the mandible, except for the roll movement and the transverse shift correction, the surgical movement can also focus on mandibular body lengthening on the affected side. In the present study, the condyle position analysis only found a consistently statistically significant difference in the vertical direction. Ko et al. (2017) found the condyle position on the affected side to be more mesial and forward. However, the age of their subjects, their reference plane, and the severity of their CFM patients' condition were different from those in the present study (37). Zhang et al. (2018) described a long-term follow-up study for CFM patients who received early mandible distraction osteogenesis. They found no significant difference between subjects who received early mandible distraction and those who did not. There was more dental alveolar compensation for the subjects who received early mandible distraction surgery, which counters the ideal presurgical orthodontic dental decompensation. If there is a large amount of dental alveolar compensation, it reduces the amount of the movement of future orthognathic surgery (35). In the present study, the maxilla canted up toward the affected side for the mild and severe groups, with statistical significance. If early mandible distraction osteogenesis is performed, there will be a relapse of the dentoalveolar complex after the large dentoalveolar compensation due to the large extrusion tooth movement, which is the least stable type of tooth movement (17-19). This outcome will affect mandible development indirectly. If an early distraction procedure is needed for the consideration of large skeletal discrepancies, functions, and psychological reasons, both maxilla and mandible should be performed simultaneously in the future. Furthermore, the surgery should focus on the correction of maxillary canting vertically and the transverse shifting, which is toward the affected side for CFM patients.

For the mandible aspect, the surgery should focus on the roll movement, lengthening of the mandible body, and transverse shifting correction. The design of the distraction direction of the distractor should also focus on correcting the most severe deformity proportion of the maxilla and the mandible.

Conclusion

1. The skeletal and dental portions of landmarks below the orbital level on the affected side in the vertical direction are in a higher position, and they show a statistically significant difference in the severe group of the maxilla and mandibular canine (L3) and antegonion point (Ag) in the mandible. In landmarks higher than the orbital position on the affected side, only the zygomatic point (Zy) and orbitale (Or) show consistency, and they are in a higher position than on the non-affected side in the severe group. The only exception is that the condyle point is canted up toward the non-affected side.
2. For the anteroposterior position, the asymmetry index does not show a significant difference between the affected and non-affected sides of the maxilla. For the mandible, L6, Go, Gop, and Ag all show statistically significant differences between the severe and control groups, which indicates that the mandible body is shorter on the affected side.
3. The transverse direction of the maxilla on the affected side is wider than on the non-affected side for CFM patients if the landmarks are closer to the anterior surface of the skull. The landmarks in the mandible all show the same result in the severe and control groups.
4. All angular measurements show that the affected side is in a higher position in all landmarks and that the affected sides are in a higher position, except the condyle point, which shows the opposite canted direction.
5. The severe group of the maxilla shows a statistically significant difference in its asymmetry index in the vertical and transverse directions. The discrepancy is

sufficiently severe that bimaxillary surgery would be considered in the event of early intervention surgery, especially for correction of the vertical height difference and correction of the transverse shift.

Future Research Directions

Due to the severe skeletal discrepancy, there is dental compensation over the first maxillary and mandibular molars vertically, anteroposteriorly, and transversely. Hence, future studies could further analyze the axis of the dentition part to clearly understand the severity of the dental compensation caused by the severe skeletal discrepancy. The amount of dental compensation present may be considered in determining whether treatment necessitates orthognathic surgery or if it may be accomplished by orthodontic treatment alone. Moreover, future analysis can include the mandibular ramus length, the mandibular body length, and their relation to the severity of the maxilla deformity.

In this study, CFM patients were divided into two groups based on whether the deformity involved the condyle, according to Pruzansky's classification (severe group: type IIb and III; mild group: type IIa and I). The CFM subjects recruited ranged from 5Y9M to 19Y4M, meaning different skeletal maturation stages were included. Moreover, the statistical results do not follow the normal distribution. Hence, future studies could recruit sufficient participants to divide the subjects into four CFM groups (type I, IIa, IIb, and III) according to the severity of the patients' symptoms. Furthermore, the age of the subjects could be limited to a specific range or dentition eruption status. With the recruitment of more subjects, the results would be closer to normal distribution.

The reference planes affected the interpretation of this study. The reference planes were used and validated in previous studies (26, 27, 57, 58). However, for CFM patients, the asymmetry involves the whole skull, even the cranial base. Few of the landmarks in this study nearly pass through the location of the axial plane and the midsagittal plane, which makes the asymmetry index larger than 1. Future studies could focus on finding and validating new reference planes utilized in the orientation of CFM patients' skulls.

In this study, the skeletal discrepancy between different severities of CFM patients and the normal population had a statistically significant difference for the maxilla and mandible in several directions. With a different angulation and direction of placement of the distractor, the distraction osteogenesis can lengthen the mandible in the vertical and horizontal directions (59-61). Future studies could propose clinical practical surgical cuts and distractor designs to achieve the surgical direction in three dimensions according to the deformity of the defects. Long-term follow-up after surgery will be necessary to monitor skeletal and dental changes and ensure an optimal result.

References

1. SEBASTIÁN VÉLIZ M PAV, NOEMÍ LEIVA V. Hemifacial Microsomia. A Literature Review. Rev Fac Odontol Univ Antioq. 2016;27(2):404-24.

2. Caron C, Pluijmers BI, Wolvius EB, Looman CWN, Bulstrode N, Evans RD, et al. Erratum to "Craniofacial and extracraniofacial anomalies in craniofacial macrosomia: A multicenter study of 755 patients" [J Craniomaxillofac Surg vol. 45(8) (August 2017), 1302-1310]. J Craniomaxillofac Surg. 2017;45(11):1906.

3. Moore K. The developing human, clinically oriented embryology, 5th ed.; Philadelphia, 2011. 5th edition.

4. Poswillo D. Hemorrhage in development of the face. Birth Defects Orig Artic Ser. 1975;11(61e81).

5. Vendramini-Pittoli S, Kokitsu-Nakata NM. Oculoauriculovertebral spectrum: report of nine familial cases with evidence of autosomal dominant inheritance and review of the literature. Clin Dysmorphol. 2009;18(2):67-77.

6. Choi JW, Kim BH, Kim HS, Yu TH, Kim BC, Lee SH. Three-dimensional functional unit analysis of hemifacial microsomia mandible-a preliminary report. Maxillofac Plast Reconstr Surg. 2015;37(1):28.

7. Pruzansky S. Not all dwarfed mandibles are alike. Birth Defects 1969;1:120-9.

8. Huisinga-Fischer CE, Vaandrager JM, Prahl-Andersen B. Longitudinal results of mandibular distraction osteogenesis in hemifacial microsomia. J Craniofac Surg. 2003;14(6):924-33.

9. Meazzini MC, Mazzoleni F, Gabriele C, Bozzetti A. Mandibular distraction osteogenesis in hemifacial microsomia: long-term follow-up. J Craniomaxillofac Surg. 2005;33(6):370-6.

10. Sant'Anna EF, Lau GW, Marquezan M, de Souza Araujo MT, Polley JW, Figueroa AA. Combined maxillary and mandibular distraction osteogenesis in patients with hemifacial microsomia. Am J Orthod Dentofacial Orthop. 2015;147(5):566-77.

11. Mehrotra D, Howladar D, Bhutia DP. Simultaneous maxillomandibular distraction osteogenesis in hemifacial microsomia: Report of 7 cases. J Oral Biol Craniofac Res. 2017;7(2):147-52.

12. Molina F. Combined maxillary and mandibular distraction osteogenesis. Semin Orthod. 1999;5(1):41-5.

13. Cho BC, Shin DP, Park JW, Baik BS. Bimaxillary osteodistraction for the treatment of facial asymmetry in adults. Br J Plast Surg. 2001;54(6):491-8.

14. Scolozzi P, Herzog G, Jaques B. Simultaneous maxillo-mandibular distraction osteogenesis in hemifacial microsomia: a new technique using two distractors. Plast Reconstr Surg. 2006;117(5):1530-41; discussion 42.

15. Trahar M, Sheffield R, Kawamoto H, Lee HF, Ting K. Cephalometric evaluation of the craniofacial complex in patients treated with an intraoral distraction osteogenesis device: a preliminary report. Am J Orthod Dentofacial Orthop. 2003;124(6):639-50.

16. Chow A, Lee HF, Trahar M, Kawamoto H, Vastardis H, Ting K. Cephalometric evaluation of the craniofacial complex in patients treated with an intraoral distraction osteogenesis device: a long-term study. Am J Orthod Dentofacial Orthop. 2008;134(6):724-31.

17. Al-Buraiki H, Sadowsky C, Schneider B. The effectiveness and long-term stability of overbite correction with incisor intrusion mechanics. Am J Orthod Dentofacial Orthop. 2005;127(1):47-55.

18. Janson G, Valarelli FP, Henriques JF, de Freitas MR, Cancado RH. Stability of anterior open bite nonextraction treatment in the permanent dentition. Am J Orthod Dentofacial Orthop. 2003;124(3):265-76; quiz 340.

19. Lopez-Gavito G, Wallen TR, Little RM, Joondeph DR. Anterior open-bite malocclusion: a longitudinal 10-year postretention evaluation of orthodontically treated patients. Am J Orthod. 1985;87(3):175-86.

20. Rachmiel A, Shilo D. The use of distraction osteogenesis in oral and maxillofacial surgery. Ann Maxillofac Surg. 2015;5(2):146-7.

21. Chen YF, Baan F, Bruggink R, Bronkhorst E, Liao YF, Ongkosuwito E. Three-dimensional characterization of mandibular asymmetry in craniofacial microsomia. Clin Oral Investig. 2020.

22. de Moraes ME, Hollender LG, Chen CS, Moraes LC, Balducci I. Evaluating craniofacial asymmetry with digital cephalometric images and cone-beam computed tomography. Am J Orthod Dentofacial Orthop. 2011;139(6):e523-31.

23. Kwon TG, Park HS, Ryoo HM, Lee SH. A comparison of craniofacial morphology in patients with and without facial asymmetry--a three-dimensional analysis with computed tomography. Int J Oral Maxillofac Surg. 2006;35(1):43-8.

24. Sanders DA, Chandhoke TK, Uribe FA, Rigali PH, Nanda R. Quantification of skeletal asymmetries in normal adolescents: cone-beam computed tomography analysis. Prog Orthod. 2014;15(1):26.

25. Ongkosuwito EM, van Neck JW, Wattel E, van Adrichem LN, Kuijpers-Jagtman AM. Craniofacial morphology in unilateral hemifacial microsomia. Br J Oral Maxillofac Surg. 2013;51(8):902-7.

26. Lin HH, Chuang YF, Weng JL, Lo LJ. Comparative validity and reproducibility study of various landmark-oriented reference planes in 3-dimensional computed tomographic analysis for patients receiving orthognathic surgery. PLoS One. 2015;10(2):e0117604.

27. Pelo S, Deli R, Correra P, Boniello R, Gasparini G, Moro A. Evaluation of 2 different reference planes used for the study of asymmetric facial malformations. J Craniofac Surg. 2009;20(1):41-5.

28. Habets LL, Bezuur JN, Naeiji M, Hansson TL. The Orthopantomogram, an aid in diagnosis of temporomandibular joint problems. II. The vertical symmetry. J Oral Rehabil. 1988;15(5):465-71.

29. Nakamura T, Okamoto K, Maruyama T. Facial asymmetry in patients with cervicobrachial pain and headache. J Oral Rehabil. 2001;28(11):1009-14.

30. Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. J Chiropr Med. 2016;15(2):155-63.

31. Ahiko N, Baba Y, Tsuji M, Suzuki S, Kaneko T, Kindaichi J, et al. Investigation of maxillofacial morphology and dental development in hemifacial microsomia. Cleft Palate Craniofac J. 2015;52(2):203-9.

32. Cassi D, Battistoni G, Magnifico M, Di Blasio C, Pedrazzi G, Di Blasio A. Three-dimensional evaluation of facial asymmetry in patients with hemifacial microsomia using stereophotogrammetry. J Craniomaxillofac Surg. 2019;47(1):179-84.

33. Shi L, Liu W, Yin L, Feng S, Xu S, Zhang ZY. Surgical guide assistant mandibular distraction osteogenesis and sagittal split osteotomy in the treatment of hemifacial microsomia. J Craniofac Surg. 2015;26(2):498-500.

34. Mulliken JB, Kaban LB. Analysis and treatment of hemifacial microsomia in childhood. Clin Plast Surg. 1987;14(1):91-100.

35. Zhang RS, Lin LO, Hoppe IC, Swanson JW, Taylor JA, Bartlett SP. Early Mandibular Distraction in Craniofacial Microsomia and Need for Orthognathic Correction at Skeletal Maturity: A Comparative Long-Term Follow-Up Study. Plast Reconstr Surg. 2018;142(5):1285-93.

36. Steinbacher DM. Discussion: Early Mandibular Distraction in Craniofacial Microsomia and Need for Orthognathic Correction at Skeletal Maturity: A Comparative Long-Term Follow-Up Study. Plast Reconstr Surg. 2018;142(5):1294-8.

37. Ko EW, Chen PK, Lo LJ. Comparison of the adult three-dimensional craniofacial features of patients with unilateral craniofacial microsomia with and without early mandible distraction. Int J Oral Maxillofac Surg. 2017;46(7):811-8.

38. Liu H, Zhang X, Liu L, Chen Q, Shao J, Luo E. Combined Bimaxillary Distraction Osteogenesis Associated with Orthognathic Surgery for Hemifacial Microsomia in Adults. Aesthetic Plast Surg. 2017;41(3):650-60.

39. Balaji SM. Change of lip and occlusal cant after simultaneous maxillary and mandibular distraction osteogenesis in hemifacial microsomia. J Maxillofac Oral Surg. 2010;9(4):344-9.

40. Luo E, Yang S, Du W, Chen Q, Liao C, Fei W, et al. Bimaxillary Orthognathic Approach to Correct Skeletal Facial Asymmetry of Hemifacial Microsomia in Adults. Aesthetic Plast Surg. 2016;40(3):400-9.

41. Kim BC, Bertin H, Kim HJ, Kang SH, Mercier J, Perrin JP, et al. Structural comparison of hemifacial microsomia mandible in different age groups by three-dimensional skeletal unit analysis. J Craniomaxillofac Surg. 2018;46(11):1875-82.

42. Xu X, Zhang ZY, Li BH, Tang XJ, Yin L, Liu W. Three-Dimensional Measurement of Maxillary Involvement in Hemifacial Microsomia in Children. J Craniofac Surg. 2020;31(2):444-7.

43. Wink JD, Paliga JT, Tahiri Y, Goldstein JA, Taylor JA, Bartlett SP. Maxillary involvement in hemifacial microsomia: an objective three-dimensional analysis of the craniofacial skeleton. J Craniofac Surg. 2014;25(4):1236-40.

44. Hyung-Kyu Noh H-SP. Does maxillary yaw exist in patients with skeletal class III facial asymmetry? AJODO. 2021;160(4):573-87.

45. Kusayama M MN, Kuroda T. Relationship between transverse dental anomalies and skeletal asymmetry. Am J Orthod Dentofacial Orthop. 2003;123(3):329-37.

46. Wood R, Sun Z, Chaudhry J, Tee BC, Kim DG, Leblebicioglu B, et al. Factors affecting the accuracy of buccal alveolar bone height measurements from cone-beam computed tomography images. Am J Orthod Dentofacial Orthop. 2013;143(3):353-63.

47. Timock AM, Cook V, McDonald T, Leo MC, Crowe J, Benninger BL, et al. Accuracy and reliability of buccal bone height and thickness measurements from cone-beam computed tomography imaging. Am J Orthod Dentofacial Orthop. 2011;140(5):734-44.

48. Sun Z, Smith T, Kortam S, Kim DG, Tee BC, Fields H. Effect of bone thickness on alveolar bone-height measurements from cone-beam computed tomography images. Am J Orthod Dentofacial Orthop. 2011;139(2):e117-27.

49. Porto OCL, Silva BSF, Silva JA, Estrela CRA, Alencar AHG, Bueno MDR, et al. CBCT assessment of bone thickness in maxillary and mandibular teeth: an anatomic study. J Appl Oral Sci. 2020;28:e20190148.

50. Kim HJ, Hong M, Park HS. Analysis of dental compensation in patients with facial asymmetry using cone-beam computed tomography. Am J Orthod Dentofacial Orthop. 2019;156(4):493-501.

51. Rachmiel A, Manor R, Peled M, Laufer D. Intraoral distraction osteogenesis of the mandible in hemifacial microsomia. J Oral Maxillofac Surg. 2001;59(7):728-33.

52. Meazzini MC, Mazzoleni F, Bozzetti A, Brusati R. Comparison of mandibular vertical growth in hemifacial microsomia patients treated with early distraction or not treated: follow up till the completion of growth. J Craniomaxillofac Surg. 2012;40(2):105-11.

53. Fan X, Thompson, B., & Wang, L. Effects of sample size, estimation methods, and model specification on structural equation modeling fit indexes. Structural Equation Modeling: A Multidisciplinary Journal. 1999;6(1):56-83.

54. Khetani MA, Collett BR, Speltz ML, Werler MM. Health-related quality of life in children with hemifacial microsomia: parent and child perspectives. J Dev Behav Pediatr. 2013;34(9):661-8.

55. Damstra J, Fourie Z, De Wit M, Ren Y. A three-dimensional comparison of a morphometric and conventional cephalometric midsagittal planes for craniofacial asymmetry. Clin Oral Investig. 2012;16(1):285-94.

56. Anderson PJ, Yong R, Surman TL, Rajion ZA, Ranjitkar S. Application of three-dimensional computed tomography in craniofacial clinical practice and research. Aust Dent J. 2014;59 Suppl 1:174-85.

57. Diemunsch C, Faure F, Trunde F, Morgon L, Bossard D, Jourlin M, et al. Three-dimensional modeling system for unilateral mandibular bone distraction: a clinical case. Comput Aided Surg. 2007;12(5):262-9.

58. Moro A, Correra P, Boniello R, Gasparini G, Pelo S. Three-dimensional analysis in facial asymmetry: comparison with model analysis and conventional two-dimensional analysis. J Craniofac Surg. 2009;20(2):417-22.

59. Chen Y, Niu F, Yu B, Liu J, Wang M, Gui L. Three-dimensional preoperative design of distraction osteogenesis for hemifacial microsomia. J Craniofac Surg. 2014;25(1):184-8.

60. Sun H, Li B, Zhao Z, Zhang L, Shen SG, Wang X. Error analysis of a CAD/CAM method for unidirectional mandibular distraction osteogenesis in the treatment of hemifacial microsomia. Br J Oral Maxillofac Surg. 2013;51(8):892-7.

61. Jun-Young PAENG J-HL, Jong-Ho LEE, Myung-Jin KIM. Condyle as the point of rotation for 3-D planning of distraction osteogenesis for hemifacial microsomia. Journal of Cranio-Maxillofacial Surgery. 2007;35:91-102.