AN ANATOMICAL EXPLORATION OF THE HYPOPLASTIC MANDIBLE IN HEMIFACIAL MICROSOMIA PATIENTS IN SOUTH AFRICA: UNDERSTANDING FACIAL ASYMMETRY, CLINICAL PRESENTATION AND AUTOLOGOUS FAT GRAFT TREATMENT

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A thesis submitted to the Discipline of Clinical Anatomy, School of Laboratory Medicine and Medical Sciences, College of Health Sciences, University of KwaZulu-Natal, Durban, South Africa

In fulfilment of the requirement for the degree of Doctor of Philosophy in Health Sciences (Clinical Anatomy)

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PREFACE

This research was carried out in the Discipline of Clinical Anatomy, School of Laboratory Medicine and Medical Sciences, College of Health Sciences, University of KwaZulu-Natal, and the Department of Plastic and Reconstructive Surgery at Inkosi Albert Luthuli Central Hospital, Durban, South Africa, from July 2021 to August 2024, under the supervision of Professor Lelika Lazarus and Professor Anil Madaree for the award of Doctor of Philosophy Degree in Health Sciences (Clinical Anatomy).

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DECLARATION 2: PUBLICATION AND SUBMISSION

PUBLICATION/ACCEPTED

Atiba, P.M., Onyangunga-Kabanga, D., Madaree, A. and Lazarus, L., 2024. Mandibular hypoplasia in hemifacial microsomia: A cross-sectional study. *Translational Research in Anatomy*, *35*, p.100291. https://doi.org/10.1016/j.tria.2024.100291.

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I carried out the study design, experimental imaging, fieldwork, data curation, analysis, and interpretation of results regarding the articles above. The co-authors contributed to the imaging analysis, data curation, editing, proofreading, and study supervision.

[redacted]

…….. ….27-11-2024…

Peterson Makinde Atiba **Date**

DEDICATION

The work is dedicated to YHWH, the ultimate source of wisdom for making this piece of writings a reality (*He makes all things beautiful in His time*). To my wife, Kehinde M. Atiba, and my children, Deborah T. and Daniel O., thank you for your sacrifices, love, and support throughout this adventure.

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LIST OF ABBREVIATION AND ACRONYMS

3D	Three-dimensional
A/C	Affected to Contralateral
AFG	Autologous Fat Grafting
CDS	Cranial Deformity Scoring
CFDS	Craniofacial Deformity Scoring
CNCC	Cranial Neural Crest Cell
CPD	Chin Point Deviation
CT	Computed Tomography
EYA1	EYA transcriptional coactivator and phosphatase 1
FA	Facial Asymmetry
GATA3	GATA Binding Protein 3
GC	Graft-to-Capacity
HFM	Hemifacial microsomia
ICC	Intra-class Correlation Coefficient
ITPR1	Inositol 1,4,5-Trisphosphate Receptor Type 1
MBH	Mandibular Body Height
MBL	Mandibular Body Length
MDO	Distraction Osteogenesis
MDO+AFG	Mandibular Distraction Osteogenesis combined with AFG
MDS	Mandibular Deformity Scoring
MNW	Mandibular Notch Width
MRH	Mandibular Ramus Height
MRI	Magnetic Resonance Imaging
MRW	Mandibular Ramus Width
MYT1	Myelin Transcription Factor 1
NCC	Neural Crest Cell
OMENS	Orbital distortion (O), Mandibular hypoplasia (M), Ear anomaly (E), Nerve involvement (N), and Soft tissue deficiency (S)
OMENS+	OMENS include extracraniofacial defects
OPA	Occlusal Plane Angle
PACS	Picture Archiving and Communication System
RBI	Ramus and Body Index
SAT	Skeletal-auricular-soft tissue deficiency
SF3B2	Splicing Factor 3b Subunit 2
TC	Treacher-Collins syndrome

TMJ	Temporomandibular joint
TNM	Tumour, Node, Metastasis-style classification

ABSTRACT

Introduction: This study uses clinical and morphometric analyses to investigate facial asymmetry (FA) in hemifacial microsomia (HFM) patients, specifically focusing on mandibular hypoplasia. It also assesses the effectiveness of autologous fat graft (AFG) camouflage for FA in a South African population.

Materials and Methods: This retrospective study analysed 25 HFM patients, confirming diagnoses through plain radiographs or computed tomography. Patient charts provided data on age, sex, laterality, deformity severity, and associated anomalies. Malformations were categorised using the OMENS classification, and patients were grouped by Pruzansky-Kaban grading (mild/severe) and age (1-5, 6-12, 13-19 years). Linear and angular measurements of the mandibular ramus and body from preoperative CT scans were used to compare severity, age groups, and affected-to-contralateral side ratios. Additionally, ten Pruzansky grades I and II patients (4-16 years) with unilateral FA received AFG, divided into AFG-treated (mean age: 5.8 ±3.89 years) and mandibular distraction osteogenesis combined with AFG (MDO+AFG)-treated (mean age: 8.8 ±4.32 years) groups, each with five patients.

Results: Twenty-five HFM patients (M:F 1:1.78; 60% Black; 32% Indian; 4% White; and 4% Coloured; R:L 1.4:1) found 100% mandibular hypoplasia and soft tissue defects, with high rates of ear (84%), orbital (40%), and facial nerve (60%) involvement. Other craniofacial and extracraniofacial anomalies were 84% and 40%, respectively. Significant differences were found in mandibular linear and angular measurements and ramus-body index (RBI) between affected and contralateral sides, excluding mandibular body length (MBL). However, mean RBI differences between mild and severe deformities were insignificant, as was the affected-to-contralateral (A/C) ratio between severity groups and across age groups. In the AFG group, mandibular ramus height (MRH) and mandibular ramus width (MRW) significantly increased post-treatment, while chin point deviation (CPD) and occlusal plane angle (OPA) significantly decreased ($p<0.05$). The MBL significantly increased in the MDO+AFG group, but mandibular body height (MBH) did not. Growth increases were comparable between affected and unaffected sides in both groups.

Conclusion: Notably, deformities in HFM vary significantly among the South African population. This study indicates that HFM is non-progressive, suggesting surgery should be delayed until skeletal maturity. MDO and AFG improve symmetry, with AFG effective for mild cases.

Keywords: Hemifacial microsomia, mandible, autologous fat graft, anatomy, age-dependent

CHAPTER ONE

INTRODUCTION AND LITERATURE REVIEW

1.1 Background of Study

Hemifacial microsomia (HFM), also referred to as craniofacial microsomia, is a congenital craniofacial anomaly that arises from the first and second pharyngeal arches and presents a spectrum of deformities characterised by underdevelopment or asymmetry of skeletal and soft tissue structures on one side of the face (Apostolopoulos et al., 2021). HFM is also known as craniofacial microstomia with cranial involvement (Taiwo, 2020). The global estimate for the prevalence of HFM ranges from 1 in 3,500 to 1 in 5,600 live births (Hartsfield, 2007). However, prevalence rates can vary widely across different regions, potentially reaching as low as 1 in 5,600 to 1 in 45,000 in certain parts of the world (Barisic et al., 2014). HFM has been speculated to be due to genetic, maternal, and environmental conditions leading to stapedial artery injury (replaced by an external carotid system in humans), dysgenesis of Meckel's cartilage and aberrant migration of neural crest cells (Chen et al., 2018). This defect is more evident in the jaw and ear areas, although involvement of the eye, cheek, nerve, soft tissue, other cranial parts, and neck may accompany it (Allam, 2021). In a clinical presentation, mandibular hypoplasia has been the cornerstone of this deformity with unilateral or bilateral microtia (Atiba et al., 2024). Although HFM implies facial involvement only, individuals with HFM often have associated extracranial defects (David et al., 1987). The systemic defects include 5-15% of neurological abnormalities (Rollnick et al., 1987, Cohen et al., 1989), 14-47% cardiac malformation (Pierpont et al., 1982), 5-6% genitourinary (Rollnick et al., 1987), 10% pulmonary and gastrointestinal (Horgan et al., 1995), and 40-60% skeletal malformations (Horgan et al., 1995). It has been reported that HFM is more present in males than females, with a 3:2 ratio and a tendency for right-sided presentation (Cousley and Calvert, 1997); other authors found no correlation in gender or laterality (Horgan et al., 1995, Xu et al., 2015). Trisomy 10p, 12p13.33 microdeletion, 22q11.2 microdeletion, large 5p deletion, and 10.7 cM on chromosome 14q32 are genetic abnormalities associated with HFM (Su et al., 2018). Other genes contributing to this abnormality include OTX2, PLCD3, MYT1, ITPR1and Pde4dip (Chen et al., 2018, Wang et al., 2023).

Several classification groups have been proposed to improve the diagnosis and treatment of HFM due to its varying physical presentation (Allam, 2021). The first widely used classification of HFM was reported by Pruzansky (1969) using mandibular hypoplasia, which Kaban et al. (1988) improved to include the temporomandibular joint. Another HFM classification is the skeletal–auricular–soft tissue (SAT) deficiency (David et al., 1987). Vento et al. (1991) introduced the O.M.E.N.S. classification pattern by associating anomalies to include orbital distortion (O), mandibular hypoplasia (M), ear anomaly (E), nerve involvement (N), and soft tissue deficiency (S). Horgan et al. (1995) expanded the anomalies to include extracraniofacial defects. Hence, it was designated as an OMENS-Plus (+). Furthermore, there is a relationship between HFM and macrostomia Tessier's cleft number 7: Treacher-

Collins syndrome (Tuin et al., 2015, Ramanathan, 2021). Macrostomia is a hallmark feature of Tessier 7 clefts within the HFM spectrum. They share overlapping features both arise from disruption in first and second pharyngeal arch but are genetically distinct from one another (Tuin et al., 2015, Ramanathan, 2021).

The face is divided into the upper, middle, and lower third by the sensory distribution of the trigeminal nerve. Facial asymmetry (FA) affects the lower face more than the middle and upper faces (Severt and Proffit, 1997, Cheong and Lo, 2011). FA classification includes congenital, acquired, or developed from an unknown aetiology (Cheong and Lo, 2011). HFM is one of the congenital anomalies responsible for FA. Asymmetry of the mandibles with regard to size, volume or positional changes could involve the different components of the bone, viz., the condyle, the ramus, the symphysis, and the body (Taiwo, 2020, Atiba et al., 2024). Some authors suggested that FA progresses with mandibular growth in patients with HFM (Chen et al., 2021b, Shetye et al., 2023, Zhang et al., 2023). Other authors have suggested FA remains the same despite mandibular growth in patients with HFM (Kaprio et al., 2023, Atiba et al., 2024).

The treatment of HFM depends on the patient's age and severity of malformations (Taiwo, 2020, Sugar et al., 2023). Distraction osteogenesis (MDO) is an effective technique for elongating the deficient mandible in HFM (Tahiri et al., 2014, Liu et al., 2022). Autologous fat graft (AFG) targets soft tissue volume restoration and contour refinement, thereby providing a comprehensive solution to the complex facial deformities associated with HFM (Luo et al., 2023).

Mild to moderate mandibular deficiencies can be treated with a series of autologous lipofilling, and severe tissue deficiencies can be treated with fasciocutaneous free tissue transfer (Sinclair et al., 2019). Osteocutaneous free tissue transfer is recommended for concurrent bony and soft tissue deficiency treatment (Sinclair et al., 2019).

An ideal filler must be easily obtainable, inexpensive, biocompatible, low donor-site morbidity, repeatable, and versatile. Fat meets all these criteria; it is the ideal standard against which all other fillers are compared (Coleman, 2001). Human fat tissue is a source of mesenchymal stem cells known as adipose-derived stem cells (ADSC), which have pluripotent capacity and produce a variety of angiogenic, osteogenic, and antiapoptotic factors (Zhu et al., 2021). ADSC can potentially promote skeletal growth through their ability to differentiate into bone cells, support tissue regeneration via paracrine signalling, and enhance vascularisation (Yuan et al., 2022). Studies have shown that for soft tissue hypoplasia management to be achieved, initial repair of the facial skeleton must be undertaken (Yamaguchi et al., 2017, Li et al., 2021).

Potential staged corrective procedures for patients with craniofacial microsomia during childhood present multiple opportunities for serial AFG (Tanna et al., 2011). Methods varied depending on the

involvement and severity of the deformity (Sugar et al., 2023). Fat grafting is used to restore volume and improve contour, especially in soft tissue reconstruction or augmentation of the face (Lim et al., 2012). Specific data on the prevalence, genetic basis, and clinical presentation of HFM in South Africa is currently unavailable except for case reports on facial restitution (Losken et al., 1983, Preston et al., 1985). There is a lack of literature reporting fat injection in children with HFM in the South African population.

1.2.0 Literature Review

1.2.1 Background Information

Reconstruction of congenital craniofacial malformations presents complex challenges. Treacher-Collins syndrome (TC) and HFM are accompanied by agenesis or hypoplasia of the facial skeleton in children (Fan et al., 2005, Tuin et al., 2015). Unilateral otomandibular dysostosis, HFM, and abnormal development of the first and second pharyngeal arches result in Tessier numbers 6, 7, and 8 facial clefts (Tessier, 1976). Unilateral mandibular hypoplasia, soft tissue, skeletal deficiencies of the midface, and microtia present varying features in individuals (Sugar et al., 2023, Atiba et al., 2024). Successful management requires an individualised treatment plan consisting of reconstructive procedures performed at specific times in the patients' lives, addressing hard- and soft-tissue defects (Mulliken and Kaban, 1987).

1.2.2 Development of the face

Pluripotent neural crest cells give rise to craniofacial structures (Ansari and Bordoni, 2022). They are migrating cells that give rise to connective tissues such as cartilage, bones, ligaments, and muscles (Ansari and Bordoni, 2022). Disruption in their migration and differentiation pathway results in congenital defects (Chen et al., 2018). During the fourth week of development, distinct face development is identifiable from five primordia that surround a central area of depression, viz., the stomodeum (Figure 1). The primordia are cranially located in one frontonasal process and bilaterally located in two maxillary and mandibular processes. The latter two processes originate from the first pharyngeal arch (Carstens, 2002). The nasal (olfactory) placodes appear as local thickenings of the surface ectoderm on both sides of the frontonasal prominence under the inductive influence of the ventral portion of the forebrain (Ansari and Bordoni, 2022).

During the fifth week of intrauterine life, the nasal placodes invaginate to form nasal pits**.** The nasal prominences are formed as a tissue ridge surrounding each pit. The pits' outer and inner edges prominences are the lateral and medial nasal prominences, respectively (Moore et al., 2018, Ansari and Bordoni, 2022).

During the following two weeks, the maxillary prominences continue to increase in size. Simultaneously, they grow medially, the medial nasal prominences are compressed toward the midline.

Subsequently, the cleft between the medial nasal prominence and the maxillary prominence is lost, and the two fuse (Figure 1). Hence, the upper lip is formed by the two medial nasal prominences and maxillary prominences. The lateral nasal prominences do not participate in forming the upper lip—the lower lip and jaw form from the mandibular prominences that merge across the midline (Ansari and Bordoni, 2022).

Initially, the nasolacrimal groove, a deep furrow, separates the lateral nasal and the maxillary prominences. The ectoderm in the floor of this groove forms a solid epithelial cord that detaches from the overlying ectoderm. After canalisation, the cord forms the nasolacrimal duct; its upper end widens to form the lacrimal sac. Following the detachment of the nasolacrimal groove, the maxillary and lateral nasal prominences merge. The nasolacrimal duct then runs from the medial corner of the eye to the inferior meatus of the nasal cavity, and the maxillary prominences enlarge to form the cheeks and maxillae (Moore et al., 2018, Ansari and Bordoni, 2022).

The nose is formed from five facial prominences: the frontal prominence gives rise to the bridge; the merged medial nasal prominences provide the crest and tip, and the lateral nasal prominences form the sides (alae) of the nose (Ansari and Bordoni, 2022).

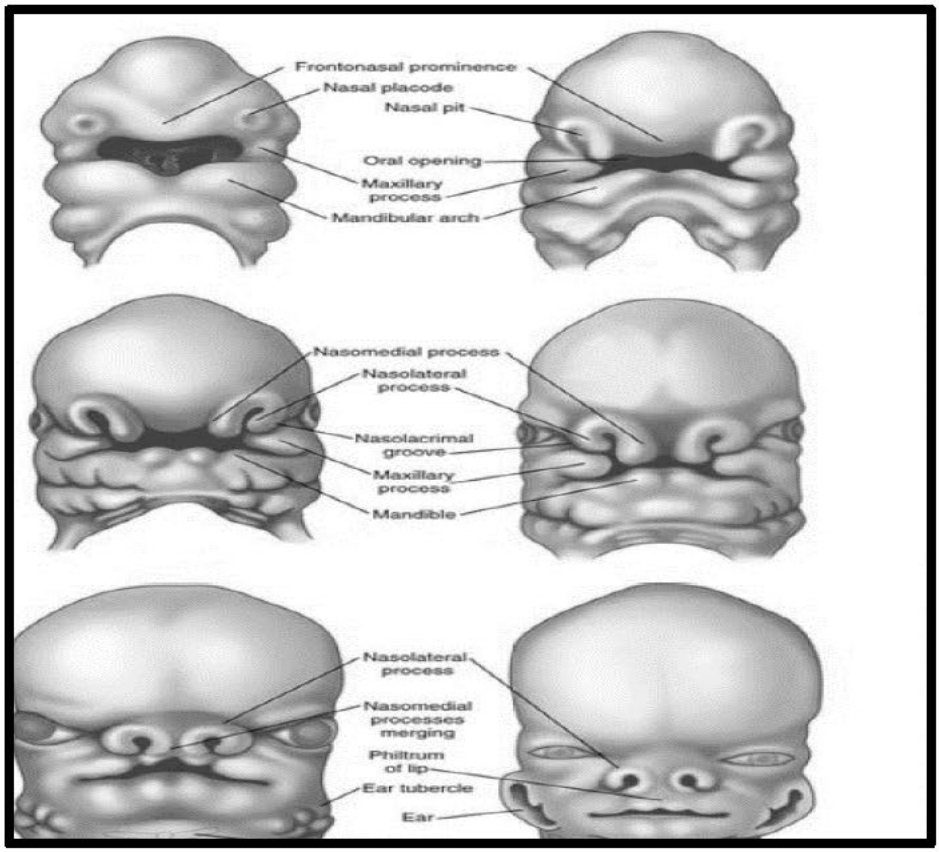

Figure 1: Schematic representation of face development
(Adapted from Moore et al., 2018)

1.2.3 Pathophysiology of Hemifacial Microsomia

Hypothetically, three pathogenic models have been postulated for the formation of HFM. None of the models are mutually exclusive but may be interrelated in HFM pathogenesis due to varying factors inducing its development (Figure 2) (Chen et al., 2018, Luo et al., 2023).

1. *Vascular abnormalities and haemorrhage*. Intrauterine haemorrhage of the stapedial artery was demonstrated in Poswillo's work as a probable reason for the presentation of HFM in animal models (Poswillo, 1973). This resulted in the malformation of surrounding structures due to hematoma and an ischemic environment. The first and second pharyngeal arches are vascularised by the stapedial artery, a precursor of the external carotid artery in humans. Local vascular haemorrhage is susceptible to the influence of thalidomide and vasoconstrictors such as epinephrine (Werler, 2006, Therapontos et al., 2009). Impaired growth factors (such as vascular endothelial growth factor) can disrupt arterial supply to Meckel's cartilage, causing mandibular hypoplasia (Wiszniak et al., 2015). The severity of vascular injury and the proximity to the bleeding area may influence the extent of hypoplastic soft tissues (such as muscle and neural structures) and bone (Zhang et al., 2023).
2. *Interference with Meckel's cartilage development*. The malleus, incus, stapes and mandible are derivatives of Meckel's cartilage, which develop from the first and second pharyngeal arch. Teratogens, haemorrhage, and genetic defects disrupt the development of Meckel's cartilage, resulting in the unilateral formation of mandibular hypoplasia and ossicles (Cousley and Wilson, 1992). Meckel's cartilage disruption model may give credence to the skeletal pathogenesis of HFM (Chen et al., 2018).
3. *Abnormal migration, proliferation, and differentiation of neural crest cells (NCC)*. Genetic defects, teratogens, and environmental factors can disrupt the migration and formation of NCC. OTX2 (homeobox family member) deletion in mandibular dysostosis is vital to NCC development. Other pathogenic genes associated with HFM include *EYA transcriptional coactivator and phosphatase 1* (EYA1) with a phenotypic presentation of mandibular and ear hypoplasia, *GATA Binding Protein 3* (GATA3) with a phenotypic presentation of hypoplastic facial bone, *Myelin transcription factor 1* (MYT1) with a phenotypic presentation of microtia, mandibular hypoplasia, renal and vertebral malformation, *Inositol 1,4,5-trisphosphate receptor type 1* (ITPR1) with a phenotypic presentation of craniofacial skeleton and cardiovascular malformation and *Splicing Factor 3b Subunit 2* (SF3B2) with a phenotypic presentation of microtia, mandibular hypoplasia, preauricular tags, epibulbar dermoid, lateral oral clefts, cardiac and skeletal abnormalities (Luo et al., 2023). Maternal diabetes resulting in increased intrauterine glucose levels can inhibit NCC tolerance to oxidative stress. Facial and cardiac anomalies may occur due to NCC apoptosis (Wentzel and Eriksson, 2011). Other risk factors include vagina bleeding during the second semester, twin pregnancies, smoking,

isotretinoin exposure, low family income, low maternal body mass index and advanced maternal age (Werler et al., 2004, Werler et al., 2009, Eseonu et al., 2014).

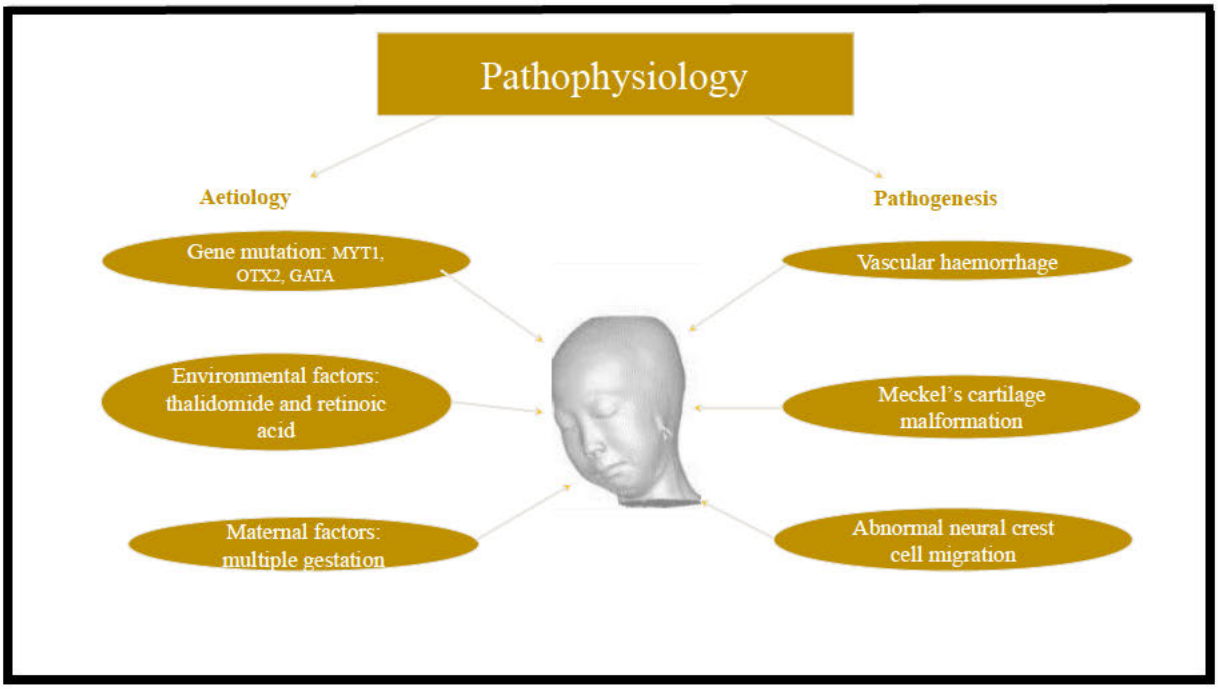

Figure 2: Diagram of the Pathophysiology of Hemifacial Microsomia
(Adapted from Luo et al., 2023)

1.2.4 Method of classification of hemifacial microsomia

Due to the varying phenotypic features of HFM, several classification groups have been proposed to improve its diagnosis and treatment. The classifications used in patients with HFM have evolved to cover an increasing range of pathological features associated with HFM. The classification was based on various presentations of the deformed mandible with subsequent modifications to include temporomandibular joint (TMJ), auricle, and soft tissue defects.

1. Classification system of Pruzansky (1969)

The first classification used in HFM subjects was compiled by Pruzansky (1969) using x-rays of the jaws of patients with this condition. He observed three types of mandibular hypoplasia viz. from a relatively complete mandible (Grade I) to one that was very small, whose deformity worsened over time (Grade III) (Table 1A). This classification is limited only to mandibular deformities and excludes other pathological aspects.

Table 1A: The Pruzansky classification systems of patients with hemifacial microsomia
(*Adapted from Véliz-M et al., 2016)*

A: Pruzansky Classification	
Grade I	Minimum mandibular hypoplasia
Grade II	Ramus, condyle, and notch are present with distorted size and shape
Grade III	Mandibular ramus hypotrophy or agenesis

2. SAT classification by David et al. (1987)

HFM grading is based on a TNM (Tumour, Node, Metastasis)-style multisystem classification for cancer patients. This classification system furthermore provides a grading for skeletal, ear and soft tissue deformities via the acronym SAT (S = skeletal, A = auricle, and T = soft tissue) (David et al., 1987). There are five levels of skeletal deformity (S1 to S5), four levels of auricular deformity (A0 to A3), and three levels of soft-tissue deformity (T1 to T3), others include the parotid gland, muscles of mastication, or cleft of the upper lip (Table 1B).

Table 1B: The SAT classification of patients with hemifacial microsomia
(*Adapted from David et al., 1987*)

B: SAT Classification	
Skeletal (S): Malformed mandible and orbit	
S1	Small but normal shape mandible
S2	Distorted ramus, condyle, and sigmoid notch in size and shape
S3	Severely deformed mandible, range from poor ramal components to complete agenesis
S4	S_3 mandible, including posterior recession of inferior and lateral orbit rims
S5	S_4 deficiency, orbit dystopia, hypoplastic and asymmetry neurocranium
Auricular (A): Malformed auricle	
A0	Normal auricle
A1	Deformed auricle with mostly normal feature
A2	The upper ear has malformed cartilaginous structures
A3	Severely deficient auricle with a deformed lobule and absent pinna
Soft tissue (T): Soft tissue deficiency	
T1	Minimal contour deformity, no cranial nerve involvement
T2	Moderate deficiency
T3	Severe deformity including facial scoliosis, muscle of mastication, parotid gland, eye, facial cleft or lip and cranial nerves

3. Pruzansky's classification modified by Kaban et al. (1988)

Kaban et al. (1988) modified Pruzansky's classification by adding the temporomandibular joint deformities using teleradiography. The modification was made to Grade II, based on the position of the glenoid cavity; hence, two sub-classifications were included, viz. normal (IIA) or altered (IIB) (Table 1C) (Figure 3).

Table 1C: The Pruzansky classification systems of patients with hemifacial microsomia modified by Kaban and colleagues
(***Adapted from Véliz-M et al., 2016)***

C: Pruzansky-Kaban Classification	
Grade I	Mandible is smaller than the normal side
Grade IIA	A short ramus with the normal glenoid fossa
Grade IIB	A malposition glenoid fossa requiring temporomandibular joint (TMJ) reconstruction
Grade III	Gross distortion or agenesis of the ramus

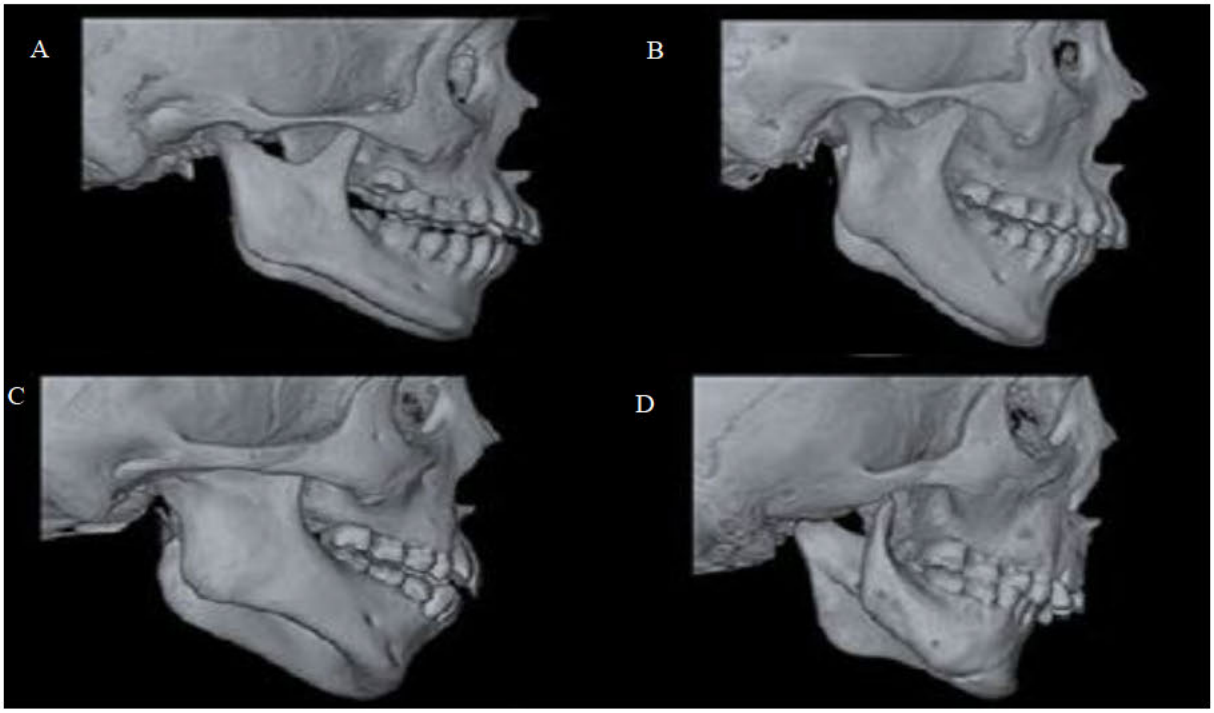

Figure 3: Reconstructed three-dimensional computed tomography scan of the Pruzansky-Kaban classification of hemifacial microsomia. (A) Pruzansky-Kaban grade I, (B) Pruzansky-Kaban grade IIA, (C) Pruzansky-Kaban grade IIB, (D) Pruzansky-Kaban grade III.

(***Adapted from Shibazaki-Yorozuya et al., 2024***)

4. OMENS classification (1991)

Vento et al. (1991) proposed that the HFM designation must be inclusive and versatile, ease the analysis of anatomic constituents, and express data in numerical grade for ease of clinical utilisation. The OMENS acronym is as follows: O- orbital asymmetry (Orbit); M- mandibular hypoplasia (Mandible); E- external ear deformity (Ear); N- nervous involvement (Nerve); S- soft tissue deficiency in (Soft Tissue) (Table 1D).

Table 1D: The OMENS classification system of patients with hemifacial microsomia
(***Adapted from Véliz-M et al., 2016)***

D: OMENS Classification	
Orbit(O): Asymmetry of the orbit	
O0	Normal size and positioned orbit
O1	Abnormal orbital size
O2	Abnormally positioned orbit
O3	Abnormal size and positioned orbit
Mandible(M): Mandibular hypoplasia	
M0	Normal mandible
M1	Small mandible and glenoid fossa with small ramus
M2A	Glenoid fossa in acceptable anatomical position regarding opposite TMJ
M2B	TMJ is inferiorly, medially, and anteriorly displaced with the severe hypoplastic condyle
M3	Complete absence of ramus, glenoid fossa and TMJ
Ear(E): External ear deformity	
E1	Normal ear
E2	Mild hypoplasia is present, but all structures are intact
E3	Absence of external auditory canal with variable hypoplasia concha
E4	The malposition lobule has an absent auricle, and the lobule remnant is displaced inferiorly and anteriorly
Nerve(N): Nervous involvement	
N0	The facial nerve is not affected
N1	Upper facial nerve is affected (temporal and zygomatic branches)
N2	Lower facial nerve is affected (buccal, mandibular, and cervical branches)
N3	Affectation of all facial nerve branches. Others are trigeminal (sensory component) and hypoglossal
Soft tissue(S): Soft tissue deficiency	

S0	No deficiency in the soft tissue or muscle
S1	Minimal soft tissue or muscle deficiency
S2	Moderate between S1 and S3
S3	Severe deficiency owing to soft tissue or muscle hypoplasia

4.1 OMENS+ classification

OMENS+ classification was proposed by adding extracranial anomalies to the OMENS classification (Horgan et al., 1995) (Table 1E). Pictographic representation of OMENS+ was introduced and modified to increase its application in clinical intervention among patients with HFM (Gougoutas et al., 2007).

Table 1E: The OMENS+ classification systems of patients with hemifacial microsomia (*Adapted from Véliz-M et al., 2016)*

	OMENS+(Plus): Systemic Malformation
	Macrostomia
C_0	No cleft
C_1	Cleft terminates medial to the anterior border of the masseter
C_2	Cleft terminates laterally to the anterior border of the masseter
	Goldenhar syndrome
	Hemifacial microsomia with epibulbar lipodermoids and fused/hemivertebrae
	Other extracranial structures
	Congenital heart defects
	Genitourinary defects
	Limb defects
	Nervous system anomalies

5. CFDS (Craniofacial Deformity Scoring)

This craniofacial deformity scoring system incorporated Mandibular Deformity Scoring (MDS) and Cranial Deformity Scoring (CDS) to form Craniofacial Deformity Scoring (CFDS), which is based on three-dimensional computed tomography on different bone structures. The maximum values are 16 points for MDS and 19 for CDS (Huisinga-Fischer et al., 2001). Although, it has not gained broad acceptance like others (Table 2A-B).

Table 2A. Mandibular Deformity Score (MDS), defined as the Sum of All Mandibular Scores, according to the Scores of the Different Mandibular Deformities
(Adapted from Huisinga-Fischer et al., 2001)

	0	1	2	3
Gonial notch	Not present	Present		
Body	Normal	Mild hypoplasia	Moderate hypoplasia	Absent
Condyle	Normal	Mild hypoplasia	Moderate hypoplasia	Absent
Coronoid process	Normal	Mild hypoplasia	Moderate hypoplasia	Absent
Ramus	Normal	Mild hypoplasia	Moderate hypoplasia	Absent
Temporomandibular joint	Normal	Mild hypoplasia	Moderate hypoplasia	Absent
The maximum score of MDS is 16				

Table 2B. Cranial Deformity Score (CDS), defined as the Sum of All Cranial Scores, according to the Scores of the Different Cranial Deformities
(Adapted from Huisinga-Fischer et al., 2001)

	0	1	2	3
Maxillary Cleft	Not present	Present		
Foramen magnum	No defect	Defect		
Maxilla	No defect	Defect		
Calvaria	No defect	Defect		
Temporal fossa	No defect	Defect		
Orbit	Normal location and shape	Abnormal location or shape	Abnormal location and shape	
Pterygoid process	Normal	Hypoplasia /dislocation	Partly absent	Complete absent
Malar	Normal	Hypoplasia	Partly absent	Complete absent
Zygomatic arch malar part	Normal	Hypoplasia	Partly absent	Complete absent
Zygomatic arch temporal part	Normal	Hypoplasia	Partly absent	Complete absent
The maximum score of MDS is 19				

1.2.5 Treatment of hemifacial microsomia

A multidisciplinary team is required to manage and treat HFM. The kind of surgery utilised depends on the level of deformities. HFM reconstruction enhances jaw function, normal occlusion, and facial symmetry (Brandstetter and Patel, 2016).

1. *Functional orthodontic (activator) appliances.* An activator appliance is employed to guide the malpositioned side of the mandible forward and downward toward the midline. The tension exerted by the activator on the affected muscles is proposed to facilitate skeletal growth (Mulliken and Kaban et al., 1987; Suppapinyaroj et al., 2021). If the activator does not successfully correct the occlusal plane tilt, surgical elongation and rotation of the mandibular ramus are undertaken during the mixed dentition stage. This approach is applicable for managing mild HFM and for preparing patients with more severe forms of HFM for surgery (Mulliken and Kaban et al., 1987; Suppapinyaroj et al., 2021).
2. *Grafts*. Grafts are obtained from the fibula, iliac crest, costochondral cartilage, temporal bone, and other calvarial bone to augment the hypoplastic mandible. Resorption of graft material, recurrence of asymmetry, wound infection, defect to the donor site, re-ankylosis of the joint and fracture are the demerits of grafting (Corcoran et al., 1997, Zanakis et al., 2009). Mandibular distraction has made grafts secondary lines of treatment in reconstructing temporomandibular joint and ramus defects (Corcoran et al., 1997).
3. *Mandibular distraction osteogenesis (MDO)*. It is done by increasing the length of the mandible. This is achieved through mandibular osteotomies; the segments are drawn apart for new bone growth to occur between them. Distraction requires new bone growth as opposed to grafting material. Lower asymmetry recurrence rates, less blood loss, shorter operative times, improved soft tissue symmetry, no donor site morbidity, and the ability to perform at a younger age are merits of MDO over grafts (McCarthy et al., 2002, van Strijen et al., 2004, Singh et al., 2009). The distraction devices can be external or internal, and the pins can be unscrewed easily without a revision operation (Rachmiel et al., 2014). Accompanied demerits include patient discomfort, external trauma, visible scars, hardware infections, and dislodgement, which led to the development of internal mandibular devices, which have shown exceptional mechanical strength. The relapse time of internal distraction (13.33%) is greater than external distraction (23.52%) (Rachmiel et al., 2014). The second operation for device removal, scarring, hardware malfunction, inappropriate distraction, tooth injury, temporomandibular joint injury, nerve injury, infection, and bony overgrowth over the devices are demerits of internal distraction (Stelnicki et al., 2002, Burstein, 2008, Rachmiel et al., 2014). For children with short mandibles and limited subperiosteal space for internal distractor placement, the external distractor is recommended (which allows for more extended distraction lengthening) (Rachmiel et al., 2014).

4. *Soft tissue correction*. This type of surgical intervention is implemented as a sequel to facial skeleton restoration. This includes autologous fat transfer, microvascular free tissue transfers, other biological or manufactured soft tissue composites, and porous polyethylene implants (Hollier et al., 1999, Tanna et al., 2012, Rai et al., 2014). AFG allows for lower volume transfer and requires more repetitive operative procedures than free tissue transfer. The merits of AFG include overall short operating time, negligible complication rates, and similar satisfaction rates between patient and surgeon (Tanna et al., 2012).
5. *Ear reconstruction*. Defects in the auricle, external auditory meatus, and middle ear are features of HFM. Defects range from mild hypoplasia to anotia, with ear cartilage reshaping needed to complete middle ear reconstruction, respectively. Synthetic implants or costal cartilage grafts are used to rebuild the auricular framework. A prosthetic ear can be an adhesive, or a surgically osseointegrated anchor is a less invasive option. The merits of prostheses include device upgrades and the absence of donor site infection (Cousley and Calvert, 1997, Brandstetter and Patel, 2016).

1.2.6 Fat graft techniques

The standard technique for structural fat grafting consists of three steps: harvesting, purification, and injection. The preparatory method for fat graft harvest is equally variable, and all have been shown to produce surviving fat cells. High-fat graft reabsorption rates have been attributed to the traumatic harvesting and handling of lipoaspirate before reinjection (Bellini et al., 2017).

Fat harvesting can be done by excision, syringe aspiration or vacuum suction. This method is achieved through wet or dry harvesting. Agostini and colleagues reported no significant difference observed between the two approaches regarding viability and morphology of the fat (Agostini et al., 2012). Cannula size also affects the viability of harvested fat and aspiration pressure (Özsoy et al., 2006, Erdim et al., 2009, Kirkham et al., 2014). The larger the cannula size, the greater the viability. Lee et al. (2013) concluded that harvest pressure did not affect graft viability, while Cheriyan et al. (2014) showed lower harvest pressure led to greater fat graft viability. However, both studies demonstrated that a slow fat injection resulted in greater fat graft viability and lower shear stress than a fast fat injection. Vyas et al. (2020) proposed that low-pressure aspiration and slow fat infusion should increase fat graft viability.

1.2.6.1 Donor-recipient site

Presently, two main theories on fat survival rates oppose each other. The first theory (graft survival theory) states that the final volume obtained after an adipose tissue transplant depends on the number of vital adipocytes present at transplantation. This theory is supported by those advocating atraumatic processing of the fat graft to ensure the highest viability before injection (Shauly et al., 2022).

The second theory (graft replacement theory) states that the adipose undergoes necrosis in the central and regenerative zones. In contrast, the adipose survives or is replaced by metaplastic fat tissue in the periphery/surviving zone and regenerating zone, respectively (Eto et al., 2012). Identifying the donor site is often based on the location of excess fatty tissue; determining the optimal donor site will help

guide surgical approaches. No significant difference is found in cell viability from various adipose depots such as the abdomen, flank, thigh, and knee (Rohrich et al., 2004). Ullmann and colleagues noticed no significant difference in the cell volume from various adipose depots of the abdomen, breast, and thigh (Ullmann et al., 2005); or in histological parameters from the flank, upper abdomen, lower abdomen, lateral thigh, and inner thigh depots in experimental animals (Li et al., 2013).

1.2.6.2 Adipocyte viability

The viability of fat cells during the fat grafting process is essential for achieving long-term volume retention and successful integration of the graft. Studies have shown that the viability of adipocytes can significantly impact the outcomes of fat grafting procedures. Viability of adipocyte is associated with graft retention, resorption rates, aesthetic, and functional results.

The survival of fat graft is dependent on the following:

Oxygen diffusion capability: Firstly, the surface area-to-volume ratio is significant for surviving hypoxia before angiogenesis begins. Positive outcomes have been observed when adhered to during grafting (Pu, 2016). These outcomes have been due to fat donor sites and the volume of fat used for grafting. Secondly, the graft-to-capacity (GC) ratio, which looks at the fat quantity injected, is inversely proportional to the volume of the recipient site (Del Vecchio and Del Vecchio, 2014).

Some growth factors promote angiogenesis at the recipient site, primal for long-term graft viability. These are vascular endothelial growth factor, insulin-like growth factor, epidermal growth factor, platelet-derived growth factor, fibroblast growth factor, and erythropoietin (Zheng et al., 2019, Yu et al., 2020, Herold and Kalucka, 2021).

Growth factors are proteins or steroid hormones that facilitate the development of specific tissues and promote cell division and differentiation (Vyas et al., 2020). Enrichment of fat grafts through vascular endothelial growth factor-activated autologous stromal vascular fraction and adipose-derived regenerative cells may improve fat graft viability (Zheng et al., 2019, Yu et al., 2020).

Other factors include the surgeon's skills, the technique of fat harvesting and processing, the vascularity of the recipient site, the patient's inflammation, and the healing response (Varghese et al., 2017, Wang et al., 2019).

1.3 Summary of the demographic features of mandibular morphometry in hemifacial microsomia

Global studies on HFM from 1965 to 2024, covering 50+ years of research. It includes more than 60 studies from countries such as the USA, UK, China, and the Netherlands, with sample sizes ranging from single case reports to large cohorts (e.g., 991 subjects). Common diagnostic tools include cephalograms, computed tomograms, and panoramic X-rays. Mandibular morphometrics such as ramus height, occlusal cant, and chin deviation are frequently assessed. Classification systems such as Pruzansky, OMENS, and OMENS+ are widely used. Treatments primarily include distraction

osteogenesis, costochondral grafts, and other surgical procedures like osteotomies and genioplasty. The table below summarises the literature on demographic features of mandibular morphometry in HFM across various countries (Table 3).

Table 3. Demographic features of mandibular morphometry in hemifacial microsomia

Author (year)	Countries	Sample	Sex		Age	Prevalence	Mandible Morphometric	Methodology (Tool)	HFM Classification	Treatment
			Male%	Female%						
Grabb (1965)	USA	102	62	38	-	1:5600	-	Medical photographs, cephalogram	-	-
Poswillo (1973)	UK (England)	-	-	-	-	1:4000	-	-	-	-
Rune et al. (1981)	Sweden	11	64	36	3-14 years	-	Occlusal plane angle	Orthopantomogram	-	-
Grayson et al., (1983)	USA	24	67	33	6-16 years	-	Mandible length, ramus height, body length, Gonial angle	Cephalogram	Pruzansky	-
Vento et al. (1991)	USA	154	-	-	-	-	-	-	OMENS	-
Morrison et al. (1992)	UK (Northern Ireland)	25	40	60	-	1:45000	-	-	-	-
Horgan et al. (1995)	USA	121	49	51	-	-	-	-	OMENS+	-
Araneta et al. (1997)	USA	7	71	29	-	1:11000	-	-		-
Padwa et al. (1998)	USA	33	-	-	2-10 years	-	Occlusal cant, piriform rim angle, intergonial angle, ramal height	Panoramic radiograph	OMENS	Costochondral grafts
Llano-Rivas et al. (1999)	Mexico	58	-	-	0.3-18 years	-	-	-	-	-
Kearns et al. (2000)	USA	67	-	-	3-21 years	-	Piriform rim angle, occlusal plane angle, intergonial angle	Cephalogram	Pruzansky-Kaban	-
Kan et al. (2002)	New Zealand	7	-	-	6-17 years	-	Condyle, mandibular foramen	Computed tomogram	Pruzansky	
Kunz et al. (2003)	Switzerland	1	-	-	13 years	-	-	Computed tomogram	Pruzansky-Kaban	Distraction osteogenesis
Poon et al. (2003)	Australia	65	54	46	-	-	-	Cephalogram, panorex	OMENS+	
Fan et al. (2005)	USA	198	51	49	1-50 years	-	-	-	-	-
Tasse et al. (2005)	Germany	53	60	40	0.2-46 years	-	-	-	-	-
İşeri et al. (2008)	Turkey	1	-	100	12 years	-	Occlusal plane cant, chin deviation	3D - Computed tomogram	Pruzansky-Kaban	Distraction osteogenesis
Balaji (2010)	India	11	27	73	14-29 years	-	Occlusal cant	Cephalogram	Pruzansky	Distraction osteogenesis
Jin et al. (2010)	China	59	-	-	-	-	-	Computed tomogram	-	-
Wu et al. (2010)	China	131	-	-	-	-	-	-	-	-
Aziza et al. (2011)	Saudi Arabia	17	-	-	-	-	-	-	-	-
Meazzini et al. (2012)	USA	14	-	-	5-7 years	-	Ramal height	Panoramic X-ray	Pruzansky	Distraction osteogenesis

Ohtani et al. (2012)	Japan	6	67	33	14-21 years	-	Occlusal cant plane, chin deviation	Cephalogram	Pruzansky	Distraction osteogenesis, bilateral sagittal split osteotomy, costochondral graft
Ongkosuwito et al. (2013a)	The Netherlands	75	48	52	4-29 years	-	Occlusal plane angle, palatal plane angle, mandibular plane angle,	Cephalogram	Pruzansky-Kaban	-
Ongkosuwito et al. (2013b)	The Netherlands	84	44	56	9 years		Ramus height	Orthopantomogram	Pruzansky-Kaban	-
Barisic et al. (2014)	Croatia, Northern Ireland, Denmark, England, Italy, Switzerland, Spain, The Netherlands, France, Norway, Ireland, Germany, Wales	321	59	41	-	1:26000	-	-	-	-
Park et al. (2014)	South Korea	100	65	35	11.6 years	-	-	3D-Computed tomogram	OMENS	
van Nunen et al. (2014)	The Netherlands	56	-	-	-	-	-	-	-	-
Beleza-Meireles et al. (2015)	Portugal	46	57	43	-	-	-	-	-	-
Silva et al. (2015)	Brazil	20	60	40	≤ 24 years	-	-	-	-	-
Tuin et al. (2015)	USA	105	58	42	-	-	-	radiograph	OMENS+	-
Lu et al. (2016)	Taiwan	7	43	57	12-16 years	-	Ramus height ratio, chin deviation	Orthopantomogram, cephalogram	Pruzansky-Kaban	Distraction osteogenesis
Bertin et al. (2017)	France	39	46	54	9-12 years	-	Chin deviation, occlusal plane cant, lip commissural line tilting	Posteroanterior cephalogram	Pruzansky-Kaban, OMENS	costochondral graft, vertical ramus osteotomy, genioplasty
Caron et al. (2017)	The Netherlands, UK, USA	755	54	46	0-25 years	-	-	Panoramic X-ray, computed tomogram	Pruzansky-Kaban, Phenotypic Assessment Tool − Craniofacial Microsomia	Distraction osteogenesis
Cohen et al. (2017)	Italy	89	57	43	0.2-46 years	-	-	Photographs, Orthopantomography, 3D-Computed tomogram	OMENS+	

Ko et al. (2017)	Taiwan	20	35	65	5-9 years	-	Ramus height, body length, ramus volume. condyle	Panoramic radiograph, 3D-Computed tomogram	Pruzansky	Distraction osteogenesis
Mehrotra et al. (2017)	India	7	86	14	18-26 years	-	Occlusal cant	Cephalogram. Computed tomogram	Pruzansky-Kaban	Distraction osteogenesis
Agurto Veas et al. (2018)	Chile	3	-	100	10-11 years	-	Occlusal plane cant, chin deviation, ramus height	Panoramic X-ray,		Distraction osteogenesis
Kaya et al. (2019)	USA UK (England) The Netherlands	8 9 5	-	-	6-19 years	-	Ramus height, body height, condyle, coronoid	3D-Computed tomogram	Pruzansky-Kaban	-
Luquetti et al. (2019)	USA	108	62	38	1-2 years	-	-	2D and 3D-Photographs	-	-
Renkema et al. (2019)	The Netherlands USA UK Canada	991	53	47	-	-	-	-	Pruzansky-Kaban, OMENS+	-
Korolenkova and Starikova (2020)	Russia	42	-	-	5-16 years	-	-	-		Distraction osteogenesis
Yang et al. (2020)	South Korea	249	55	45	7.07 ± 3.99 years	-	-	Panoramic X-ray, computed tomogram	Pruzansky-Kaban	-
Allam (2021)	Egypt	39	41	59	≤ 21 years	-	-	Panoramic x-ray, computed tomogram	OMENS+	-
Chen et al. (2021b)	Taiwan	36	47	53	17-31 years	-	Condylar width, condylar height, condylar volume, mandibular plane angle, chin deviation, occlusal plane cant, incisor deviation	Cone-beam computed tomogram	Pruzansky-Kaban	-
Johns et al. (2021)	USA South America (Colombia Peru)	94 75	59 61	41 39	0-18 years	-	-	OMENS Medical Photographs	-	-
Suppapinyaroj et al. (2021)	Taiwan	20	45	55	20.72 ± 2.96 years	-	Ramus height ratio, body length ratio	Cone-beam computed tomogram	Pruzansky-Kaban	Distraction osteogenesis
Dashti et al. (2022)	Iran	1	-	-	-	-	-	-	-	-
Renkema et al., (2022b)	The Netherlands	110	51	49	3-56 years	-	Chin point	Medical photographs, X-ray	Pruzansky-Kaban, OMENS	-
Kaprio et al. (2023)	Finland	40		-	7-17 years	-	Gonial angle, total mandible length, ramus height	Orthopantomogram	Pruzansky	-
Kuu-Karkku et al. (2023)	Finland	156	50	50	-	1:10000	-	-	-	-
Prasetyo et al. (2023)	Indonesia	1	100	-	-	-	-	Computed tomograph angiogram	-	-

Rachmiel et al. (2023)	Israel	15	60	40	14-25 years	-	Occlusal plane cant	Posteroanterior cephalogram	-	Distraction osteogenesis
Shetye et al. (2023)	USA	30	70	30	5-14 years	-	Ramus height, body length, total mandible length	Lateral cephalogram	Pruzansky	-
Zhang et al., (2023)	China	210	60	40	< 13 years	-	Ramus height, body length and hemimandibular volume	3D-Computerised Tomogram	Pruzansky-Kaban	-
Atiba et al. (2024)	South Africa	20	40	60	1-16 years	-	Ramal height, notch width, ramus width, gonial angle, body length, body height, total mandible length, chin point deviation, ramus index, body index	3D-Computerised Tomogram	Pruzansky-Kaban	-
Thomas et al. (2024)	Canada	11	36	64	-	-	-	-	-	-

HFM: hemifacial microsomia.

1.4 Problem Statement

The pioneering classification of HFM by Pruzansky (1969), modified by Kaban and colleagues, has paved the way for further classification, management, and treatment (Kaban et al., 1988). HFM is the most common congenital craniofacial deformity of the face after cleft lip and palate, with a prevalence rate of 1: 3,500-5,600 among the general population (Hartsfield, 2007). Mandibular deformity has been categorised as the hallmark of HFM. Still, advancement in its management has been expanded to include presenting anomalies in the orbit, mandible, ear, nerve, soft tissues, and extracranial structures (Vento et al., 1991, Horgan et al., 1995). However, divergent views exist regarding FA worsening by mandibular hypoplasia in patients with HFM (Renkema et al., 2022b, Shetye et al., 2023, Zhang et al., 2023). The treatment includes mandibular distraction, orthognathic treatment, costochondral graft, and soft tissue reconstruction (including pedicled flap, microvascular free tissue transfer, structural lipofilling, alloplastic implant, and functional reconstruction) (Sinclair et al., 2019, Meazzini et al., 2020, Liu et al., 2022).

Psychosocial stigma and body image awareness due to structural and functional impairment may necessitate the need for intervention to HFM in children (Ascenço et al., 2014). Surgical correction of bony hypoplasia improves secondary defects and better body image development (Kaban et al., 1988). The growing patient requires mandibular distraction treatment, while the older patient requires orthognathic treatment (Wittenborn et al., 2004, Meazzini et al., 2020). These treatments do not address soft tissue contour defects.

Serial autologous fat transfer can be performed concurrently with other HFM treatment modalities on patients with mild to severe defects. Hence, patients can access earlier interventions to improve facial contour (Tanna et al., 2011).

Studies from different countries utilise AFG to correct soft tissues in HFM among children (Tanna et al., 2011, Ohtani et al., 2012, Sinclair et al., 2019). However, there is a lack of information regarding complete reports on HFM from the South African population.

HFM presents a significant challenge in the field of craniofacial surgery, particularly in South Africa, where few reports on the anatomical features of the hypoplastic mandible in the affected individuals (Losken et al., 1983, Preston et al., 1985, Atiba et al., 2024). This knowledge gap has contributed to the lack of effective treatment specific to the needs of South African patients. Furthermore, AFG has shown potential in managing FA linked with HFM, but its effectiveness and suitability in South Africa have not been documented (Losken et al., 1983, Preston et al., 1985, Atiba et al., 2024). Therefore, there is a need for an in-depth anatomical exploration of the hypoplastic mandible in patients with HFM in South Africa, aimed at elucidating patterns of FA, whether it is progressive or remains the same with age, defining clinical presentations, and assessing the potential of AFG treatment. Addressing these gaps in

knowledge is crucial for improving diagnostic precision and optimising treatment outcomes for individuals impacted by HFM in South Africa (Allam, 2021, Atiba et al., 2024).

1.4.1 Justification of Study

Hemifacial microsomia (HFM) is a congenital anomaly in which one-half of the face does not develop normally (Young and Spinner, 2022). Facial asymmetry (FA) classification includes congenital, acquired, or developed from an unknown aetiology (Cheong and Lo, 2011). HFM is one of the congenital conditions responsible for FA. Asymmetry of the mandibles could involve the condyle, the ramus, the symphysis, and the body, which may result in size, volume, or position changes (Renkema et al., 2022b, Shetye et al., 2023, Zhang et al., 2023). A deformed mandible may accentuate FA in HFM (Taiwo, 2020). Craniofacial growth in the affected patients depends on the extent of the deformity (Young and Spinner, 2022). Regarding the progression of FA in HFM, some literature has suggested that FA increases with time, which is progressive in nature (Shetye et al., 2023, Zhang et al., 2023). Other literature has indicated that FA remains constant with time in HFM, which is non-progressive (Pluijmers, 2019, Renkema et al., 2022b). Based on functional treatment types, the Pruzansky-Kaban classification of the mandible is grouped as mild (Types I and IIA) or severe (Type IIB and III) (Chen et al., 2021b). The growth pattern in the mild deformity appears to be non-progressive, while data from patients with HFM with severe deformities show otherwise (Chen et al., 2021b, Renkema et al., 2022b, Zhang et al., 2023). However, there is a lack of literature on FA due to hypoplastic mandibles in patients with HFM in the South African population. Only two South African studies have reported on surgical intervention in patients with HFM (Losken et al., 1983, Preston et al., 1985). Understanding FAs and phenotypic features in HFM is relevant to diagnosing and managing patients with HFM (Liu et al., 2022). A comprehensive investigation into AFG treatment outcomes in South African patients can yield valuable insights into its effectiveness and help refine treatment protocols. The findings from this study can contribute to the advancement of craniofacial surgery, both in South Africa and globally.

1.4.2 Research Question

1. What is the current understanding regarding whether FA in patients with HFM progresses or remains constant over time?
2. What parameters are used to evaluate FA progression in patients with HFM?
3. What is the spectrum of clinical presentation of HFM in a South African population?
4. What is the association between the affected and contralateral sides (A/C) ratio in HFM in South Africa?
5. What are the other benefits of AFG treatment in the hypoplastic mandible apart from lipofilling of soft tissues in growing children?

1.5 Aim

This study aims to document a detailed account of FA resulting from the presence of a hypoplastic mandible in HFM via clinical and morphometric analyses. Moreover, it aimed to assess the use of AFG camouflage in FA in a South African population.

1.6 Objectives

1. To evaluate the current literature available on the progression of FA in HFM.
2. To document the clinical presentation of HFM and other associated systemic defects in a South African population.
3. To describe the detailed anatomy of mandibular hypoplasia in HFM in the South African population.
4. To investigate the role of AFG in the hypoplastic mandible in growing patients with HFM.

1.7 General Overview of Research Methodology

1.7.1 Study Design, Population and Size

To achieve the objectives of this study, specific study design approaches were used to answer the research questions. In addition, population and sample size depended on case availability concerning a particular design approach for each objective.

In chapter three (achieving objective two), a retrospective study identified patients with HFM treated at the Department of Plastic and Reconstructive Surgery, Inkosi Albert Luthuli Central Hospital, from June 2003 to December 2022. Patients were diagnosed by a craniomaxillofacial surgeon through clinical presentation and confirmed by plain radiograph or computed tomography (CT) images and assessed using OMENS+ classification (Horgan et al., 1995). A differential diagnosis was made to rule out other phenotypic similar syndromes of first and second pharyngeal arches, such as Treacher-Collins, branchio-oto-renal, Miller-Dierker CHARGE, and Parry Romberg. The author retrieved thirty-five patients' medical records from the hospital's electronic archive, but ten were excluded due to the incomplete records. Charts, photographs, and radiographs were reviewed to document demographic data and clinical findings in patients presented with HFM. The patient's charts were reviewed for age, sex, laterality, deformity severity, and associated craniofacial and extra-craniofacial anomalies using OMENS+ classification (Horgan et al., 1995). The photographic evaluation included analysis of standardised patient photographs and reviewing any previous photographs during facial growth phases (if available). Imaging studies, including cephalometric films, panoramic films, and CT, were reviewed and analysed to document skeletal elements of the deformity and underdevelopment of soft tissues. Imaging studies for suspected extracraniofacial anomalies (e.g. echocardiography, abdominal ultrasonography, brain magnetic resonance imaging (MRI), CT spine, etc.) were also reviewed. The authors obtained written informed consent or consent permission for each patient in this study and

informed consent from all subjects or their legal guardians to publish images in an online open-access publication. All patients with HFM were seen and followed by a multidisciplinary craniofacial team.

In chapter four (achieving objective three), a serial retrospective study was conducted using two-dimensional preoperative computed tomography (CT) and three-dimensional CT head scans acquired from the Departments of Plastic and Reconstructive Surgery database at the Inkosi Albert Luthuli Central Hospital, Durban, South Africa. This study comprised scans of 20 consecutive patients (age range of 1-16 years) with HFM presented to the craniofacial unit at Inkosi Albert Luthuli Central Hospital between September 2009 and November 2021. They were grouped according to the Pruzansky-Kaban grading pattern into mild (Types I and IIa) and severe (Types IIb and III) (Chen et al., 2021b). We selected patients with unilateral involvement for inclusion in the study. They were categorised into mild or severe groups by the Pruzansky-Kaban grading and into three age-dependent groups (1–5, 6–12 and 13–19 years old). We investigated the association between the mandibular ramus height (MRH) and mandibular ramus width (MRW), mandibular notch width (MNW), mandibular body length (MBL), mandibular body height (MBH), and chin point deviation (CPD) in patients with HFM. The affected side to the contralateral side values (A/C ratio) of linear measurements were also calculated. Informed consent or assent was obtained from patients before getting image data.

In chapter five (achieving objective four), a longitudinal study consisted of ten patients (age range: 4-16 years) diagnosed with HFM. Pruzansky-Kaban classification was used to grade the severity of HFM. The first group (AFG group) of five patients (age range: 2-12 years; mean age: 5.8±3.89 years) were classified as mild (Type I and IIA) according to Pruzansky-Kaban grading and received AFG treatment only. The second group (MDO+AFG group) of five patients (age range: 5-16 years; mean age: 8.8±4.32 years) was classified as severe (Type IIB) according to Pruzansky-Kaban grading. The second group received MDO (through oblique osteotomy overcorrection of occlusion with univector external distractors) for functional impairment intervention before AFG. In the MDO+AFG group, mandibular distraction was performed two years before AFG. CT scans of the mandible were performed before the first fat transfer and after the last transfer. These scans were compared and analysed. The parameters included MRH, MRW, MBL, MBH, CPD and occlusion plane angle (OPA). Fat harvesting was performed from preferred donor sites like the lower abdomen, outer-medial thighs, and gluteal region under general anaesthesia. Coleman's technique with centrifugation was used to harvest and process fat grafts, ensuring good-quality purified fat. Fat transfer was done using lipo-injection cannulas in small aliquots to various layers. Patients were followed up postoperatively at one week and 1, 3, 6, and 12 months. Further fat transfers were decided based on physical examination findings. Of the ten patients, 2 received one episode of AFG, 5 received two episodes of AFG, 2 received three episodes of AFG, and 1 received four episodes of AFG. CT scans were conducted at least three months after the last fat transfer to assess outcomes.

1.7.2 Rationale for the use Pruzansky-Kaban or OMENS+ classification in the proceeding experimental chapters

The Pruzansky-Kaban classification provides a detailed assessment of the mandibular deformity, which is often central to HFM management. The OMENS+ classification offers a broader and more comprehensive description of the entire craniofacial spectrum of HFM, including associated extracraniofacial anomalies. Both classifications are valuable tools for diagnosis, treatment planning, and research in HFM.

1.7.3 Ethical Consideration

This study was conducted with the approval of the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (Ref No: BREC/00004225/2022) and the Department of Health in the Province of KwaZulu-Natal (NHRD Ref.: KZ_202206_031). All methods were carried out following the University of KwaZulu-Natal standard-approved guidelines and regulations and all experimental protocols per the declaration of Helsinki (WMA, 2013).

This study also maintained 100% confidentiality and de-identification by documenting only patients' age, sex, image, and population grouping. Other health information obtained was strictly used for this study only. A password access control was created on the workstation used for this study to protect all images' information and data. The researchers implemented a plan to destroy images and electronic data obtained from the radiology department of this hospital five (5) years after completing the study.

1.7.4 Study Sample Criteria

Inclusion Criteria: CT images clearly showing HFM (defects on the orbit, mandible, ear, nerve, and soft tissue structures) on the unilateral or bilateral side and scans with no motion artefacts.

Exclusion Criteria: CT images not clearly showing hemifacial microsomia (defects on the orbit, mandible, ear, nerve, and soft tissue structures) on the unilateral or bilateral side and scans with motion artefacts.

1.7.5 Core Technology

Computed tomography scanning offers the greatest structural definition of any available imaging modalities using X-ray technology and advanced computer analysis to create detailed body pictures (Mariam, 2020). This cross-sectional scanning method allows for the visualisation at different levels or slices of the temples or sides of the skull bone using a rotating X-ray beam. When a patient is scanned, a volume of data is captured. This captured data allows for linear measurements, volumetric surface rendering, multiplanar reconstruction, 3D reconstruction, and visual analysis at coronal, sagittal, and axial planes at any level. The CT images used for this study were from these modern CT scanners, which can produce numerous slices from a single patient scan at 0.625-3.00 mm thickness.

1.7.6 Imaging Protocol

Image Acquisition and Analysis Axial CT scans of selected patients were retrieved from the hospital's Picture Archiving and Communication System (PACS) and saved in Digital Imaging and Communication in Medicine (DICOM) format. These CT images were acquired routinely with either a 128-slice SOMATOM Definition AS scanner or a SOMATOM Definition Flash CT Scanner (Siemens Healthineers, Forchheim, Germany, 2013). Before the image acquisition, the patients were positioned in a supine position using 140 kV, modulated mAs ranging between 280 – 400 mA (beam collimation 64 × 0.625; rotation 0.5 sec) with 30% dose reduction and ASIR-V application in a bony algorithm with a window width of >3000 hU and a window level of 500 hU. The axial view was reconstructed parallel to the orbito-meatal line using a slice thickness of 0.625 mm, detector coverage of 20mm, and a PITCH of 0.5. The voxel size of images is isotropic.

1.7.7 Method of Data Collection

The standard protocol was to perform a coronal and sagittal reconstruction on the bone and soft tissue settings. The slice thickness of the scans of patients with HFM ranged from 0.6–3 mm with a 0.3 mm increment. The low resolution did not affect the data interpretation. The acquired axial CT images were reformatted into sagittal and coronal planes in a three-dimensional (3D) multiplanar reconstruction view and analysed using the Horos Open-Source Medical Image Viewer software version 3.3.6 (Horos Project, Annapolis, MD). The Horos software automatically calibrated the CT scan images and manually verified the calibration. Computed tomography scans were aligned in the orbitomeatal and Frankfort-horizontal planes in axial and sagittal planes, respectively. Linear measurements were performed on the bone window using length and angle tools. Measurements were taken three times to ensure accuracy and reliability. A specialist radiologist and an anatomist interpreted the images.

1.7.8 Scientific Validity

Inter-examiner reliability was analysed to assess the reliability of the measurements. Initially, one observer performed the measurement according to the previously standardised specific mandibular landmarks (Polley et al., 1997, Renkema et al., 2022b, Shetye et al., 2023, Zhang et al., 2023). Other two independent researchers performed repeated measurements at intervals to ensure the accuracy and reproducibility of the measurements in the study. The inter-researcher reliability was assessed by the intra-class correlation coefficient (ICC). The mean values were finally calculated for further analysis. The results for each inter-examiner reliability test are provided in their corresponding manuscripts.

1.7.9 Data Analysis

The inter-examiner assessment was measured to ensure accuracy. Normality was tested using the Shapiro–Wilk test, and homogeneity of variance was tested using the Levene test for all quantitative data. When the data express normality and homogeneity of variance, independent *t*-tests were used to assess the differences in measurements by severity; paired *t*-tests were used to compare the differences

between the affected and contralateral sides in the same mandible ramus and body; ANOVA tests were used to compare the differences between different age groups. Other tests were specified in each manuscript. Nonparametric tests were used when data failed to meet normality test and homogeneity of variance ($P > 0.05$). The categorical variables were described as counts and percentage frequencies. A $P < 0.05$ value was considered a statistical difference. All statistical analyses were completed using SPSS 28.0 (IBM Corp., Armonk, NY, USA).

1.8 Overview of thesis

This thesis is written and submitted in manuscript form. As recommended by the University of KwaZulu-Natal College of Health Sciences guidelines, this thesis comprises six (6) chapters and appendices as follows:

Chapter 1: This provides information on the background of the study, the reviewed literature, the problem statement and research gap, the study justification, the research questions, the research objectives, the general overview of research methodology, the overview of the thesis, and the references.

Chapter 2: This chapter contains the first manuscript from the study and presents results for Objective 1. This is a scoping review of studies conducted on the progression of FA in patients with HFM. An assessment of the included studies revealed that FA does not increase with age in HFM. Hence, FA is non-progressive in patients with HFM. **Peterson Makinde Atiba**, Bukola Rukayat Omotoso, Anil Madaree, and Lelika Lazarus authored this manuscript, and it has been published by **Oral and Maxillofacial Surgery;** https://doi.org/10.1007/s10006-024-01276-5.

Chapter 3: This chapter contains the second manuscript from the study and presents results for Objective 2. There is a high degree of variability in the clinical presentation of HFM in the South African population, distinguishing it from the international population. A multidisciplinary approach is required for its treatment and management. **Peterson Makinde Atiba**, Anil Madaree, and Lelika Lazarus authored this manuscript, and it has been accepted by the **Journal of Plastic Surgery and Hand Surgery** (**Manuscript number:** JPHS-D-2024-0028).

Chapter 4: This chapter contains the third manuscript from the study and presents results for Objective 3. Mandibular asymmetry is more noticeable in patients with HFM between 13 and 19 years old. The A/C ratio of the MRB did not worsen with different age groups and severity grading in this study. Hence, clinicians should postpone surgery until patients with HFM attain skeletal maturity. **Peterson Makinde Atiba**, Dolongo Onyangunga-Kaban, Anil Madaree, and Lelika Lazarus authored this manuscript, and it has been published by **Translational Research in Anatomy;** https://doi.org/10.1016/j.tria.2024.100291.

Chapter 5: This chapter contains the fourth manuscript from the study and presents results for Objective 4. In severe HFM, MDO may be the initial procedure of choice. AFG can be used a few years later to improve symmetry and deformity further, mainly in the MBL. In the mild group, where MDO is not considered, AFG has significantly improved MRW, MRH, CPD and OPA symmetry and deformity. **Peterson Makinde Atiba**, Okikioluwa Stephen Aladeyelu, Dolongo Onyangunga-Kaban, Anil Madaree, and Lelika Lazarus authored this manuscript, and it is under peer review by the **Plastic Surgery Journal; manuscript number (Manuscript number:** PSG-24-0209**).**

Chapter 6: This chapter contains the synthesis, conclusion, recommendation, suggestions for future research, limitations, a summary of findings and contribution to knowledge, and references.

Appendices: This contains the ethical and hospital approvals, data collection sheet, and the informed consent form.

Finally, as per the format required by the University of KwaZulu-Natal, aspects of the sample demographics and methods had to be reported in each manuscript. However, the specific methodology employed for each aspect of the study is contained in the respective manuscripts to address the objectives. All manuscripts were prepared according to the guidelines of the respective journals.

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BRIDGING TEXT
FROM CHAPTER ONE TO TWO

The previous chapter highlighted the definition of HFM, different theories proposed to elucidate the aetiology and pathogenesis of this anomaly, diverse classifications developed to cover the pattern of severity from one individual to another (this includes the skeletal and soft tissue involvements), and the treatments approach with emphasis on AFG. The mandible is identified as the structure typically impacted by HFM. The presence of the mandible deformity increases FA in patients with HFM. However, there is a debate on the progression of FA in patients with HFM as either progressive or non-progressive with age. The next chapter is a scoping review of the literature on the progression of FA due to deformed mandibles in patients with HFM**,** highlighting its relationship with sex, population, and age group.

The review in chapter two, entitled **"*Hemifacial microsomia: A scoping review on progressive facial asymmetry due to mandibular deformity*,"** was submitted to Oral and Maxillofacial Surgery on 17th February 2024 and published on 02nd July 2024. (Manuscript and references are presented according to the journal's specification).

CHAPTER TWO

MANUSCRIPT ONE

Hemifacial microsomia: A scoping review on progressive facial asymmetry due to mandibular deformity

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REVIEW

Hemifacial microsomia: a scoping review on progressive facial asymmetry due to mandibular deformity

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Abstract

Purpose This scoping review explores various parameters of the mandible in progressive facial asymmetry (FA) in hemifacial microsomia (HFM) patients, highlighting its relationship with sex, population, and age group.

Methods The review was based on a comprehensive search of PubMed, EBSCOhost, and Web of Science. Eligible studies that met the inclusion criteria form part of the selection study. The included studies were appraised using screening and quantitative criteria of mixed-method appraisal tools. The authors utilised a pre-set data extraction form to obtain information from the included studies.

Results Eleven studies met the inclusion criteria. The mandible parameters used were angular measurements, chin point, ramal height, body length, and total length. There was no relationship between FA and sex in HFM patients in the included studies. Most of the studies were comprised of European participants (55%), followed by Americans (36%) and Chinese (9%). The age groups included in the selected studies were categorised as dentition age (18%), early-to-middle childhood (18%), and varied ages (64%). The data presented in this review only pertains to the anomalous characteristics recorded on the affected side in HFM patients. No concomitant control data was recorded in this review.

Conclusion An assessment of the included studies revealed that FA does not increase with age in HFM. Hence, FA is non-progressive in HFM patients. This information is relevant to diagnosing and managing HFM patients. More reports are needed on the progression of FA in HFM patients.

Keywords Hemifacial microsomia · Progressive facial asymmetry · Mandible · Mandibular morphometrics

Abbreviations

FA	Facial Asymmetry
HFM	Hemifacial Microsomia
MMAT	Mixed Method Appraisal Tool
OMENS (+)	Orbit distortion, Mandible hypoplasia, Ear anomaly, Nerve involvement, Soft tissue deficiency, Extracraniofacial defects
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-analyses
SAT	Skeletal Auricular Soft tissue
USA	United States of America
WHO	World Health Organization

Introduction

Hemifacial microsomia (HFM) is a congenital anomaly in which one-half of the face does not develop normally. HFM is derived from the first and second pharyngeal arches malformation [1]. It is the second most prevalent congenital craniofacial defect after cleft lip and palate (1: 3,500-5,600 in the United States of America) [2]. It has been speculated to be due to genetic, maternal, and environmental conditions leading to stapedial artery injury (replaced by an external carotid system in adults), dysgenesis of Meckel's cartilage and aberrant migration of neural crest cells [3]. This defect

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is more evident in the jaw and ear areas, though the involvement of the eye, cheek, nerve, soft tissue, other cranial parts, and neck may accompany it. HFM can also be described as skeletal or soft-tissue defects or a combination of skeletal and soft-tissue defects [4]. Although HFM implies facial involvement only, individuals with HFM often have associated extracranial defects such as neurological, cardiac, genitourinary, pulmonary, gastrointestinal, and skeletal malformations [5–9]. In a clinical presentation, mandibular hypoplasia has been the cornerstone of this deformity with unilateral or bilateral microtia. Craniofacial growth in the affected patients depends on the extent of the deformity [1]. Mandibular size, shape, and location to the maxilla and base of the skull are determined by bone deposition and resorption on the periosteal and endosteal surfaces [10, 11]. The increase in vertical height of the ramus and its posterior movement occurs due to bone deposition on the posteroinferior surface and resorption on the anterior surface [10]. Resorption occurring along the anterior border of the ramus also adds to the length of the mandibular body [10, 11]. The mandibular body, the arch's shape and width are determined by resorption on the medial surface and deposition on the lateral surface [10]. The mandibular skeletal midline deviates to the affected side with unilateral growth impairment [11].

During the 4th week of embryonic life, distinct face development is identifiable from five facial primordia structures surrounding the stomodeum [12–14]; these include one frontonasal prominence and paired maxillary and mandibular processes [15, 16]. The latter two processes originate from the first branchial arch [16, 17]. The innervation to the face arises from the first and second pharyngeal arches, while the blood vessels are derived from the third aortic arch [17]. All these develop to form the structures of the future face [16, 17]. Disruption in the migration and differentiation pathway of the pluripotent neural crest cells results in congenital abnormalities [12, 14].

Facial asymmetry (FA) classification includes congenital, acquired, or developed from an unknown aetiology [18]. HFM is one of the congenital disabilities responsible for facial asymmetry. Asymmetry of the mandibles could involve the ramus, the condyle, the body, and symphysis, which may result in size, volume, or position changes. Skeletal deviation equal to or greater than 4 mm is considered asymmetry noticeable in an individual's face, while a skeletal deviation less than 4 mm is identified as mild and unnoticeable [19, 20]. In addition to skeletal deformity, soft tissue thickness also influences facial disproportion; hence, a deviation equal to or greater than 2 mm of the soft tissue is marked as facial asymmetry [21, 22].

Some authors hypothesised that mandibular growth defect contributes to FA in HFM patients [23]. Other authors have suggested that mandibular growth defect does not influence FA in HFM patients. The indicators of FA include changes in the maxillary occlusal plane, piriform rim angle, intergonial angle, and chin point deviation [24, 25]. Hence, there are contrasting data on the influence of mandibular growth defects on FA in HFM.

Previous reviews focused on FA, temporomandibular disorders, and mandibular asymmetry. However, only a few discussed the progression of FA due to mandibular disproportion (asymmetry) in HFM patients [23, 26–29]. The knowledge of skeletal and soft tissue defects is fundamental in the reconstructive approach to facial surgery [30, 31]. This review aims to map out various parameters of the mandible (i.e., the deviation of occlusal plane, piriform angle, intergonial angle, chin point, mandibular ramus height, body length and total mandibular length) in the progression of FA in HFM patients, highlighting its relationship with sex, population, and age group.

Materials and methods

A scoping review based on the framework developed by Arksey and O'Malley [32] and further expanded by Levac et al. [33] was used in this analysis. The literature on the progression of FA due to the mandibular morphology and disproportion (asymmetry) in HFM patients was extensively searched. The following steps were taken in the search process: identifying the research question, identifying relevant studies, study selection, charting the data, and collating, summarising, and reporting the results.

Research question

What were the available studies on the progression of FA due to a deformed mandible in HFM patients?

Sub–question

a. In which countries were these studies completed?
b. What age range or grouping was used to report these studies?
c. To determine facial asymmetry, what parameters were used (i.e., changes in the maxillary occlusal plane, piriform rim angle, intergonial angle, chin point deviation, mandibular ramal height, mandibular body length, total mandibular length)?

Search strategies

A systematic search of the literature was conducted on PubMed (National Centre of Biotechnology Information, Bethesda, Maryland, United States), EBSCOhost (EBSCO Information Services, *Ipswich*, Massachusetts, USA), and Web of Science (Clarivate Analysis, PLC, Philadelphia, Pennsylvania, USA). The keywords used for this search include hemifacial microsomia, progressive facial asymmetry, mandibular asymmetry, mandibular growth restriction, mandibular hypoplasia, facial asymmetry, and mandibular morphology. These keywords were used in combination with the Boolean term (AND, OR), such as "hemifacial microsomia AND facial asymmetry" OR "hemifacial microsomia AND mandibular growth restriction" OR "hemifacial microsomia AND mandibular growth" OR "hemifacial microsomia AND mandibular hypoplasia" OR "hemifacial microsomia AND mandibular asymmetry" OR "hemifacial microsomia AND mandibular morphology" OR "facial asymmetry AND mandibular morphology" OR "facial asymmetry AND mandibular hypoplasia" OR "hemifacial microsomia AND progressive facial asymmetry" OR "progressive facial asymmetry AND mandibular asymmetry". An initial limited search of PubMed was completed by analysing the text words in titles, abstracts, and index terms used to describe articles (see Appendix I). A second search using identified keywords and index terms was used across all databases. The third step search was also conducted across all databases using a reference list of all identified articles. The most recent search of this review was accessed on 31st December 2023.

The scoping review results were reported using the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-analysis) guidelines for Scoping review.

Inclusion criteria

The inclusion criteria included studies on the progression of FA in HFM. Original articles on mandibular asymmetry, morphology, and hypoplasia between 1969 and 2022. Articles, reports, and books available in English, articles already translated into English, and articles in dual languages formed part of this review.

Exclusion criteria

Research articles, reviews, and reports on the progression of FA in HFM before 1969 were excluded during study selection (Pruzansky reported the first study on mandibular hypoplasia classification in 1969). Reviews of HFM in progressive FA were excluded. Studies not primarily on the progression of FA in HFM and animal-based HFM studies did not form part of this review.

Study selection

A set of questions aligned with the study's objective assessed the relevant studies identified during the literature search. Following the search, all identified citations were collated and uploaded into EndNote 20 (Clarivate Analytics, PA, USA), and duplicates were removed. Study selection was made by two authors (PMA, BRO), who screened titles and abstracts of all retrieved studies to assess eligibility. When eligibility could not be determined, full articles were retrieved.

Quality appraisal

The quality appraisal of the included studies was conducted using screening criteria for all studies (Table 1). Quantitative descriptive criteria of the Mixed Methods Appraisal Tool (MMAT)-Version 2018 were used for the included studies [34]. The appraisal was done by colleagues (OA and OF), not part of this review. A score of 20% is given when an eligible study fulfils one quantitative criterion, 40% if it fulfils two criteria, 60% if it fulfils three criteria, 80% if it fulfils four criteria, and 100% if it fulfils all quantitative criteria.

Table 1 Mixed Methods Appraisal Tool (MMAT), version 2018 indicators for screening questions and quantitative descriptive studies (adapted from Hong et al. [34])

Category of study designs	Methodological quality criteria
Screening questions	*1. Are there clear research questions or objectives?*
	2. Do the collected data allow to address the research questions?
Quantitative descriptive studies	*1. The sampling strategy is relevant to address the research questions*
	2. The sample is a representative of the population study
	3. Appropriate and validated measurements
	4. Low risk of nonresponse bias
	5. Appropriate statistical analysis was done to answer the research question

Note: Studies were deemed acceptable when the first two screening questions for all study types and at least one of the indicators in the category of the study designs were met

Data extraction and analysis

A data extraction form was used to extract details on characteristics of the included studies by two authors (PMA, BRO), such as author name, date of publication, population, sample size, male (%), female (%), age range, aim of the study, methodology, and significant findings. The extraction form was subjected to review. Co-authors LL and AM independently used this form to extract data from all eligible studies. Microsoft Excel 2019 was used to compile all data on a spreadsheet. The content analysis of each article included in the review was done.

Results

Description of included studies

A total of 3491 articles were identified during the literature search, including research papers, reports, and books. Two thousand four hundred and thirty-two duplicates were removed. After screening titles and abstracts, 1015 articles were excluded based on the exclusion criteria. Forty-four full-text articles that met the eligibility criteria were reviewed. Thirty-three articles were excluded because they lacked evidence on the progression of FA, although they showed evidence of mandibular morphology, morphometrics, asymmetry, and surgical intervention. However, eleven articles were eligible and included in this review (Fig. 1).

Table 2 summarises the included studies and their significant findings. Table 3 shows the frequency distribution of FA parameters in the included studies. Figure 2 shows the level of knowledge of included studies on the progression of FA in relation to Pruzansky-Kaban type classification, dentition age range and mandibular morphometrics. Figure 3 illustrates an assessment of all the included studies based on the facial asymmetry parameters in hemifacial microsomia patients. Most (55%) of the included studies were conducted in Europe [25, 35–39], 36% were conducted in the United States of America [24, 40–42], and 9% were conducted in the People's Republic of China [43]. The largest sample size is 210 [43], while the lowest is 7 [40].

All included studies were observational; 82% were retrospective studies [24, 25, 36, 37], while 18% were prospective studies [35, 38]. Only three of the included studies (27%) were cross-sectional [24, 39, 43], while the remaining (82%) were longitudinal studies [25, 35–42] (Table 2). A total of 67% of the included studies described sex in their report [25, 36–41, 43]. Age grouping varied among the included studies; two (18%) utilised dentition age grouping [24, 39], two (18%) utilised infancy to childhood [41, 43], while others (64%) used varied age grouping [25, 35–40, 42]. Three (27%) of the included studies suggested the progression of facial asymmetry [24, 42, 43], while the remaining (73%) suggested that FA remains constant in HFM patients [25, 35–41].

The methodological quality of the included studies

The eleven included studies were deemed good quality as they answered the first two screening questions and fulfilled at least three quantitative criteria of MMAT. Regarding the quantitative criteria, one study met three criteria- 60% and ten met four criteria- 80% (Table 2).

Table 3 shows the frequency distribution of FA parameters in the eleven included studies. The more common parameters used in the included studies were: 64% used ramus height [35, 36]. 27% used chin point [25, 40, 41], 27% used occlusal plane angle [24, 37, 38], 36% used gonial/intergonial angle [24, 39–41], 27% used total mandibular length [39–41], 27% used mandibular body length [41–43]. In addition, a few of the included studies discussed the treatment approach and outcome (Table 4).

Studies suggesting evidence of progressive facial asymmetry in relation to Pruzansky-Kaban type classification, dentition age range and mandibular morphometrics

Ten (91%) of the included studies utilised either Pruzansky [35, 39–42] or Pruzansky-Kaban [24, 25, 36, 37, 43] types to classify the mandibular asymmetry in HFM. Two (18%) of the included studies utilised dentition age [24, 39], two (18%) of the included studies utilised infancy to childhood stage [41, 43] for age grouping. The majority (91%) of the included studies showed evidence of knowledge of mandibular morphometry in HFM patients [24, 25, 35–37].

Assessment of all the included studies based on their conclusion on the progressiveness of FA in hemifacial microsomia patients

An assessment of mandibular morphometric parameters was used to determine the progressiveness of FA in the HFM population in all (100%) of the included studies [24, 25, 35–39]. An increase in the values of the parameters is associated with progressive FA and was denoted as 'Yes' (Fig. 3). These include occlusal plane/angle [24], gonial/intergonial angle [24], piriform angle [24], ramus height [42, 43], mandibular length [42], and body length [42, 43].

A decrease or no change in the parameters' values is associated with FA's non-progressiveness and was denoted as 'No' (Fig. 3). These include chin point [25, 38, 41], gonial/

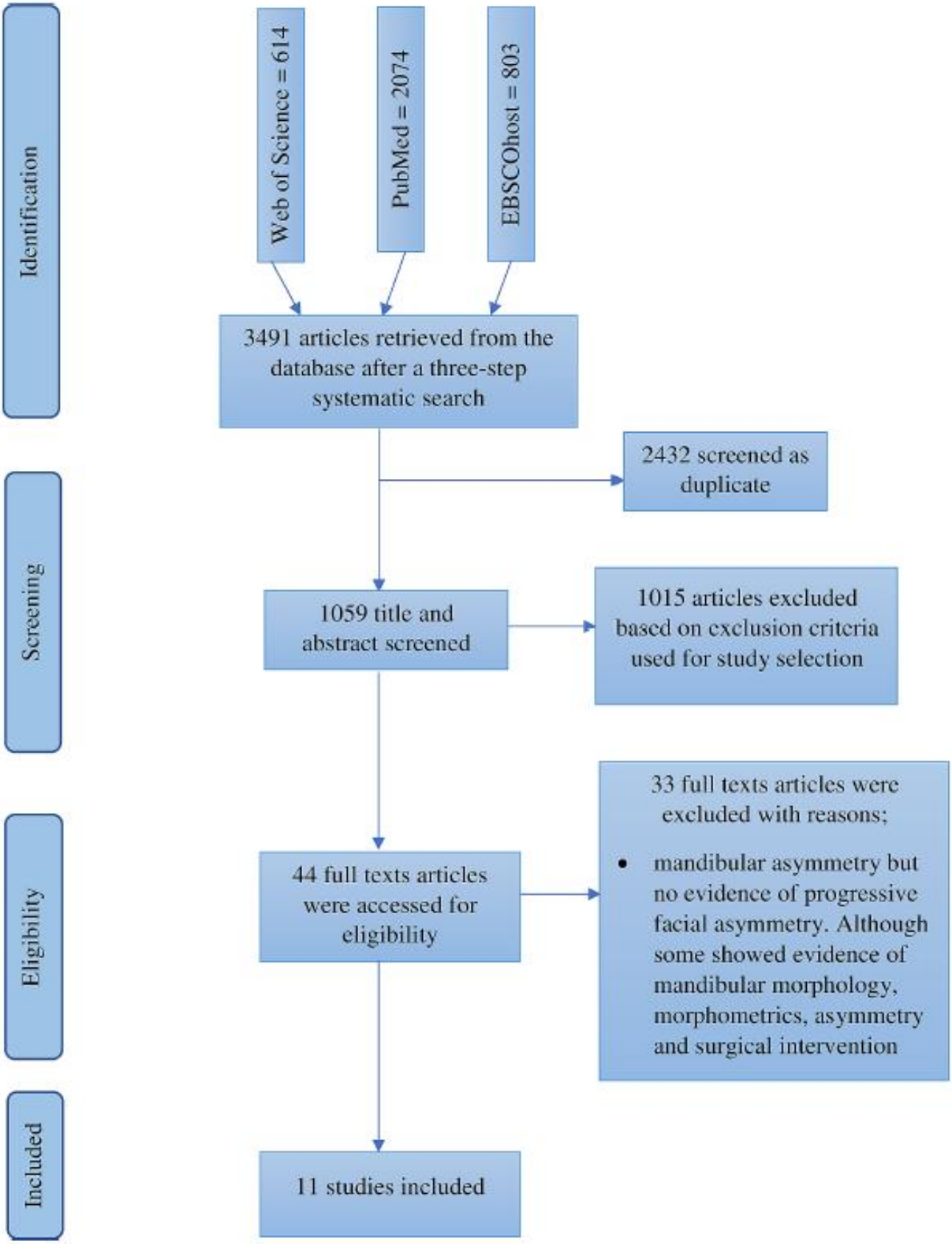

Fig. 1 Flow diagram of study selection

Table 2 Characteristics of included studies

Author (Year)	Population	Sample size	Male %	Female %	Age Range	Aim of Study	Methodology (Cross-sectional/ Longitudinal study)	Major Finding	Progressive Facial asymmetry (Yes/No)	MMAT Score
Runeet al., 1981	Sweden	11	64	36	3–14 years	The displacement of the mandible and the maxillary bones with growth was studied in 11 children with HFM.	Roentgen stereophotogrammetry with metallic implants was utilised to record growth relative to the frontal bone. (Longitudinal study)	No correlation was found between the extent of the mandibular deformity, as seen on orthopantomograms, and the displacement of the mandible with growth.	No	80%
Polley et al., 1997*	USA	26	58	42	3.1–16.7 years (mean age)	To analyse mandibular skeletal growth longitudinally in unoperated hemifacial microsomia patients from childhood to adolescence and determine whether asymmetry improves, remains constant or progresses during development.	Posteroanterior cephalograms were used to evaluate each patient's horizontal and vertical mandibular asymmetry. (Longitudinal study)	The skeletal mandibular asymmetry in hemifacial microsomia is not progressive, and the growth of the affected side in these patients parallels that of the non-affected side. The grade and the side of the mandibular deformity did not progress with time.	No	80%
Kusnoto et al. 1999*	USA	7	66	33	14–19 years	To analyse the longitudinal growth patterns of unoperated patients before and after distraction osteogenesis in three dimensions.	Lateral and posteroanterior cephalograms were used preoperatively for nine years. Computerised three-dimensional models were constructed from lateral and posteroanterior using a vector intercept algorithm. (Longitudinal study)	Unoperated patients with HFM maintain asymmetric facial proportions and do not worsen with time. There was a reversal to the initial presentation 18 months after distraction osteogenesis.	No	60%
Kearns et al., 2000*	USA	67	-	-	Deciduous dentition: 3.4–4.1 years (mean age) Mixed dentition: 8.0-8.6 (mean age) Permanent dentition: 21 (mean age)	To test the hypothesis that facial asymmetry in HFM is a progressive deformity.	A retrospective review of medical records and posteroanterior cephalometrics radiographs in HFM patients. Mandibular asymmetry was determined by measurement angles between the actual horizontal plane and the following planes: piriform rim, maxillary occlusal plane, and intergonial angle. (Cross-sectional study)	The data from the study suggested that facial asymmetry is progressive by increasing the piriform rim, maxillary occlusal plane, and intergonial angles. Surgical correction is advocated during the mixed dentition stage.	Yes	80%

Table 2 (continued)

Author (Year)	Population	Sample size	Male %	Female %	Age Range	Aim of Study	Methodology (Cross-sectional/ Longitudinal study)	Major Finding	Progressive Facial asymmetry (Yes/No)	MMAT Score
Meazzini *et al.*, 2012^a	Italy	22	-	-	5–7 years	To compare children with HFM, a group was treated with distraction osteogenesis (either during deciduous or mixed dentition), and another group was not treated until the completion of growth.	Mandibular vertical changes were measured on panoramic radiographs taken at different points in time. (Longitudinal study)	Untreated hemifacial microsomia patients maintained facial proportions throughout development. Esthetics and psychological gains were observed but lost due to inherent genetic factors. There was a relapse of facial asymmetry at 12 months of treatment.	No	80%
Ongkosuwito *et al.*, 2013a*	Netherlands	84	44	56	9.9 years (mean age)	To design mandibular ramal height growth curves for patients with HFM and compare them with Dutch controls.	To determine the mandibular ramal distances using an orthopantomogram of 84 HFM patients and compare with 329 healthy individuals without hemifacial microsomia. (Longitudinal study)	HFM patients start and end with smaller mandible but grow like the healthy population. Therefore, growth is similar in both HFM patients and healthy populations.	No	80%
Ongkosuwito *et al.*, 2013b*	Netherlands	75	48	52	4–29 years	To design a craniofacial linear growth curve for an unoperated mandible with HFM and Dutch controls.	A cephalometrics analysis of hemifacial microsomia in a longitudinal study on serial lateral cephalograms. (Longitudinal study)	Patients with HFM have more vertical and retruded growth than control as severity increases. The growth curve is estimated for each patient to determine the best treatment age from a growth perspective. Hence, an individual approach is advocated.	No	80%
Renkema *et al.*, 2022*	Netherlands	110	51	49	3–56 years	To investigate the potential progressiveness of mandibular asymmetry and to study factors that influence chin point deviation in patients with unilateral craniofacial microsomia (CFM).	Radiographic images and medical photographs of patients with unilateral craniofacial microsomia were utilised. Clinical photographs were used to determine chin point deviation. (Longitudinal study)	A linear mixed model for repeated measurements showed no significant association between age and chin point deviation. Although an association exist in the Pruzansky-Kaban score between sex and chin point deviation. The potential progressiveness of CFM could not be affirmed.	No	80%

Table 2 (continued)

Author (Year)	Population	Sample size	Male %	Female %	Age Range	Aim of Study	Methodology (Cross-sectional/ Longitudinal study)	Major Finding	Progressive Facial asymmetry (Yes/No)	MMAT Score
Kapiro *et al*., 2023*	Finland	40	-	-	Mixed dentition: 7.4 ± 1.49 years (mean age) Late mixed dentition: 10.9 ± 1.63 (mean age) Permanent dentition: 17 ± 5.23 (mean age)	To describe craniofacial microsomia (CFM) patients' mandibular growth from early childhood to adolescence with attention to symmetry.	The assessment of ramus height in anteroposterior and panoramic radiographs, mandible length in anteroposterior radiographs, maxillary protrusion, and mandibular retrognathia in lateral cephalograms were conducted across four distinct age cohorts. (Cross-sectional study)	Findings suggest that mild-type CFM is not progressive. During growth, mandibular asymmetry measured in the horizontal, vertical and sagittal planes did not increase.	No	80%
Shetye *et al*., 2023*	USA	30	70	30	5-14years	To examine the growth rate discrepancy of the affected and unaffected ramus heights in Pruzansky Type I and Type II mandibles.	A serial retrospective longitudinal growth study of untreated patients with HFM (Unilateral Craniofacial) classified based on Pruzansky type I and II mandible, with a mean follow-up of 3.7 years. (Longitudinal study)	The growth rate discrepancy of the affected and unaffected ramus heights was more severe in Pruzansky Type II mandibles than in Pruzansky Type I mandibles. This study suggests the progressive nature of facial asymmetry in Pruzansky Type II mandibles.	Yes	80%
Zhang *et al*., 2023*	China	210	60	40	0.2–11 years	To quantitively analyse the mandibular ramus and body deformities, assessing the asymmetry and progression in different components.	Linear and volumetric measurements of the ramus and the body were collected via their preoperative imaging data (using three-dimensional computed tomography) to compare the different sides and severities. (Cross-sectional study)	There were asymmetries in the mandibular ramus and body regions, which involved the ramus more. A significant contribution to progressive asymmetry from the body suggests treatment focus in this region.	Yes	80%

*Studies that reported the severity of HFM according to Pruzansky or Pruzansky-Kaban classification

#Studies reported on follow-up period (range between eighteen months to ten years and above)

All the included studies assessed FA changes in the overall HFM sample

Table 3 The frequency table shows the parameters of facial asymmetry in the eleven included studies

Parameters	Numbers of articles (%)
Chin Point	27 [25, 39, 40]
Ramus Height	64 [35, 36, 39–43]
Total Mandibular Length	27 [40, 41, 43]
Mandibular body length	27 [40–42]
Occlusal plane angle	27 [24, 37, 38]
Piriform rim angle	9 [24]
Gonial/Intergonial angle	27 [24, 39, 40, 43]

intergonial angle [39–41], ramus height [35, 36, 39–41], mandibular length [38, 39, 41] and body length [40].

Some studies did not report on these parameters (Fig. 3). These include chin point [24, 35–37, 39, 40, 42, 43], occlusal plane/angle [25, 35–39], gonial/intergonial angle [25, 35–38, 42, 43], piriform angle [25, 35–39], ramus height [24, 25, 37, 38], mandibular length [24, 25, 35–37, 40] and body length [24, 25, 35–39, 41, 43].

Discussion

This review seeks to map out the various parameters of the mandible in the progression of FA in HFM patients, highlighting its relationship with sex, population, and age group. This review suggests that FA in HFM patients remain constant with time (age). All included studies were completed in countries such as the United States of America, China, Sweden, Italy, Finland and the Netherlands. Kearns et al. [24] and Kaprio et al. [39] used dentition age groups, Polley et al. [41] and Zhang et al. [43] utilised infancy to childhood age grouping, while others utilised various age groups in the included studies. FA was evaluated using parameters such as chin point, occlusal plane/angle, gonial/intergonial angle, piriform angle, ramus height, mandibular length, and body length [24, 25, 35–39]. The most reported parameter is ramus height, while the least reported parameter is piriform rim angle [24, 25, 35–39].

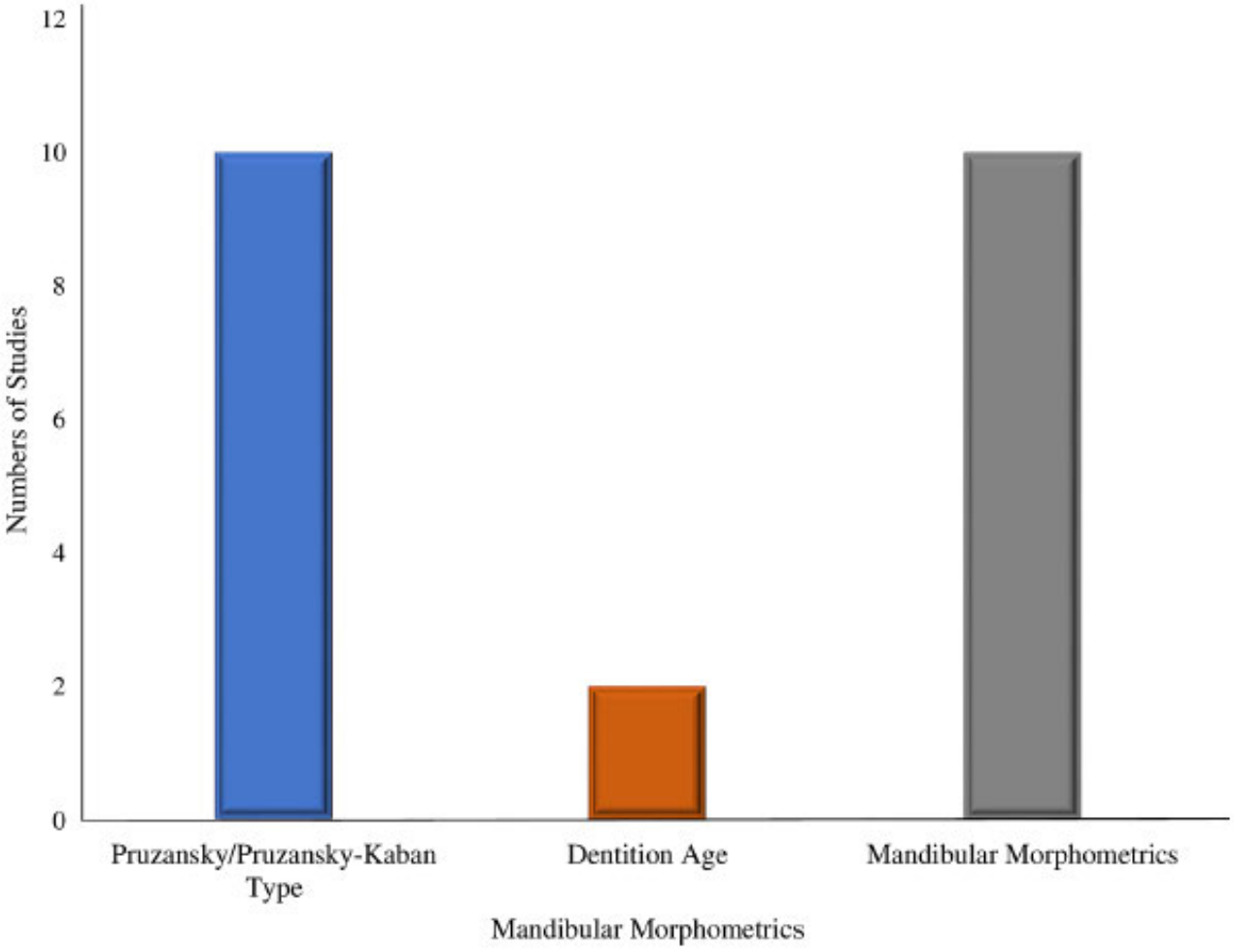

Fig. 2 Number of studies suggesting the progression of facial asymmetry in relation to Pruzansky-Kaban type classification, dentition age range and mandibular morphometrics in the literature from 1969 to date. The X-axis shows the classification, dentition age and measurement of the deformed mandible, and the Y-axis illustrates the number of studies

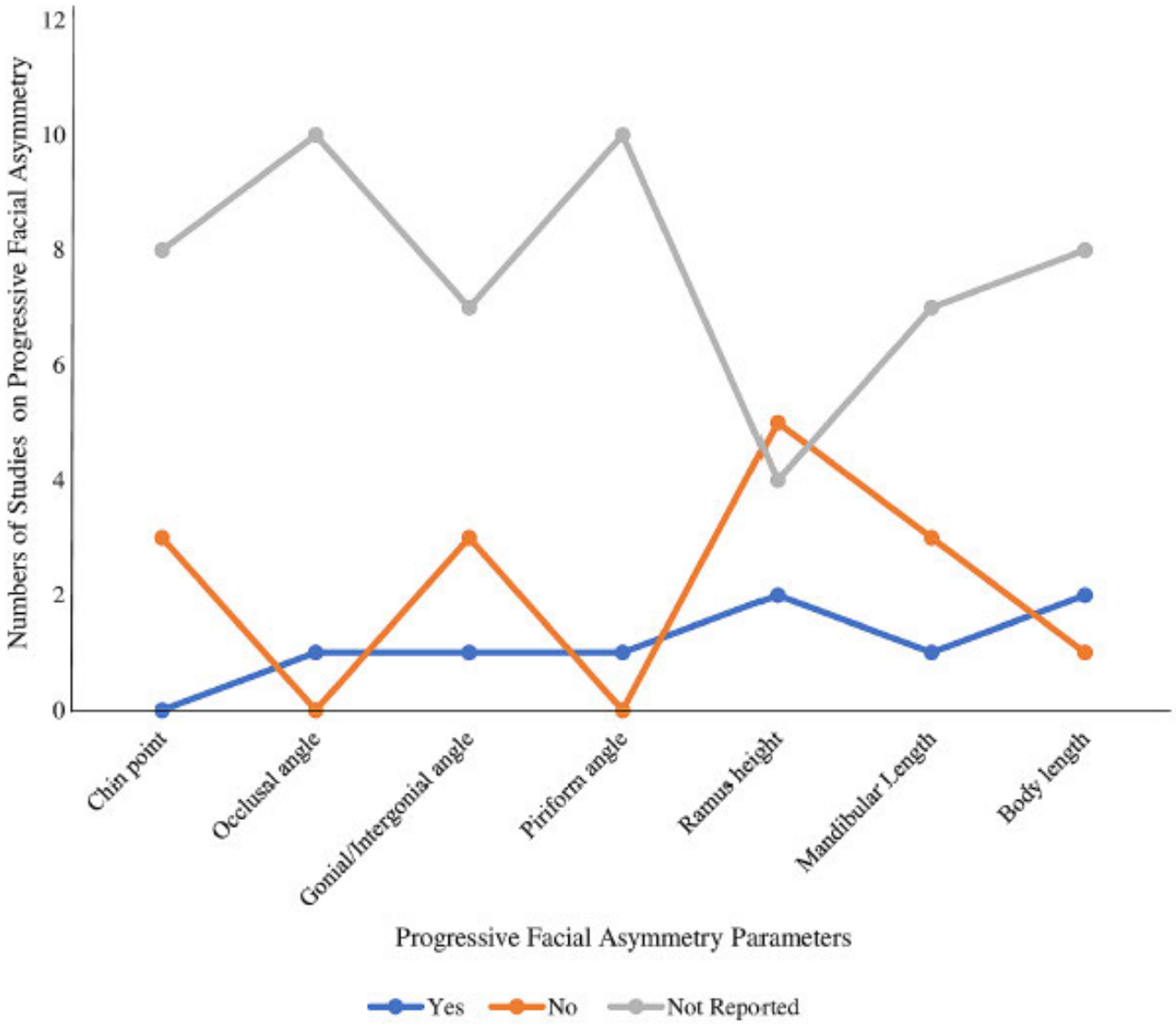

Fig. 3 Line graph showing assessment of all the included studies based on the facial asymmetry parameters in hemifacial microsomia patients. The X-axis represents facial asymmetry parameters, and the Y-axis represents the number of studies showing the progression of facial asymmetry

The mandible is the most affected facial bone in HFM, with FA reported as either increasing or remaining constant with age in HFM patients [25, 39, 42, 43]. Authors reporting progressive FA advocate for early surgical intervention to minimise end-stage deformity and psychosocial-economic impact, whereas others view FA as non-progressive, recommending surgical intervention at the end of growth due to the need for revisional surgery and increased psychosocial-economic burden [23, 25, 42]. The severity of the deformed mandible can be determined using various classification methods, with the Pruzansky or Pruzansky-Kaban classification being the gold standard for hypoplastic mandible in HFM [8, 44, 45]. Other classifications, such as SAT, OMENS, and OMENS+, were not used in the included studies [6, 9, 46]. Understanding these classifications ensures a proper treatment approach to mandibular lengthening through osteotomy, distraction osteogenesis, and grafting in maxillofacial or plastic surgery and orthodontics [47]. In addition to skeletal correction, structural fat grafts are used to augment soft tissue deformity in HFM patients, although this technique often requires multiple revisions [48]. New visualising techniques, including three-dimensional printed operation templates, offer advanced intervention planning despite challenges in treatment timelines and availability [49]. There are opposing views regarding the growth potential of the mandible in HFM patients. Some clinicians report the affected mandible becomes retarded in growth compared to the unaffected side [50], while others state the affected mandible grows parallel to the unaffected side [51, 52]. Evidence from dentition age groupings suggests an increase in

Table 4 Mandibular parameters used to measure facial asymmetry and treatment in selected studies

Author(s)	Mandibular parameters to measure FA	Received HFM treatment	Treatment modality	Age at treatment (years)	Treatment duration (years)	Treatment outcome on FA
Rune et al. 1981	occlusal plane angle	No	Nil	Nil	Nil	Nil
Polley et al. 1997	chin point, ramus height, total mandibular length, mandibular body length, gonial/intergonial angle	No	Nil	Nil	Nil	Nil
Kusnoto et al. 1999	chin point, ramus height, gonial/intergonial angle	Yes	distraction osteogenesis	5.9 ± 0.8	5	The initial gain was a loss due to the relapse facial asymmetry at the completion of growth
Kearns et al. 2000	occlusal plane angle, piriform rim angle, gonial/intergonial angle	No	Nil	Nil	Nil	Nil
Meazzini et al. 2012	ramus height	Yes	distraction osteogenesis	12.5 ± 2.4	1.5	Improve facial symmetry, but the affected and unaffected grew at the same rate before treatment
Ongkosuwito et al. 2013a	ramus height	No	Nil	Nil	Nil	Nil
Ongkosuwito et al. 2013b	occlusal plane angle	No	Nil	Nil	Nil	Nil
Renkema et al. 2022	chin point	No	Nil	Nil	Nil	Nil
Kapiro et al. 2023	ramus height, total mandibular length, gonial/intergonial angle	No	Nil	Nil	Nil	Nil
Shetye et al. 2023	ramus height, total mandibular length, mandibular body length	No	Nil	Nil	Nil	Nil
Zhang et al. 2023	ramus height, mandibular body length	No	Nil	Nil	Nil	Nil

deformity severity with age [24], although some studies, such as Polley and colleagues, indicate that the asymmetric mandible remains constant throughout growth [41]. Overall, while the growth pattern for different HFM severities appears non-progressive, severe HFM cases show otherwise [43]. This is crucial for diagnosing and managing HFM patients [24, 41, 53]. Also, it is noteworthy that rotations can still increase in one axis and decrease in another even when there are no overall growth changes [54]. An inherent genetic factor may cause asymmetry and increased angular measurement in FA [42]. However, some studies report that chin point values remain constant with age [25]. It is recommended that mandibular asymmetry correction in HFM be carried out during the mixed dentition age (6–12 years), though this is not the primary focus of this review [4, 55].

Assessment of HFM can be done either quantitatively or qualitatively [4] to determine the progressiveness of FA. Researchers have used parameters such as chin point, occlusal plane/angle, gonial/intergonial angle, piriform rim angle, ramus height, mandibular body length and total mandibular length to ascertain the extent of FA in HFM patients. Individual assessment of the indicators of FA on either progressive or non-progressive from the included articles in this review favoured the more non-progressive nature of HFM compared to few studies that favoured the progressive nature of the condition. Some authors have hypothesised that early treatment of HFM could promote midfacial growth and facial symmetry [3, 56]. At the same time, a report by Pluijmers et al. [57] does not support the hypothesis of the long-term stability of early treatment in HFM patients.

All the included studies in this review were completed in countries such as the United States of America, China, and various European nations; none were from Africa. Although there is a large body of existing literature on HFM, reports are primarily from international populations, with a few from the African continent [58–62]. It does not translate to Africa being spared of the burden of this congenital anomaly.

Psychological and biological features influence sexual dimorphism. Facial sexual dimorphism becomes more distinct after puberty due to the increased levels of androgen and oestrogen [63]. The shape difference decreases with age as the female mandible becomes like the male mandible while both sexes gain size [64]. Evidence from the included study shows no relationship between FA and gender dimorphism in the HFM population. Correspondingly, Nagy et al. [65] reported a similar distribution between sexes and dismissed the concept of prevalence in male patients and laterality to the right side. There is no sexual dimorphism in both

progressive and non-progressive FA from the included studies. Therefore, there is no difference in treatment approach to HFM in both sexes. FA is typically found in humans; this becomes obvious in HFM patients due to the apparent defect to the mandible and associated facial skeleton [36, 42]. Multi-interventional approaches by healthcare providers such as otolaryngologists, audiologists, orthodontics, orthognathic surgeons, plastic surgeons, medical geneticists, and clinical psychologists are needed to manage and treat HFM.

The limitations of this review include the use of heterogenous age grouping, small sample size, less reporting on sex distribution in the sample size, insufficient empirical data on the severe skeletal or soft tissue deviation, the use of orthopantomograms to measure mandibular growth in some of the included studies may not cover the true depth of three-dimensional growth of the mandible and inconsistent use of angular measurement of FA in the included studies do not allow us to explore further facial asymmetry progression in other eligible studies. Furthermore, there is a lack of robust studies in the field of HFM; thus, no definitive conclusions can be drawn regarding the collective characteristics of this anomaly. All the included articles were longitudinal [25, 35, 38, 40, 42], except two [24, 43]. In the study reported by Shetye et al. [42], there is confusion regarding using the terms rate and ratio between the affected and unaffected sides in the HFM. Many of the eligible studies are case series studies [57]. Case series studies are regarded as low levels of evidence-based medicine. Therefore, caution is required to make firm conclusions when interpreting the information from these types of studies [57].

Conclusion

The included studies widely use the Pruzansky or Pruzansky-Kaban classification systems. There is a correlation between progressive FA and dentition-age grouping. The FA parameters used in this review include chin point, gonial/intergonial angle, piriform angle, mandibular ramus height, mandibular length, and body length. An assessment of the included studies on FA parameters favoured more on the non-progressive nature of HFM. American and European populations have reported more on the progression of FA, with fewer reports from the Asian population. Evidence from the included studies indicates that FA does not increase in HFM patients, as demonstrated by the constant ratio of the affected side compared to the non-affected side during growth. The substantial establishment of a significant increase in FA with age in HFM remains uncertain. Hence, we premise that there is no progression of FA in HFM patients. However, the timing of the surgical intervention should be based on the functional or aesthetic needs of the patients. HFM patients with functional requirements such as obstructive sleep apnoea and feeding difficulty due to micrognathia or retrognathia may require interventions before skeletal maturity. The decision to operate on HFM prior to or after skeletal maturity should be individual-specific, considering both functional and psychosocial factors. More data are required from African and Asian populations for scholarly contribution to managing and treating HFM.

Appendix I: search strategy

MEDLINE via PubMed on 15th July 2022

PubMed 15/07/2022 = 625.

((((((((“hemifacial microsomia” AND “facial asymmetry”) OR (“hemifacial microsomia” AND “mandibular growth restriction”)) OR (“hemifacial microsomia” AND “mandibular growth”)) OR (“hemifacial microsomia” AND “mandibular hypoplasia”)) OR (“hemifacial microsomia” AND “mandibular asymmetry”)) OR (“hemifacial microsomia” AND “mandibular morphology”)) OR (“facial asymmetry” AND “mandibular morphology”)) OR (“facial asymmetry” AND “mandibular hypoplasia”)) OR (hemifacial microsomia AND progressive facial asymmetry)) OR (progressive facial asymmetry AND mandibular asymmetry) NOT (review[pt]))))))))))

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Author contributions PMA and BRO conceptualisation; PMA & BRO collected and data analysis; PMA wrote the manuscript first draft; PMA, BRO, AM, & LL wrote and edited manuscript; A.M. and LL supervision. All authors reviewed the manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate This paper is a systematic scoping study that relies strictly on reviewing existing literature. Ethical approval is not required since no animal or human participants were in this study.

Competing interests The authors declare no competing interests.

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BRIDGING TEXT
FROM CHAPTER TWO TO THREE

As indicated in chapter two, eleven studies reported on the progression of FA due to mandibular deformity in HFM. There was no difference in the progression of FA between males and females. The age groups used include dentition, infancy-to-childhood, childhood-to-adolescent and unspecified age groupings. FA was evaluated using parameters such as chin point, occlusal plane/angle, gonial/intergonial angle, piriform angle, ramus height, mandibular length, and body length. Individual assessment of the indicators of FA on either progressive or non-progressive from the included articles in this review favoured the more non-progressive nature of HFM compared to few studies that favoured the progressive nature of the condition. Evidence from the included studies suggested that FA remains constant with age in patients with HFM. The included studies were from high-income countries and none from African countries. The next chapter investigates the clinical presentation of HFM in a select South African population compared to others.

The manuscript in chapter three, entitled **"*Clinical Presentation of Hemifacial Microsomia in a South African Population*,"** was submitted to the Journal of Plastic Surgery and Hand Surgery on 27th July 2024 and accepted for publication on 30th October 2024. (Manuscript and references are presented according to the journal's specification).

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a revision has been submitted (JPHS-2024-0028.R1)	Contact Journal ED: Elander, Anna EO: Honeth, Ingrid • Minor Revision (18-Oct-2024) • a revision has been submitted view decision letter	JPHS-2024-0028	Clinical Presentation of Hemifacial Microsomia View Submission	27-Jul-2024	18-Oct-2024

CHAPTER THREE

MANUSCRIPT TWO

Clinical Presentation of Hemifacial Microsomia in a South African Population

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ORIGINAL RESEARCH ARTICLE

Clinical presentation of hemifacial microsomia in a South African population

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ABSTRACT

Background: Hemifacial microsomia (HFM) presentation includes gross distorted ramus, malposition temporomandibular joint, small glenoid fossa, distorted condyle and notch, malformed orbit, cupping ear or absent external ear, and facial nerve palsy. HFM is the second most prevalent congenital deformity of the face, with little literature from the South African population. This retrospective study elucidated the demographic characteristics and clinical presentations of HFM patients in a select South African population and compared it to the literature.

Methods: A retrospective study of HFM patients diagnosed through clinical presentation and confirmed by plain radiograph or computed tomography was conducted. The patient's charts were reviewed for age, sex, laterality, side, the severity of the deformity, and associated craniofacial and extra-craniofacial anomalies. The clinical presentation of malformations was categorised according to the OMENS classification, using five major craniofacial manifestations of HFM.

Results: Twenty-five patients were included, with a male-to-female ratio of 1:1.78. The population distribution is 60% Black, 32% Indian, 4% White and 4% Coloured. A right-to-left laterality ratio of 1.4:1 and 4% bilateral affectation. This study showed 100% mandibular hypoplasia, 84% ear deformity, 40% orbital deformity, 60% facial nerve defect and 100% soft tissue defect affectation with noticeable facial asymmetry. Other craniofacial anomalies were recorded in 84%, while extracraniofacial anomalies were recorded in 40% of this HFM population.

Conclusion: There is a high degree of variability in the deformities in HFM in the South African population, distinguishing it from the international population. A multidisciplinary approach is required for its treatment and management.

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Introduction

Symptoms of the first and second pharyngeal arch syndrome include otomandibular dysplasias (Hemifacial microsomia [HFM]), mandibulofacial dysostosis, oculoauriculovertebral dysplasias, branchio-oto-renal syndrome, Pierre Robin sequence and Nager acrofacial dysostosis. HFM is the second most prevalent congenital deformity of the face, with an incidence of 1:3,500–5,600 [1–3]. HFM is due to genetic, maternal, and environmental conditions leading to haemorrhage of the stapedial artery, dysgenesis of Meckel's cartilage and aberrant migration of neural crest cells [2]. The clinical features of HFM include a unilaterally deformed mandible with malformed ear structures comprising of the gross distorted ramus, malpositioned temporomandibular joint (TMJ), small glenoid fossa, distorted condyle and notch, malformed orbit, cupping ear, absent external ear and facial nerve palsy [4]. HFM affects skeletal and overlying soft tissues [5, 6]. The first widely used classification of HFM was by Pruzansky [7] using mandibular hypoplasia; this was further improved upon by Kaban et al. [8], who included the TMJ. Another HFM classification is the skeletal–auricular–soft tissue (SAT) deficiency [9]. Vento et al. [10] introduced the OMENS classification pattern by classifying HFM-associated anomalies, including orbital distortion (O), mandibular hypoplasia (M); ear anomaly (E); nerve involvement (N); and soft tissue deficiency (S). Horgan et al. [11] expanded these anomalies to include extracraniofacial defects, thus making the revised classification system OMENS-Plus (+). In addition, there is an association between HFM and macrostomia, Tessier's cleft number 7: Treacher-Collins syndrome [12, 13]. Several genes are implicated in the HFM population, such as OTX2, PLCD3, MYT1 and Pde4dip [2, 14]. Although there are large bodies of literature on HFM, most reports are from the international population, with a few reports from the African continent [3, 5, 15–17]. South Africa has a multiracial population, which includes Blacks, Whites, Coloured and Indians [18, 19]. The population distribution of KwaZulu-Natal is 86.8% Blacks, 7.4% Indians (Asian), 4.2% White and 1.4% Coloured. The percentage distribution of males to females is 47.5 and 52.5%, respectively [20]. There is a lack of literature on the clinical presentation of HFM in a South African population [15, 16]. This retrospective study was designed to understand the demographic characteristics and clinical presentations of HFM patients in a South African population and compare it to the literature.

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Materials and methods

A retrospective study identified patients with HFM treated at the Department of Plastic and Reconstructive Surgery, Inkosi Albert Luthuli Central Hospital, from June 2003 to December 2022. Patients were diagnosed by a craniomaxillofacial surgeon through clinical presentation and confirmed by plain radiograph or computed tomography (CT) images and assessed using OMENS classification [10] (Table 1). A differential diagnosis was made to rule out other phenotypic similar syndromes of first and second pharyngeal arches, such as Treacher-Collins, branchio-oto-renal, Miller-Dierker CHARGE, and Parry Romberg. The first author retrieved 35 patients' medical records from the hospital's electronic archive, but 10 were excluded due to the incomplete records. Charts, photographs, and radiographs were reviewed to document demographic data and clinical findings in patients presented with HFM. The patient's charts were reviewed for age, sex, laterality, side involved, deformity severity, and associated craniofacial and extra-craniofacial anomalies using OMENS+ classification [11]. The photographic evaluation included analysis of standardised patient photographs and reviewing any previous photographs during facial growth phases (if available). Imaging studies, including cephalometric films, panoramic films, and CT, were reviewed and analysed to document skeletal elements of the deformity and underdevelopment of soft tissues. The imaging studies for suspected extracraniofacial anomalies, including echocardiography, abdominal ultrasonography, brain magnetic resonance imaging (MRI), and CT spine, were reviewed. Written informed consent or consent permission was obtained for each patient involved in this study. In addition, informed consent was secured from all subjects or their legal guardians to publish images in an online open-access publication. All HFM patients were seen and followed by a multidisciplinary craniofacial team (such as an otolaryngologist, orthodontist, geneticist, audiologist, speech therapist, ophthalmologist, neurologist, clinical psychologist, social worker, paediatrician, maxillofacial and plastics surgeon).

Statistical analysis

The categorical variables were described as counts and percentage frequencies. A Chi-Square test was used to determine the association between categorical variables, and when the distribution of the cross-tabulations contains an expected value of less than five, a Fisher's exact test was applied. The level of significance was kept at $p < 0.05$. All statistical analyses were completed using SPSS 28.0 (IBM Corp., Armonk, NY, USA).

Ethics

This study was conducted with the approval of the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (Ref No: BREC/00004225/2022) and the Department of Health in the Province of KwaZulu-Natal (NHRD Ref.: KZ_202206_031). All methods were carried out following the University of KwaZulu-Natal standard-approved guidelines and regulations and all experimental protocols per the declaration of Helsinki.

Results

Patient characteristics

This study included 25 patients with HFM: 9 males (36%) and 16 females (64%). The following details were based on the medical records, information patients or their families provided and follow-up care. The population distribution among the patients includes 15 (60%) of Black descent, 8 (32%) of Indian descent, 1 (4%) of White descent and 1 (4%) of Coloured descent. Age at first assessment ranged from 9 days to 36 years (mean 5.4 years). Based on their records and follow-up care by the surgeon, eight patients (32%) were considered to have reached full facial growths, while 17 patients (68%) were still growing. The right side was affected in 14 patients (56%), while the left side was affected in 10 patients (40%), and 1 patient (4%) had a bilateral presentation of HFM. There were no significant differences between the sexes ($p = 0.27$) ratio and right-to-left-sidedness ($p = 0.29$).

OMENS classification

The clinical presentation was categorised according to the OMENS classification, and the five major craniofacial manifestations of HFM (orbit, mandible, ear, nerve, and soft tissue) were assessed (Figure 1–3). Each anatomic abnormality was graded from 0 to 3 according to the dysmorphic severity by OMENS classification (Table 1). For bilateral cases, each side is considered a separate subject. The 25 patients were considered 26 subjects, and the OMENS score was as follows in Table 2. There was no significant difference when comparing each substrate of the OMENS classification to the affected side: orbit ($p = 0.47$), mandible ($p = 0.27$), ear ($p = 0.82$), nerve ($p = 0.44$) and soft tissue ($p = 0.49$). There was no significant difference when comparing each substrate of the OMENS classification to sexes: orbit ($p = 0.47$), mandible ($p = 0.29$), ear ($p = 0.09$), nerve ($p = 0.19$) and soft tissue ($p = 0.06$).

Other craniofacial anomalies

Other accompanied craniofacial anomalies are malocclusion, ocular defects (such as blindness, nystagmus, telecanthus, hypertelorism, glaucoma, coloboma, cataract, blindness, anophthalmia and lagophthalmos),

Table 1. OMENS classification in hemifacial microsomia patients.

Orbit(O): Asymmetry of the orbit	
O0	Normal size and positioned orbit
O1	Abnormal orbital size
O2	Abnormally positioned orbit
O3	Abnormal size and positioned orbit
Mandible(M): Mandibular hypoplasia	
M0	Normal mandible
M1	Small mandible and glenoid fossa with small ramus
M2A	Glenoid fossa in acceptable anatomical position regarding opposite TMJ
M2B	TMJ is inferiorly, medially, and anteriorly displaced with the severe hypoplastic condyle
M3	Complete absence of ramus, glenoid fossa and TMJ
Ear(E): External ear deformity	
E1	Normal ear
E2	Mild hypoplasia is present, but all structures are intact
E3	Absence of external auditory canal with variable hypoplasia concha
E4	The malposition lobule has an absent auricle, and the lobule remnant is displaced inferiorly and anteriorly
Nerve(N): Nervous involvement	
N0	The facial nerve is not affected
N1	Upper facial nerve is affected (temporal and zygomatic branches)
N2	Lower facial nerve is affected (buccal, mandibular, and cervical branches)
N3	Affectation of all facial nerve branches. Others are trigeminal (sensory component) and hypoglossal
Soft tissue(S): Soft tissue deficiency	
S0	No deficiency in the soft tissue or muscle
S1	Minimal soft tissue or muscle deficiency
S2	Moderate between S1 and S3
S3	Severe deficiency owing to soft tissue or muscle hypoplasia

TMJ: temporomandibular joint

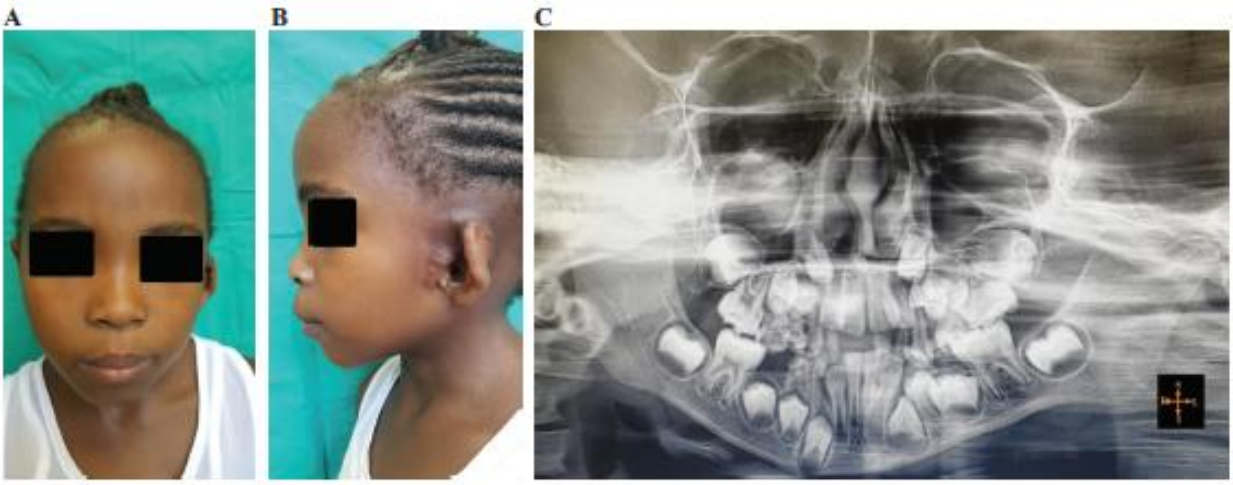

Figure 1. Characteristic features of HFM presentation in a 6-year-old patient based on OMENS classification. (A) A frontal view of a left-sided hemifacial microsomia (HFM) with mild soft tissue defects and a deformed ear. (B) The lateral view shows a mild hypoplasia of the external ear (E1) with most structures intact and mild soft tissue defects (S1). (C) A panoramic radiograph showing a deformed mandible (M2A), crowded teeth. The OMENS classification is O0M2AE1N1S1.

macrostomia, cranial nerve XI palsy, cleft lip and palate, isolated craniofacial palate, major craniofacial cleft, Treacher Collins syndrome, palatoglossal band, retrognathia, prelingual hearing loss, brachycephaly, craniosynostosis and hypoplastic muscle of mastication. The summary of the frequency of distribution is shown in Table 3.

Extracraniofacial anomalies

Extracraniofacial anomalies were recorded in this study's 10 (40%) patients. Respiratory anomalies were reported in 9 (36%) patients; these include tracheomalacia, congenital pneumonia accompanied by asthma, sleep dyspnoea, and a blocked nose. Limb anomalies were reported in 4 (16%) patients; these include duplicate thumb, clinodactyly, club foot and achondroplasia. Three (12%) patients reported central nervous system anomalies, including periventricular leukomalacia, neurofibromatosis, hemiparesis, and mental deficit. Anomalies of the neck were reported in 3 (12%) patients, including torticollis and web neck. Vertebral anomalies were reported in 2 (8%) patients, including scoliosis, spinal fusion, hemivertebra, thoracic hyperkyphosis, Spinal bifida of T2–T8 and extranumeral rib. Congenital heart anomalies were reported in 2 (8%) patients, including dextrocardia, murmur and Tetralogy of Fallot with transposition of the great vessel. Genital abnormalities were reported in one patient (4%), including chordee and hypospadias. Renal agenesis was reported in one (4%) patient. Congenital recto-vaginal fistula was reported in one (3.85%) patient. The summary of the frequency of distribution is shown in Table 4.

Discussion

This study was designed to understand the demographic characteristics and clinical presentation of HFM patients in a South African

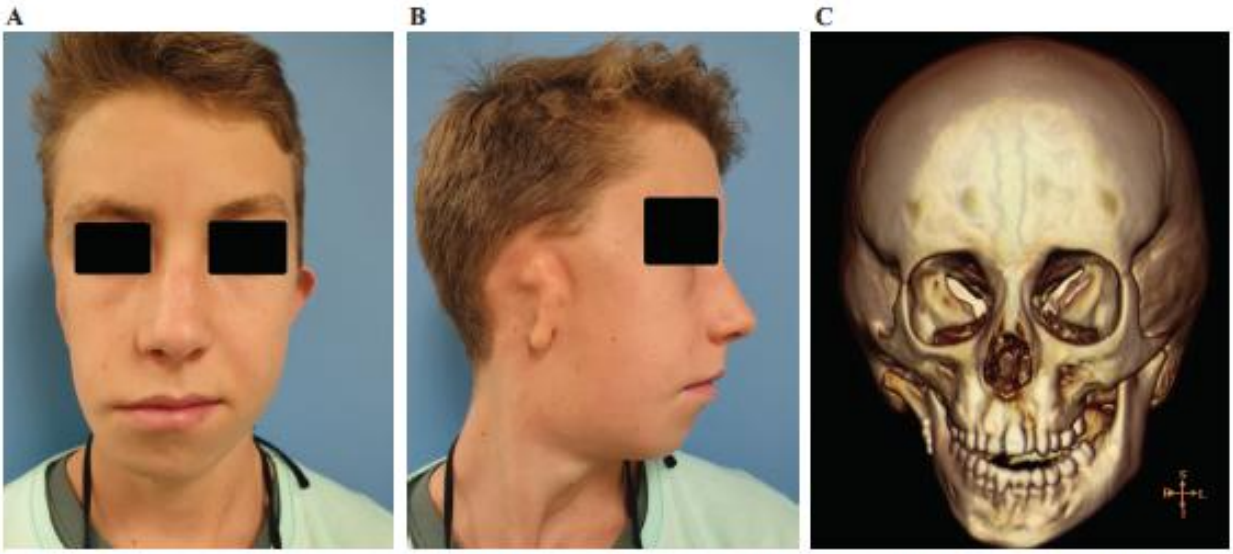

Figure 2. Characteristic features of hemifacial microsomia (HFM) presentation in a 15-year-old patient based on OMENS classification. (A) A frontal view of the face shows a right-sided HFM with marked facial nerve palsy, ear, and lower jaw deformities. (B) Lateral view showing remnant ear lobule and retrognathia. (C) A 3D reconstructed CT showing deformed mandible (M2B) and malocclusion class III with marked facial asymmetry. The OMENS classification is O1M2BE3N3S1.

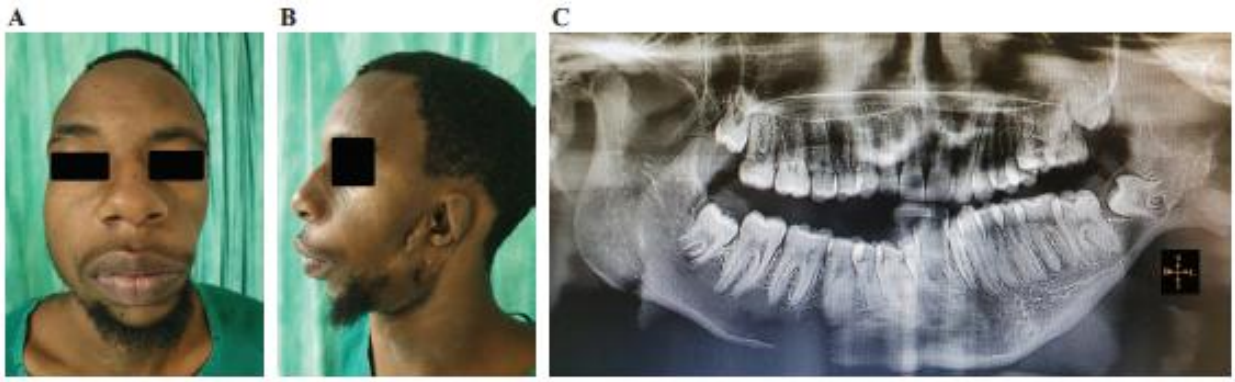

Figure 3. Characteristic features of hemifacial microsomia (HFM) presentation in a 21-year-old patient based on OMENS classification. (A) A frontal view showing a left-sided HFM with prelingual hearing loss, chin deviation, severe soft tissue deformity and facial asymmetry. (B) Lateral view showing ear (E1), retrognathia, and severe soft tissue deformities (S3). (C) A panoramic radiograph showing a deformed mandible (M3), malocclusion class III and chin deviation. The OMENS classification is O1M3E1N2S3.

population. The presentation of HFM differs from one individual to another, with or without extracraniofacial deformity [21]. Mandibular hypoplasia with or without ear deformity is the cornerstone for the phenotypic classification of HFM, distinguishing it from other craniofacial anomalies of first and second branchial arches [22]. This study showed 100% mandibular hypoplasia, 84% ear deformity, 40% orbital deformity, 60% facial nerve defect, 100% soft tissue defects, and 100% facial asymmetry. A total of 25 patients were included, with a male-to-female ratio of 1:1.78. The distribution within the included patients is 60% Black, 32% Indian, 4% White, and 4% Coloured. There is a right-to-left laterality ratio of 1.4:1 and 4% bilateral affectation. Other craniofacial anomalies were recorded in 84%, while extracraniofacial anomalies were recorded in 40% of this HFM population, which were not captured by the OMENS classification [10, 11]. The patients received no prior surgical intervention before presentation to our facility.

This study shows no significant difference between the male-to-female ratio and right-to-left-sidedness. Opinions differ about gender and laterality differences in the incidence of HFM. While some authors have reported that HFM is more present in males to females with a ratio of 3:2, respectively, and right-side laterality preponderance [23], others found no correlation between gender or laterality [11,24]. A population-based HFM study in Canada and the United States reported a demographic distribution of 63% White, 26% Hispanic, 5% Black, 4% Asian, and 3% Native American [17]. The differences reported in our study and the above studies could be due to the disparity in the sample size and socio-cultural factors. In addition, international data often lacks detailed racial stratification, emphasising the need for localised studies to understand the epidemiology of HFM better.

Deformities in the orbit size or position were recorded in 40% of patients in this study. This value falls within the range of previous studies (4–43%) in HFM [25, 26]. Ocular anomalies often accompany HFM. The presence of coloboma and epibulbar dermoid, along with features of HFM, is diagnosed as Goldenhar syndrome [27]. Ocular anomalies were present in 6.7–100% of patients [26]. This study had a 20% incidence of ocular defects. Surgical treatment to restore visual acuity is recommended before 5 years of age [25]. Mandibular hypoplasia is present in 73 to 91% of HFM patients [26, 28]. This study recorded higher mandibular hypoplasia in 100% of cases of HFM patients [3]. The hypoplastic mandible is associated with malocclusion, made noticeable by occlusal canting and retrognathia linked to obstructive sleep apnoea, cleft lip and palate, dental hypoplasia, feeding difficulty, speech and language difficulties, and macrostomia. Deformity of the mandible makes facial asymmetry noticeable in the HFM population [29]. Based on Kaban and colleagues' severity grading and functional requirements [8], the treatment modalities used in the mild hypoplastic mandible (Type 1 and 2A) are osteotomy, distraction osteogenesis and genioplasty for lengthening the shortened mandible. In contrast, severe hypoplastic mandible (Type 2B and 3) involved orthognathic intervention and reconstruction of the mandible using alloplastic materials, costochondral or bone graft [5, 26, 30–33]. There is a lack of consensus on the timing of the treatment modalities. Some advocated an early age, while others elected for a late stage of development. Early treatment may improve facial symmetry and psychosocial acceptance but requires multiple revisional surgeries [5, 26]. In this series of patients, we employed early-age intervention for severe mandibular hypoplasia, while late-age intervention was used for mild cases. The degree of severity and functional requirements determine the mode of surgical intervention

Table 2. Percentage distribution of OMENS score grading in 26 subjects.

	0 (%)	1 (%)	2 (%)		3 (%)
			A	B	
Mandible (M)	0 (0)	2 (7.69)	8 (30.77)	10 (38.46)	6 (23.07)
Orbit (O)	15 (57.69)	8 (30.77)	2 (7.69)		1 (3.84)
Ear (E)	4 (15.39)	12 (46.15)	2 (7.69)		8 (30.77)
Facial nerve (N)	10 (38.46)	6 (23.08)	5 (19.23)		5 (19.23)
Soft tissue (S)	0 (0)	8 (30.77)	12 (46.15)		6 (23.08)

Table 3. Percentage distribution of associated craniofacial deformity in hemifacial microsomia patients.

Craniofacial deformity	Number of patients (%)
Malocclusion	8 (32)
Macrostomia	6 (24)
Ocular anomalies	5 (20)
Prelingual hearing loss	4 (16)
Pre-auricular tag	3 (12)
Cranial nerve 11	3 (12)
Isolated cleft palate	3 (12)
Cleft lip and palate	2 (8)
Major craniofacial cleft (2–12)	2 (8)
Treacher Collins Syndrome	2 (8)
Hypoplastic Salivary glands	2 (8)
Retrognathia	2 (8)
Hypoplastic Muscle of Mastication	2 (8)
Hypoplastic cheekbone	2 (8)
Pigmentation of the eye and forehead	1 (4)
Craniosynostosis	1 (4)
Brachycephaly	1 (4)
Palatoglossal band	1 (4)
Total	**21 (84)**

Table 4. Percentage distribution of associated extracraniofacial anomalies in hemifacial microsomia patients.

Extracraniofacial anomalies	Numbers of patients (%)
Respiratory anomalies	9 (36)
Limb anomalies	4 (16)
CNS anomalies	3 (12)
Neck anomalies	3 (12)
Congenital heart defect	2 (8)
Vertebral anomalies	2 (8)
GIT anomalies	1 (4)
Genital deformity	1 (4)
Renal deformity	1 (4)
Total	**10 (40)**

in HFM patients [4]. Several reports have suggested an increasing association between the severity of the ear and mandibular deformities. The deformity can affect external, middle, or internal ear structures. This study has a high prevalence of auricular deformity, with mild (46.15%), moderate (7.69%), and severe (30.77%) cases. Other accompanying anomalies, including preauricular tags, hypoplastic mastoid, low-set ears, low hairline, and hearing loss, were noticed. Detection of hearing problems in patients with HFM is vital to mitigate learning difficulties, speech development delay, and impaired social functioning [34]. The derivatives of the second pharyngeal arches (such as stapes, stylohyoid ligament, the lesser horn of hyoid, stapedius, platysma, and muscles of facial expression) are affected by the defect to the facial nerves. Facial nerve palsy affected about 60% of the HFM patients in this study [35]. The incidence of facial palsy in other studies is 22% [36] and 23.9% [37]. Multifactorial factors may cause this disparity compared to our study [2, 14]. Soft tissue defects accentuate facial asymmetry in HFM patients. The modalities include alloplastic implants, microvascular free tissue transfer, the pedicled flap, fat grafting, and functional reconstruction with cross-facial nerve grafting [36]. Mild-to-moderate soft tissue defects require fat grafting. The positive outcomes of fat grafting, the lowest complication rates, and a minor treatment burden make fat grafting a reasonable option for most HFM patients in whom soft-tissue correction is administered. Soft-tissue reconstruction may influence other types of treatment, such as mandible or ear reconstruction, and should, therefore, be coordinated within a multidisciplinary treatment plan [26, 36, 38]. The prevalence of extracraniofacial anomalies in international studies focusing on HFM patients was reported at 35.9% [3], 44% [39], 47% [40], 55% [11], 69% [41], and 85% [34]. In this study, we registered 40% of extracraniofacial anomalies in HFM patients. Noticeably, respiratory deformities account for the highest occurrence (36%). Renkema and co-authors reported only 3% of respiratory deformities (n = 991) [40] in their large population multinational study. We hypothesised that this disparity may be due to genetic or environmental factors. Extracraniofacial anomalies in this study were associated with severe mandibular, facial nerve, and soft tissue deformities. Renkema et al. [40] reported a similar association. The HFM population should be screened by physical examination and diagnostic tools such as electrocardiography, echocardiography, spine radiography, and renal ultrasound for extracraniofacial deformities. Some genes have been linked to the incidence of HFM; this includes mutation of OTX2, which may result in anophthalmia, microphthalmia and brain malformation [2, 14]; PLCD3 may result in aberrant migration of cranial neural crest cells in the development of head and neck [2, 14]; Itgb4 and Pde4dip may result in the inhibition osteogenesis of the mandible and other facial bones [14]. The genetic basis of HFM varies from one individual to another and not all cases of HFM have genetic causes. HFM is multifactorial in origin. Currently, research is still ongoing regarding the suggested genetic basis of HFM in South Africa and other parts of the World [14].

To the best of our knowledge, this is the first study in the South African population documenting demographic and clinical presentation in HFM with a higher prevalence in females. In this study, the right side is more affected with a higher incidence of facial nerve palsy. A deformed mandible accentuates facial asymmetry in the HFM population. There is a high degree of variability in the deformities of the mandible, ear, facial nerve, orbit, and soft tissue presentation in HFM in the South African population. Due to multiple deformities associated with HFM, a multidisciplinary (such as an otolaryngologist, orthodontist, geneticist, audiologist, speech therapist, ophthalmologist, neurologist, neurosurgeon, craniofacial surgeon, orthopaedic surgeon, hand surgeon, spinal surgeon, cardiologist, cardiac surgeon, urologist, nephrologist, colorectal surgeon, gynaecologic surgeon, maxillofacial and plastics surgeon) approach is required for its treatment and management.

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Declaration of Interest

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BRIDGING TEXT
FROM CHAPTER THREE TO FOUR

Chapter three documented the demographic and clinical characteristics of HFM in a South African population using OMENS+ classification. There is a higher prevalence in females, right-sided laterality, and incidence of facial nerve palsy. A high degree of variability in the deformities of the mandible, ear, facial nerve, orbit, soft tissue, and systemic anomalies presented in HFM makes the South African population distinct from other international populations. Due to its multifaceted presentation, we recommended a multidisciplinary team to manage and treat HFM. Hypoplastic mandibles with or without ear anomalies are the hallmark of HFM deformity. The mandibular ramus is the most implicated component of the mandible in HFM individuals. The next chapter investigated the anatomical differences between affected and unaffected mandible ramus and body in a cohort of patients with HFM in South Africa.

The manuscript in chapter four, titled **"*Mandibular hypoplasia in hemifacial microsomia: A cross-sectional study*,"** was submitted to the Translational Research in Anatomy on 31st December 2023 and published on 19th February 2024. (Manuscript and references were according to the journal specification).

CHAPTER FOUR

MANUSCRIPT THREE

Mandibular hypoplasia in hemifacial microsomia: A cross-sectional study

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Mandibular hypoplasia in hemifacial microsomia: A cross-sectional study

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ABSTRACT

Background: Hemifacial microsomia (HFM) results from the malformation of facial structures derived from the first and second pharyngeal arches. The ramus of the mandible is the most deformed part of the mandible in HFM, which subsequently affects the linear measurements of the different parts of the mandible. This study evaluated the anatomical differences between the affected and contralateral mandibular ramus and body (MRB) in a select cohort of HFM patients in South Africa.

Methods: This is a serial retrospective study of 20 HFM patients. They were categorised into mild or severe groups by the Pruzansky-Kaban grading and into three age-dependent groups (1–5, 6–12 and 13–19 years old). Linear and angular measurements of the MRB components were recorded from preoperative computed tomography scans to compare severity, age groups, ramus and body index (RBI), and the affected to contralateral (A/C) sides ratio.

Result: Significant differences existed in the linear and angular measurements of the mandible and RBI between affected and contralateral sides, except for the MBL. The mean differences between the mild and severe RBI deformities were insignificant. The A/C ratio was insignificantly smaller in the severe group than in the mild group. Age grouping did not significantly affect the A/C ratio in the mandible ramus and body.

Conclusion: Mandibular asymmetry is more noticeable in HFM patients between 13 and 19 years old. The A/C ratio of the MRB did not worsen with different age groups and severity grading in this study. Hence, clinicians should postpone surgery until HFM patients attain skeletal maturity.

1. Introduction

Facial structures originate from the first and second pharyngeal arches during intrauterine life's fourth to eighth weeks [1,2]. Facial malformation can occur due to genetic or environmental factors or a combination of the two [3]. This deformity includes DiGeorge, Pierre Robin, Treacher Collins syndromes, cleft lip and palate and hemifacial microsomia [4]. The prevalence of hemifacial microsomia (HFM) is 1:3500–5600 of the world population, second only to cleft lip and palate in the congenital anomalies of the face [5]. The hypoplastic mandible and unilateral ear deformities are the positive markers of HFM [5]. Clinicians have proposed several classification systems to help improve the diagnosis and treatment of HFM due to its varying physical presentation. The seminal work of Pruzansky [6] emphasised the malformation of the mandible and glenoid fossa, while Kaban and colleagues modified the classification to include the temporomandibular joint [7]. David et al. [8] incorporated skeletal malformation, auricular deformity, and soft tissue defect (SAT), which was further modified by Vento et al. [9] to encompass orbit-mandible-ear-nerve-soft tissue deformity (OMENS). Horgan et al. [10] later expanded the OMENS classification to include extracraniofacial deformities (OMENS+). Based on functional treatment types, the Pruzansky-Kaban classification of the mandible is grouped as mild (Types I and IIA) or severe (Types IIB and III) [11,12].

The mandibular ramus is the most affected component of the mandible in HFM. The ramus deformity has an impact on the linear measurements of ramus-condyle height, ramus width (RW), sigmoid notch, mandible body length, mandible body height, chin point deviation (CPD) and mandible gonial angle [12–14]. Although HFM is presented as a unilateral deformity, the contralateral (unaffected) side is also slightly affected by this defect [11,15,16]. Hence, this paper will refer to the unaffected side as contralateral. The literature reports that the affected mandibular body length (MBL) may be longer than the contralateral MBL in the growing HFM subjects [14]. There is a lack of

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Abbreviations

A/C ratio	Affected to contralateral ratio
BI	Body index
CPD	Chin point deviation
CT	Computed tomography
FA	Facial asymmetry
HFM	Hemifacial microsomia
ICC	Intra-class correlation coefficient
IQR	Interquartile range
MBH	Mandibular body height
MBL	Mandibular body length
MGA	Mandibular gonial angle
MNW	Mandibular notch width
MRB	Mandible ramus and body
MRH	Mandibular ramus height
MRW	Mandibular ramus width
OMENS+	Orbit-mandible-ear-nerve-soft tissue and extra craniofacial deformities
RBI	Mandibular ramus and body index
RI	Ramus index
RW	Ramus width
SAT	Skeletal malformation, auricular deformity, and soft tissue defect
TML	Total mandibular length

literature on the angle between affected and contralateral MBL and affected and contralateral total mandibular length (TML) in HFM patients. Studies have suggested that HFM affects the ramus more than the body or equally in the hypoplastic mandible [12–14,16]. The mandible ramus to body index (BI) in HFM patients has not been reported in the literature. This study aims to evaluate the anatomical differences between the affected and contralateral mandibular ramus and body (MRB) in select HFM patients in South Africa.

2. Materials and method

2.1. Patients

This serial retrospective study was conducted using two-dimensional preoperative computed tomography (CT) and three-dimensional CT of head scans acquired from the Departments of Plastic and Reconstructive Surgery database at the Inkosi Albert Luthuli Central Hospital, Durban, South Africa. Thirty-five patients' medical records were from the hospital's electronic archive, but 15 were excluded due to the unavailable CT records and previous surgical intervention. This study comprised preoperative scans of 20 consecutive HFM patients (age range of 1–16 years) who presented to the Craniofacial Unit at Inkosi Albert Luthuli Central Hospital between September 2009 and November 2021. The patients were grouped according to the Pruzansky-Kaban classification, grading them into mild (Types I and IIa) and severe (Types IIb and III) [12]. We selected patients with unilateral involvement for inclusion in the study. The patients included were divided into age groups (childhood-adolescence): 1–5, 6–12, and 13–19 years. The mandible ramus and body index (RBI) in HFM patients were investigated. The linear measurements of the affected side and the contralateral side value (A/C ratio) were calculated. Informed consent was obtained from patients before obtaining the image data.

2.2. Image acquisition

Image Acquisition and Analysis Axial CT scans of selected patients were retrieved from the hospital's Picture Archiving and Communication System and saved in Digital Imaging and Communication in Medicine (DICOM) format. These CT images were acquired routinely with either a 128-slice SOMATOM Definition AS scanner or a SOMATOM Definition Flash CT Scanner (Siemens Healthineers, Forchheim, Germany). Before the image acquisition, the patients were positioned in a supine position. The standard protocol is to do a coronal and sagittal reconstruction on the bone and soft tissue settings. The slice thickness of the scans of HFM patients ranged from 0.6 to 3 mm with a 0.3 mm increment. The acquired axial CT images were reformatted into sagittal and coronal planes in the three-dimensional (3D)-multiplanar reconstruction view and analysed using the Horos Open-Source Medical Image Viewer software version 3.3.6 (Horos Project, Annapolis, MD) (accessed 19 June 2023). The Horos software automatically calibrated the CT scan images and manually verified the calibration. Computed tomography scans were aligned in the orbitomeatal plane. Linear measurements were performed on the bone window using length and angle tools (Fig. 1 A–C). Measurements were taken three times to ensure accuracy and reliability. The dimensions recorded from the reconstructed 3D-CT scans are outlined in Table 1. A specialist radiologist and an anatomist interpreted the images.

2.3. Statistical analysis

Inter-examiner reliability was analysed to assess the credibility of the measurements. Two independent researchers performed identical measurements. The same researchers performed repeated measurements after two weeks of initial measurements. The inter-researcher reliability was assessed by the intra-class correlation coefficient (ICC). The mean values were finally calculated for further analysis.

Normality was tested using the Shapiro–Wilk test, while homogeneity of variance was tested using the Levene test for all quantitative data. When the data express normality and homogeneity of variance, independent *t*-tests were used to assess the differences in measurements by severity; paired *t*-tests were used to compare the differences between the affected and contralateral sides in the same MRB; one-way analysis of variance (one-way ANOVA) tests were used to compare the differences between different age groups. Non-parametric tests were used when data failed to meet normality test and homogeneity of variance ($P > 0.05$). A $P < 0.05$ value was considered a statistical difference. All statistical analyses were completed using the SPSS 28.0 software (IBM Corp., Armonk, NY, USA).

3. Results

Twenty patients with HFM were involved in this study; eight were male (40%), and twelve were females (60%), with a mean age of 7.75 ± 5.45. The right side was affected in twelve patients (60%), while the left was affected in eight (40%). Seven (35%) patients had mild HFM, while thirteen (65%) patients had severe HFM. Ten (50%) patients were aged 1–5 years, five (25%) patients were aged 6–12 years, and five (25%) patients were aged 13–19 years.

3.1. Inter-examiner and reliability test

The ICC calculation results are shown in Table 2. Each researcher's mean values were used for inter-researcher reliability analysis. The inter-researcher reliability (ICC 0.790–0.978) was high. All measurements showed good reliability.

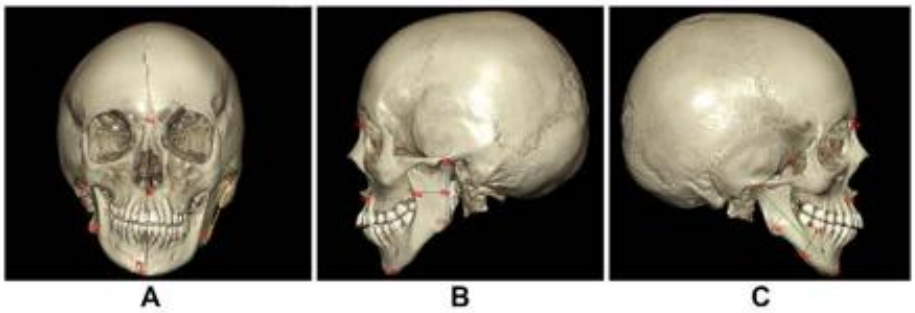

Fig. 1. 3DCT scans of a 14-year-old female right-sided HFM patient with the right hyperplastic coronoid process. (A) Frontal view (B) Left lateral view (C) Right lateral view. *A representation of the mandibular landmarks as defined in* Table 1. *Co condylion, Cr coronoideus, Ra anterior margin of the ascending ramus, Rp posterior margin of the ascending ramus, Go gonion, Pg pogonion, Me menton.*

Table 1
Measurements taken on the reconstructed 3D-CT scan.

Mandibular Components	Definition
Mandibular ramus height (MRH)	distance between the condylion (Co) and the gonion (Go).
Mandibular notch width (MNW)	distance between the condylion (Co) and the coronoideus (Cr).
Mandibular ramus width (MRW)	horizontal distance midway between the anterior (Ra) and posterior (Rp) margins of the ascending ramus.
Mandibular body height (MBH)	the vertical distance between the mandibular first molar tooth superior alveolar process (Al) and the mandibular plane (Mp) line (a line drawn from the gonion to the pogonion).
Mandibular body length (MBL)	distance between the gonion (Go) and the pogonion (Pg).
Mandibular gonial angle (MGA)	the angular distance between the Co, Go and Pg.
Chin point deviation (CPD)	distance between the midline [a sagittal line crossing the nasion (Na) and the subnasal (Sb) point was defined as the midline] and the second line from the nasion through the menton (Me) - distance of the Me from this midline.
Total mandibular length (TML)	distance between the Co and Pg.
Ramus index (RI)	the ratio between MRW and MRH.
Body index (BI)	the ratio between MBH and MBL.

3.2. Morphometric parameters of the mandible in the affected and contralateral sides

There was a significant difference between affected and contralateral sides in MRH, MRW, MNW, MBH, and TML except for MBL (Table 3A). There was a significant difference between affected and contralateral MGA with a median of 133.74 (interquartile range of 126.11–136.22) and 131.32 (interquartile range of 124.54–134.45) degrees, respectively (Table 3B).

Table 2
Inter-researcher reliability analysis.

Parameters	ICC	95% CI
MRHAffected	0.978	0.956–0.997
MRHContralateral	0.937	0.905–0.964
MRWAffected	0.837	0.805–0.864
MRWContralateral	0.868	0.818–0.897
MNWAffected	0.877	0.815–0.898
MNWContralateral	0.890	0.806–0.892
MBLAffected	0.798	0.761–0.830
MBLContralateral	0.823	0.782–0.856
MBHAffected	0.794	0.786–0.880
MBHContralateral	0.832	0.775–0.871
MGAAffected	0.807	0.770–0.838
MGAUnaffected	0.870	0.842–0.893
CPD	0.921	0.905–0.964
TMLAffected	0.797	0.720–0.848
TMLContralateral	0.790	0.751–0.823

ICC, intra-class correlation; CI, confidence interval.

Table 3
a Linear mean difference between morphometric parameters of the MRB in the affected and contralateral sides.

Morphometric parameters	Mean difference ± SD (mm)	p-value
MRHAffected – MRHContralateral	−12.52 ± 8.17	<0.001*
MRWAffected – MRWContralateral	−5.65 ± 3.19	<0.001*
MNWAffected – MNWContralateral	−5.98 ± 3.95	<0.001*
MBLAffected – MBLContralateral	−2.07 ± 8.83	0.31
MBHAffected – MBHContralateral	−1.27 ± 1.81	<0.001*
TMLAffected –TMLContralateral	−12.46 ± 11.99	<0.001*

MRHAffected: affected mandibular ramus height, MRHContralateral: contralateral mandibular ramus height, MRWAffected: affected mandibular ramus width, MRWContralateral: contralateral mandibular ramus width, MNWAffected: affected mandibular notch width, MNWContralateral: contralateral mandibular notch width, MBLAffected: affected mandibular body length, MBLContralateral: contralateral mandibular + body length, MBHAffected: affected mandibular body height MBHContralateral: contralateral mandibular body height, TBLAffected: affected total mandibular length, TBLContralateral: contralateral total mandibular length. SD: standard deviation, p-value: <0.05 is significant. (Paired T-Test).

3.3. Ramus and body index

The ramus index (RI) between the affected and contralateral sides changed significantly (Table 4A). The BI between the affected and contralateral sides changed significantly (Table 4B). The mean difference between affected and contralateral RI in the mild and severe grading of HFM is −0.14 ± 0.14 and −0.18 ± 0.41, respectively. At the same time, the mean difference between affected and contralateral BI in the mild and severe grading of HFM is −0.03 ± 0.60 and 0.15 ± 0.55, respectively. The differences between the mild and severe deformities were insignificant (Table 4C). This suggested the mandible body may be equally affected as the mandible ramus in HFM. The RI increases across age groups (1–5, 6–12, and 13–19 years). The contralateral RI increases significantly in age groups 1–5 and 13–19 years (Table 4D). The affected BI increases between age groups 1–5 and 6–12 years but decreases

Table 3
b Median angle between the affected and contralateral mandibular gonial angle.

Morphometric parameters	Affected Median (IQR)°	Contralateral Median (IQR)°	p-value
MGA	133.74 (126.11–136.22)	131.32 (124.54–134.45)	<0.001*

MGAAffected: affected gonial angle, MGAContralateral: contralateral gonial angle. Median (°), p-value: <0.05 is significant. (Wilcoxon ranked signed Test).

Table 4
a Mandible ramus index.

Parameters	Affected Mean ± SD (mm)	Contralateral Mean ± SD (mm)	p-value
MRH	27.79 ± 9.19	40.31 ± 9.84	<0.001*
MRW	20.36 ± 4.62	26.01 ± 5.28	<0.001*
MRH:MRW	1.39 ± 0.45	1.55 ± 0.29	0.002*

MRH: mandibular ramus height, MRW: mandibular ramus width, MRH: MRW: mandibular ramus height: mandibular ramus width (Ramus) index. Mean ± SD (mm), p-value: <0.05 is significant. (Paired T-Test).

Table 4
b Mandible body index.

Parameters	Affected Mean ± SD (mm)	Contralateral Mean ± SD (mm)	p-value
MBL	49.28 ± 17.56	51.36 ± 18.13	<0.001*
MBH	18.63 ± 4.89	19.90 ± 4.63	<0.001*
MBL:MBH	2.39 ± 0.58	2.55 ± 0.47	0.049*

MBH: mandibular body height, MBL: mandibular body length, MBL: MBH: *mandibular body length: mandibular body height (Body) index. Mean ± SD (mm), p-value: < 0.05 is significant. (Paired T-Test).*

Table 4
c Mandible ramus and body index (RBI) vs HFM grading.

Parameters	Mild		Severe		p-value
	Affected	Contralateral	Affected	Contralateral	
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Ramus index	1.38 ± 0.37	1.52 ± 0.37	1.39 ± 0.50	1.57 ± 0.24	0.83
Body index	2.37 ± 0.51	2.40 ± 0.38	2.77 ± 0.58	2.63 ± 0.51	0.52

Ramus index MRH: MRW, Body index MBL: MBH. HFM grading: mild deformity, severe deformity. SD: Standard deviation, p-value: < 0.05 is significant. (Independent T-Test using mean difference between affected and contralateral).

between age groups 6–12 and 13–19 years. The contralateral BI decreases between age groups 1–5 and 6–12 years but increases between age groups 6–12 and 13–19 years (Fig. 2)..

3.4. Affected to contralateral ratio vs HFM grading and age

The mandibular asymmetry ratio was smaller in the severe group than in the mild group. The median affected to contralateral (A/C) ratio did not change significantly in the effect of severity (between mild and severe group) in the ramus height (RatioMRH), body length (RatioMBL) and total mandibular length (RatioTML) (Table 5A). There was no significant effect of severity on the A/C ratio in the RW (p-value = 0.44), notch width (p-value = 0.21), and body height (p-value = 0.30) (Table 5A–B). Age grouping did not significantly affect the A/C ratio in the mandible ramus and body (Figs. 3–4). The A/C ratio decreases with increasing age groups in MRH and MRW, whereas the ratio increases with increasing age groups in MBL and TML. These changes were insignificant across all age groups (Figs. 3–4).

3.5. Chin point deviation

The median value of CPD in this study is 5.11 (3.71–6.22) °. The mandibular asymmetry ratio was smaller in the severe group than in the mild group. The median value did not change significantly in the effect of severity (between mild and severe groups) in the CPD (Table 6). The angles in the CPD varied but were not significant (0.47) across all age groups. The angle decreases insignificantly between age groups 1–5 and 6–12 years but increases insignificantly between age groups 6–12 and 13–19 years (Fig. 5).

4. Discussion

The mandibular deformity in HFM patients varies in its presentation from one person to another. The mandible features in the general population differ in size, shape, sagittal and vertical discrepancies relative to the maxilla and cranial base [11,15]. This study evaluated the anatomical differences between the affected and contralateral MRB in select HFM patients in South Africa.

The mandibular ramus is reported to be the most affected part of the mandible in HFM. The ramus height, ramus width, ramus index, body length, body height, body index, and gonial angle on the affected side are shorter than the contralateral side in HFM subjects. This finding suggests the ramus and body are involved in HFM patients. This report aligns with the results of the studies by Chen et al. [11] Renkema et al. [13] and Zhang et al. [16]. Shetye et al. [14] suggested the mean value of MBL on the affected side might be longer than the contralateral side.

Regarding the severity grading of HFM in this study, the ramus and body (R-B) index, the A/C ratio (RatioMRH, RatioMRW, RatioMNW, RatioMBH, and RatioTML) and CPD change insignificantly between the mild and severe groups in HFM patients, except RatioMBL shows insignificant similarity between severity levels. However, Zhang et al. [16] reported a significant change in the mild and severe groups in the A/C ratio in the ramus height and body length. The small sample size and multifactorial origin of HFM in this current study may account for this variation [3].

Age impacts the development of the HFM ramus index, A/C ratio of MRH and MRW in this study. The affected and contralateral RI, RatioMRH and RatioMRW continue to increase directly proportional to age from early childhood to adolescence. This growth pattern was not seen in this study's mandible body and the CPD (Figs. 2–5). The ramus-condyle unit, gonial angle, mandibular symphysis and some parts of the alveolar ridges develop from endochondral bone formation and others

Table 4
d Post-hoc analysis of MBAffectedindex.

Multiple Comparisons							
Tukey HSD							
Dependent Variable	(I) Recoded Age	(J) Recoded Age	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Contralateral RI	1–5	6–12	−0.20458	0.13532	0.310	−0.5517	0.1426
		13–19	−0.38821*	0.13532	0.027	−0.7354	−0.0411
	6–12	1–5	0.20458	0.13532	0.310	−0.1426	0.5517
		13–19	−0.18363	0.15626	0.483	−0.5845	0.2172
	13–19	1–5	0.38821*	0.13532	0.027	0.0411	0.7354
		6–12	0.18363	0.15626	0.483	−0.2172	0.5845

*Contralateral RI: mandibular body length: body height index on the contralateral side. Age group 1–5, 6–12, and 13–19 years. Mean ± SD (mm), *. The mean difference is significant at the 0.05 level. (Tukey's Test).*

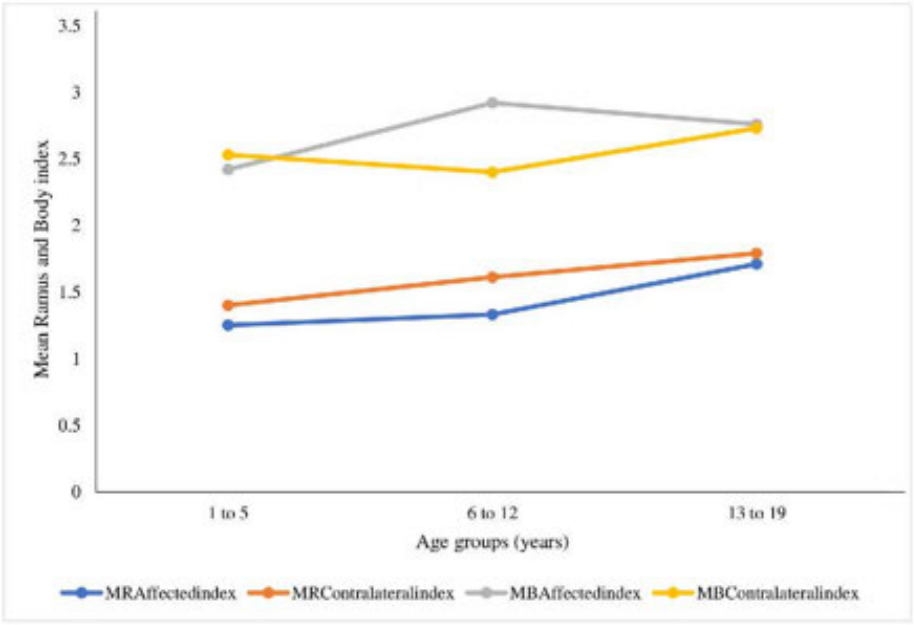

Fig. 2. Mandible ramus and body index (RBI) vs. Age group. X-axis illustrates age grouping in years, and Y-axis displays the mean ramus-body index. *MRAffectedindex: mandibular ramus height: ramus width ratio on the affected side, MRContralateralindex: mandibular ramus height: ramus width ratio on the contralateral side, MBAffectedindex: mandibular body length: body height ratio on the affected side, MBContralateralindex: mandibular body length: body height ratio on the contralateral side.* (°): *degree. Age group 1–5, 6–12, and 13–19 years. (One-way ANOVA).*

Table 5
a Mean ratio between the affected and contralateral mandible ramus width, notch width, and body height compared with HFM grading.

Parameters	Pruzansky-Kaban Type		*p*-value
	Mild	Severe	
	Mean ± SD	Mean ± SD	
RatioMRW	0.82 ± 0.12	0.77 ± 0.11	0.44
RatioMNW	0.69 ± 0.19	0.55 ± 0.28	0.21
RatioMBH	0.96 ± 0.09	0.92 ± 0.08	0.30

RatioMRW: A/C ratio ramus width, RatioMNW: A/C ratio notch width, RatioMBH: A/C ratio body height. HFM grading: mild deformity, severe deformity. SD: Standard deviation, p-value: <0.05 is significant. (Independent sample T-Test).

Table 5
b Median ratio between the affected and contralateral mandible ramus height, body length and total mandibular length compared with HFM grading.

Parameters	Pruzansky-Kaban Type		*p*-value
	Mild	Severe	
	Median (IQR)	Median (IQR)	
RatioMRH	0.75 (0.63–0.82)	0.74(0.56–0.82)	0.42
RatioMBL	0.97(0.86–1.04)	0.97(0.86–1.00)	0.71
RatioTML	0.97(0.83–0.98)	0.89(0.77–0.93)	0.28

RatioMRH: A/C ratio ramus height, RatioMBL: A/C ratio body length, RatioTML: A/C ratio total mandible length. HFM grading: mild deformity, severe deformity. IQR: interquartile range, p-value: <0.05 is significant. (Mann-Whitney Test).

from intramembranous osteogenesis [17]. These distinguishing osteogenic patterns during prenatal and postnatal development may result in different features of HFM [16–18]. This may account for our study's varying characteristics of the mandibular components.

The buccal fat pad may mask facial asymmetry (FA) in HFM patients during infancy. The buccal fat pad shrinks considerably in adults, accentuating FA in HFM patients [19,20]. FA is suggested to worsen with age and severity grading in HFM patients [11,14]. When the ratio between the two sides remains constant, the affected side's growth rate is slower than the contralateral side [21]. Some authors consider the affected side's growth rate not parallel to the contralateral side [11,16,22]. In contrast, others consider that the growth rate remains constant with time between the two sides [13,23]. This study aligns with the latter as the ratio between the affected and contralateral sides of the MRB across different age groups changed but was not significant (RatioMRH = 0.74, RatioMRW = 0.14, RatioMNW = 0.67, RatioMBL = 0.48, RatioMBH = 0.78, and RatioTML = 0.68). Some studies have suggested that mandibular asymmetry increases with the increasing severity of HFM, especially in severe deformities of HFM [11,16]. No significant changes in the MRB existed in our study's mild and severe deformities. Regarding the progression of FA in HFM, some authors have suggested that FA increases with time, which is progressive in nature. Early surgical correction (between ages 6–12 years) is advocated, thus promoting midfacial growth [11,14,16,24,25]. Others have disputed the long-term stability of early treatment in HFM patients [13,23,26]. The treatment approach of HFM, such as distraction osteogenesis and costochondral grafting, requires multiple revisional interventions due to the relapse of previous gains in facial symmetry and the recurrence of FA after initial interventions [26,27]. Hence, FA remains constant with time in HFM, which is non-progressive [13,26–28]. The peak facial growth in males is around 16–18 years, while in females, it is about 14–16 years of age in the general population [29,30]. Therefore, to ease psychosocial and economic burdens, surgeons should delay intervention until after the growth completion of the mandible in HFM patients. New visualising techniques for planning interventions can generate 3D printed operation templates; the challenge lies in the treatment timeline and availability [31].

4.1. Limitation

The limitation of this study is the small sample size due to the prevalence of HFM in the population, and a large sample size from multiple health facilities may strengthen the statistical power of the analyses; it is a retrospective cross-sectional study using mean age

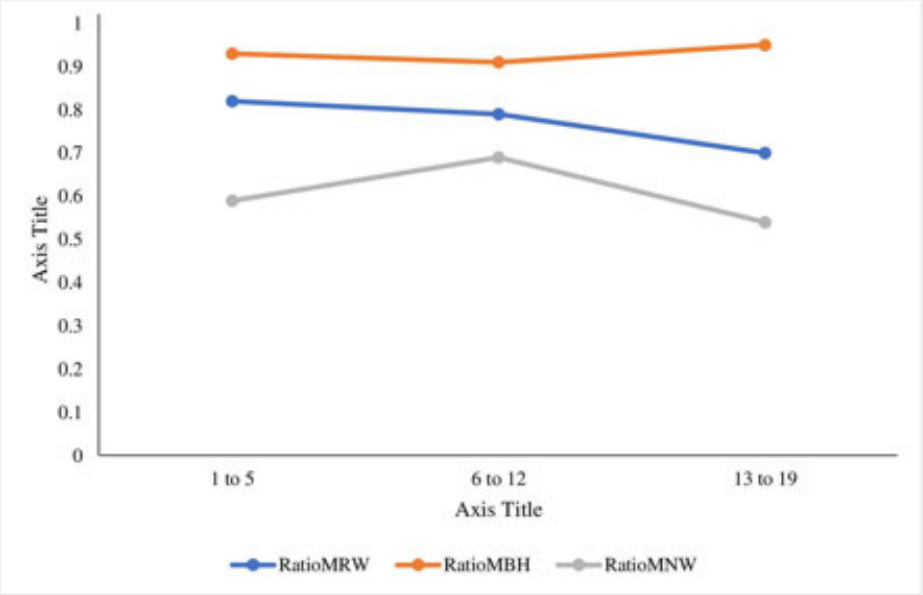

Fig. 3. Mean ratio between the affected and contralateral mandible ramus width, notch width, gonial angle and body height compared with age group. X-axis illustrates age grouping in years, and Y-axis displays the mean ratio MRW, MNW and MBH. *RatioMRW: A/C ratio ramus width, RatioMNW: A/C ratio notch width, RatioMBH: A/C ratio body height. Age group = 1–5, 6–12, and 13–19 years. (One-way ANOVA).*

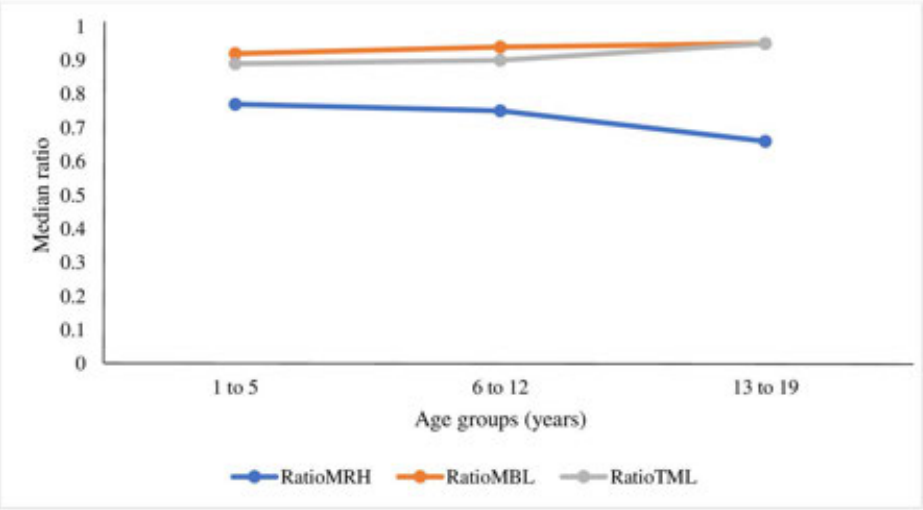

Fig. 4. Median ratio between the affected and contralateral mandible ramus height, body length and total length compared with age group. X-axis illustrates age grouping in years, and Y-axis displays the median ratio MRH, MBL and TML. *RatioMRH: A/C ratio ramus height, RatioMBL: A/C ratio body length, RatioTML: A/C ratio total mandible length. Age group = 1–5, 6–12, and 13–19 years. (Kruskal-Wallis Test).*

Table 6
Chin point deviation vs HFM grading.

Parameters	Pruzansky-Kaban Type		*p*-value
	Mild	Severe	
	Median (IQR) °	Median (IQR) °	
CPD	5.12 (4.28–5.63)	4.36 (3.59–6.45)	0.94

CPD: Chin Point Deviation. HFM grading: mild deformity, severe deformity. IQR: interquartile range, p-value: <0.05 is significant. (Mann-Whitney Test).

groups. Longitudinal data can provide a specific growth model of MRB features in subjects with HFM in future research on HFM. The lack of subgroup analysis within the specific sex groups would have examined the similarities or differences in the developmental growth of HFM patients. A comparative analysis of the measurements between hemifacial group and control group would have significantly improve study.

The heterogeneous characteristics of HFM presentation require a distinct understanding of individual-to-individual variation in diagnosing, treating, and managing this deformity. Therefore, a well-structured, tailored interventional approach based on individual needs is recommended.

5. Conclusion

This study's findings include a ramus influenced by HFM severity grading and age grouping insignificantly, a body not influenced by HFM severity grading and age grouping, FA is more noticeable in HFM

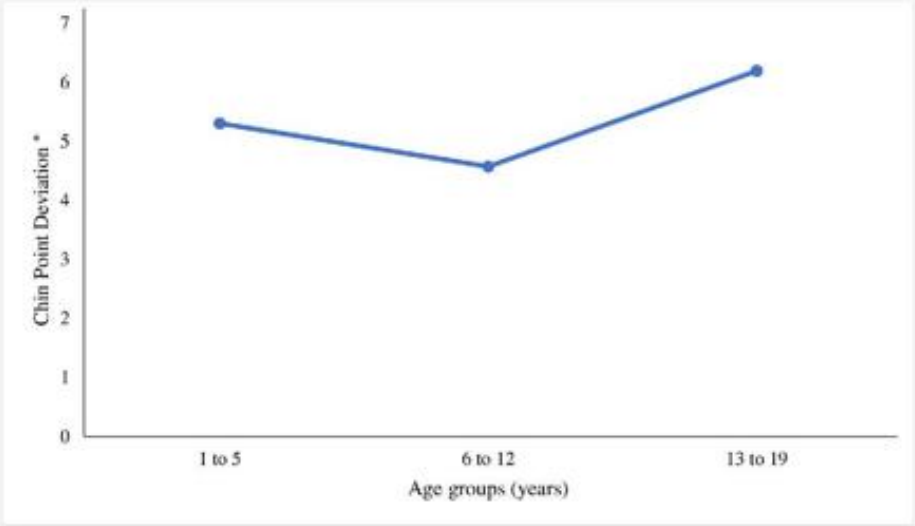

Fig. 5. Median angle between chin point deviation compared with age group. X-axis illustrates age grouping in years, and Y-axis displays the median ratio CPD. *CPD: chin point deviation. (°): degree. Age group 1–5, 6–12, and 13–19 years. (Kruskal-Wallis Test).*

patients between the ages of 13–19 years. The A/C ratio of the MRB did not worsen with different age groups and severity grading in this study. Hence, clinicians should postpone surgery until HFM patients attain skeletal maturity.

Ethical statement

Ethical approval for this study was obtained from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (BREC/00004225/2022) and the Department of Health in the Province of KwaZulu-Natal (NHRD Ref.: KZ_202206_031). All methods were carried out following the University of KwaZulu-Natal standard-approved guidelines and regulations, and all experimental protocols were conducted as per the Helsinki Declaration. Written informed consent has been obtained from the participants of this study.

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CRediT authorship contribution statement

Peterson Makinde Atiba: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Dolongo Onyangunga-Kabanga:** Writing – review & editing, Validation, Resources, Investigation. **Anil Madaree:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Lelika Lazarus:** Writing – review & editing, Supervision, Resources, Conceptualization.

Declaration of competing interest

None.

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BRIDGING TEXT
FROM CHAPTER FOUR TO FIVE

Chapter four evaluated anatomical differences between affected and MRB in a select cohort of patients with HFM in South Africa. The cohort of untreated patients with HFM was classified into mild and severe groups using the Pruzansky-Kaban classification. Linear and angular measurements of the MRB components were recorded from preoperative CT scans to compare severity, age groups, RBI, and the A/C sides ratio. Significant changes were observed in linear and angular measurements of the mandible and RBI between affected and contralateral sides, except for the MBL. An insignificant severity grading in RBI and A/C ratio was found. FA becomes more pronounced during the adolescent stage. FA did not worsen with age and severity grading in patients with HFM. Hence, FA is not progressive in HFM. AFG is a treatment option used to obscure FA in HFM. The next chapter explored AFG treatment in patients with HFM and its potential effect on the growth of the affected mandible.

The manuscript in chapter five, entitled **"*An assessment of autologous fat graft administration in hemifacial microsomia patients with or without distraction osteogenesis: A preliminary study*,"** was submitted to the Plastic Surgery Journal on 01st November 2024 and is currently under review (Manuscript number: PSG-24-0209. Manuscript and references are presented according to the journal's specification).

CHAPTER FIVE

MANUSCRIPT FOUR

An assessment of autologous fat graft administration in hemifacial microsomia patients with or without distraction osteogenesis: A preliminary study

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Declaration of conflict interest

None

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Ethical approval and informed consent statements

Ethical approval was obtained from the Biomedical Research Ethics Committee of the institution (BREC/00004225/2022) and the Department of Health in the Province (NHRD Ref.: KZ_202206_031). All methods followed the institution's standard-approved guidelines and regulations, and all experimental protocols were conducted as per the Helsinki Declaration. Participants or their parents were provided informed written consent (or assent, where applicable) for this study.

Data availability statement

All data generated or analysed during this study are included in this manuscript and available on request to the corresponding author.

Authors Contribution

Peterson Makinde Atiba: Conceptualisation, Methodology, Formal analysis, Investigation, Data Curation, Writing- Original Draft, Writing- Reviewing and Editing. **Okikioluwa Stephen Aladeyelu**: Methodology, Formal analysis, Writing- Reviewing and Editing. **Dolongo Onyangunga-Kabanga**: Validation, Investigation, Resource, Writing- Reviewing and Editing. **Anil Madaree**: Conceptualisation, Methodology, Investigation, Writing- Reviewing and Editing, Supervision. **Lelika Lazarus**: Conceptualisation, Resource, Writing- Reviewing and Editing, Supervision. All authors have read and approved the final manuscript.

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Under peer review: 01st November 2024

Abstract

Purpose: This study aims to assess the impact of autologous fat graft (AFG) administration in patients with HFM with or without distraction osteogenesis (MDO).

Methods: The patients were divided into AFG-treated (mean age: 5.8 ±3.89 years) and MDO+AFG-treated (mean age: 8.8 ±4.32years) groups based on functional requirement, each comprising five patients. Computed tomography scans of the mandible were used for the measurement of the ramus height (MRH), ramus width (MRW), body length (MBL), body height (MBH), chin point deviation (CPD) and occlusion plane angle (OPA) of the affected and unaffected sides.

Results: Following fat treatment in the AFG group, there were significant increases in the affected MRH and MRW, while both CPD and OPA showed a significant decrease ($p < 0.05$). Following fat treatment in the MDO+AFG group, a significant increase was observed in the affected MBL, whereas the increase in the affected MBH was not significant. In the AFG group, the growth increases in the affected MRH and MBL were not significantly different compared to the unaffected side. Additionally, in the MDO+AFG group, the growth increases in the unaffected MRH, MRW, MBL, and MBH did not significantly differ from the affected side.

Conclusion: In the AFG group, AFG significantly improves MRW, MRH, CPD and OPA symmetry and deformity. In the MDO+AFG group, AFG significantly improves symmetry and deformity in the MBL. AFG is a valuable procedure in the management of mild and severe HFM.

Keywords: Hemifacial microsomia; autologous fat graft; distraction osteogenesis; mandible

INTRODUCTION

Hemifacial microsomia (HFM), also referred to as craniofacial microsomia, is a congenital craniofacial anomaly that arises from the first and second pharyngeal arches and presents a spectrum of deformities characterised by underdevelopment or asymmetry of skeletal and soft tissue structures on one side of the face.[1,2] It involves the mandible, ear, orbit, cheek, and soft tissues, affecting facial aesthetics and function.[1,3] HFM deformity grading ranges from mild to severe, and treatment modalities differ based on functional requirements, such as autologous fat grafting (AFG) treatment in mild cases and distraction osteogenesis (MDO) or orthognathic surgery in severe cases.[4,5] Among the array of treatment modalities for the hypoplastic mandible, AFG has emerged as a valuable procedure for managing HFM.[6] This minimally invasive technique offers a versatile route to rectify soft tissue deformities, restores volume and improves facial symmetry, either as a separate intervention or combined with MDO.[7,8]

Human fat tissue is a source of mesenchymal stem cells known as adipose-derived stem cells (ADSC), which have pluripotent capacity and produce a variety of angiogenic, osteogenic, and antiapoptotic factors.[9] ADSC can potentially promote skeletal growth through their ability to differentiate into bone cells, support tissue regeneration via paracrine signalling, and enhance vascularisation.[10] AFG involves harvesting adipose tissue from the patient's body, typically from areas with excess fat deposits, and re-injecting it into the deficient areas of the face.[11,12] The procedure seeks to augment facial contours, fill soft tissue defects, and enhance overall facial harmony.[13] The donor site for AFG includes the anterior abdominal, thigh, hip, and gluteal regions.[14] In the context of HFM, fat grafting can play a crucial role in achieving more balanced facial proportions, improving aesthetic outcomes, and addressing functional concerns related to soft tissue deficiencies.[13] The pluripotent capacity of the human fat tissue may have also contributed to the effectiveness of AFG.

When combined with MDO, a surgical technique used to lengthen or reshape bones, AFG offers a comprehensive approach to addressing both skeletal and soft tissue abnormalities in HFM.[6,15] MDO aims to gradually elongate or reposition bony structures to correct facial asymmetry (FA) and restore symmetry. However, MDO may not fully address soft tissue deficiencies despite its effectiveness in addressing skeletal deformities, highlighting the complementary role of fat grafting in achieving optimal facial aesthetics and function.[7,15] The synergy between MDO and AFG lies in their ability to address the multidimensional nature of HFM.[13,16] While MDO focuses on skeletal reconstruction, fat grafting targets soft tissue volume restoration and contour refinement, thereby providing a comprehensive solution to the complex facial deformities associated with HFM.[5]

Moreover, the minimally invasive nature of fat grafting makes it an appealing option, particularly in growing patients who may benefit from early intervention to optimise facial growth and development.[5,13] Studies have shown that surgeons must undertake initial repair of the facial skeleton for soft tissue hypoplasia management to be achieved.[3,5,16] Currently, the literature is sparse regarding the concurrent use of AFG after distraction in patients with HFM. This study assesses the impact of autologous fat transfer administration in patients with HFM with or without MDO.

METHODS

The study consisted of ten patients (age range: 2-16 years) diagnosed with HFM at a public hospital's Department of Plastic and Reconstructive Surgery from June 2013 to December 2023. Pruzansky-Kaban classification was used to grade the severity of HFM into mild and severe cases.[17] In mild cases (Type I and IIA), AFG was applied for cosmetic and structural improvement without functional issues. In contrast, severe cases (Type IIB) presented with significant functional impairments, such as airway obstruction and occlusal issues, necessitating MDO to correct the underlying structural deformities before fat grafting. MDO

provides immediate structural correction, while AFG primarily augments facial asymmetry, which is more appropriate for milder deformities without functional difficulties.

The first group (AFG group) of five patients (age range: 2-12 years; mean age: 5.8±3.89 years) were classified as mild (Type I and IIA) according to Pruzansky-Kaban grading and received AFG treatment only. The second group (MDO+AFG group) of five patients (age range: 5-16 years; mean age: 8.8±4.32 years) was classified as severe (Type IIB) according to Pruzansky-Kaban grading. The second group received MDO (through oblique osteotomy overcorrection of occlusion with univector external distractors) for functional impairment intervention before AFG. In the MDO+AFG group, mandibular distraction was performed two years before AFG.

The patients' preferred donor sites for AFG were the lower abdomen, outer-medial thighs, and gluteal region based on fat deposit. Fat harvesting, processing and transfer were done using Coleman's technique.[18] Fat transfer was facilitated using 1.0 and 1.5 lipo-injection cannulas with 1ml syringe. Fat graft is injected subperiosteally to facilitate mandibular osteogenesis in the AFG group (Pruzansky-Kaban Type I and IIA) without functional problems. The fat grafts were carefully deposited in various layers using 0.1–0.3ml aliquots injected through discrete access points.[7,12] Patients were released after 24 hours and scheduled for routine follow-ups. Patients visited the Craniofacial Clinic postoperatively after one week of fat grafting and at 1, 3, 6, and 12 months afterward. At each visit, patients underwent a physical examination (by palpation, visual inspection, functional assessment and photographic documentation) to assess the graft status and potential growth of the mandible. The outcomes of the physical examination would suggest whether there would be a need for further fat transfer. Of the ten patients, 2 received one episode of AFG, 5 received two episodes of AFG, 2 received three episodes of AFG, and 1 received four episodes of AFG. The AFG and MDO+AFG groups received a total volume of fat grafts of 163.5 ml and 150.5 ml, respectively, on the affected side. Computed tomography (CT) scans of the affected and unaffected mandible were performed before the

first fat transfer and after the last transfer. The interval between the first and last CT scans is 2-5 years in AFG and 2-6 years in MDO+AFG groups. These scans were compared and analysed.

The image acquisition was made according to the procedure adopted in a previous study by Atiba et al. [19] The measurements were on the affected and unaffected mandibular ramus height "(MRH)- the *distance between the condylion (Co) and the gonion (Go)*, ramus width (MRW)- *horizontal distance midway between the anterior (Ra) and posterior (Rp) margins of the ascending ramus*, body length (MBL)- the *distance between the gonion (Go) and the pogonion (Pg)*, body height (MBH)- *the vertical distance between the mandibular first molar tooth superior alveolar process (Al) and the mandibular plane (Mp) line (a line drawn from the gonion to the pogonion*, chin point deviation (CPD)- *distance between the midline (a sagittal line crossing the nasion and the subnasal point was defined as the midline) and the second line from the nasion through the menton (Me) - distance of the Me from this midline*, and occlusal plane angle (OPA)- *the angle between the occlusal plane (a line joining the interincisal point of the upper central incisors and mesiobuccal cusps of the first upper right or left molar) and Frankfort-Horizontal (F-H) plane (a plane extending from the orbitale (Or) to porion (Pr) point*.[19,20]" CT scans were aligned in the orbitomeatal plane and Frankfort-Horizontal planes in axial and sagittal planes, respectively, and linear measurements were conducted on the bone window utilising length and angle tools (Fig. 1). All the measurements were taken from the lateral view except the CPD, which was measured from the frontal view. Measurements were repeated three times to ensure accuracy and reliability, with image interpretation performed by a consultant radiologist and an anatomist.

The inter-researcher reliability was assessed by the intra-class correlation coefficient (ICC). A paired sample t-test was used to compare the changes in the mandibular parameters (MRH, MRW, MBL, MBH, CPD, and OPA) before and after AFG. In contrast, the independent sample t-test was used to compare the growth rate between the affected and unaffected sides in the

AFG group and MDO+AFG group, given that the data were normally distributed. A $P < 0.05$ value was considered a statistical difference. All statistical analyses were completed using the SPSS 26.0 software (IBM Corp., Armonk, NY, USA).

Fig. 1. 3DCT scans of a 5-year-old female right-sided HFM patient (A) Frontal view (B) Right lateral view *A representation of the mandibular landmarks is defined as Al = alveolar process Co = condylion, Ra = anterior margin of the ascending ramus, Rp = posterior margin of the ascending ramus, Go = gonion, Pg = pogonion, Pr = porion, Me = menton, Mp = mandibular plane, Na = nasion, Or = orbitale, Sb = subnasale.*

RESULTS

The episodes of the fat transfer range from 1-4, a mean of two fat transfer sessions with an average fat volume of 13.63±3.68 ml in the AFG group and 10.55±4.44 ml in the MDO+AFG group. The interval of fat transfer in patients ranges from 3-7 (mean: 4.64±1.43) months of age. The average time between the first and last scans was 3 years in the AFG group and 3.4 years in the MDO+AFG group. The inter-observer reliability ranges from 0.807–0.981. All measurements showed good reliability (Table 1).

Table 1. Inter-researcher reliability analyses

ICC, intra-class correlation; CI, confidence interval

Measurements of mandibles pre- and post-autologous fat grafting in both the AFG and MDO+AFG groups

AFG group

Following fat grafting in the AFG group, significant increases were observed in the affected and unaffected MRH. A significant increase was observed in the affected MRW (p= 0.01), but no significant increase was observed in the unaffected MRW (Table 2A).

Following fat grafting in the AFG group, a significant increase was observed in the unaffected MBL, but an insignificant increase was observed in the affected MBL. No significant increases

were observed in the affected and unaffected MBH (Table 2A). A significant decrease was seen in the CPD (p=0.02) and OPA (p=0.03)

MDO+AFG group

Following fat grafting in the MDO+AFG group, no significant increases were observed in the affected and unaffected MRH. No significant increases were observed in the affected and unaffected MRW (Table 2B).

Following fat grafting in the MDO+AFG group, a significant increase was observed in the affected MBL (p=0.02), but no significant increase was observed in the unaffected MBL. A significant increase was observed in the unaffected MBH (p=0.04), but no significant increase was observed in the affected MBH (Table 2B). An insignificant decrease was seen in the CPD but increased OPA (Table 2B) (Fig. 2).

Fig. 2. 3DCT scans of a female patient at 3 and 6 years, respectively, with a right-sided HFM showing a decrease in CPD post-AFG *(A) A pre-AFG scan showing a CPD of 3.4° (B) A post-AFG scan showing a CPD of 2.6°*

Table 2A. Measurements of mandibles pre- and post-autologous fat grafting in the AFG group

MRH: mandibular ramus height, MRW: mandibular ramus width, MBH: mandibular body height, MBL: mandibular body length. Mean ± SD (mm). CPD: Chin Point Deviation, OPA: occlusal plae angle. Mean ± SD (°): degree, **p-value: <0.05 is significant.*

Table 2B. Measurements of mandibles pre- and post-autologous fat grafting in the MDO+AFG group

MRH: mandibular ramus height, MRW: mandibular ramus width, MBH: mandibular body height, MBL: mandibular body length. Mean ± SD (mm). CPD: Chin Point Deviation, OPA: occlusal plae angle. Mean ± SD (°): degree, **p-value: <0.05 is significant.*

Growth change of the mandible in the AFG and AFG+MDO groups

Following fat grafting in the AFG group over an average of 3 years, the mean growth of the affected MRH and MBL increased, but not significantly compared to the unaffected side. The

mean growth of the unaffected MRW and MBH increased, but not significantly compared to the affected side (Table 3A).

Following fat grafting in the MDO+AFG group over an average of 3.4 years, the mean growth of the unaffected MRH, MRW, MBL and MBH increased, but not significantly compared to the affected side (Table 3B).

Table 3A. Measurements of the mandible growth change following fat treatment in the AFG (average of 3 years) group

*MRH: mandibular ramus height, MRW: mandibular ramus width, MBH: mandibular body height, MBL: mandibular body length. Mean ± SD (mm), *p-value: <0.05 is significant.*

Table 3B. Measurements of the mandible growth change following fat treatment in the MDO+AFG (average of 3.4 years) group

*MRH: mandibular ramus height, MRW: mandibular ramus width, MBH: mandibular body height, MBL: mandibular body length. Mean ± SD (mm), *p-value: <0.05 is significant.*

DISCUSSION

HFM presents multifaceted challenges in craniofacial reconstruction due to skeletal and soft tissue deficiencies, which can result in mild or severe cases.[2,21] Severe cases accompanied by functional issues, such as airway obstruction, are managed by mandibular distractions, but this does not fully resolve soft tissue deficiencies. Mild cases require AFG for soft tissue restoration and may promote mandibular growth.[13,16] Studies have not fully explored the impact of combining MDO with AFG, as opposed to AFG alone, particularly concerning the severity of HFM deformity and growth outcomes.

In this study, fat graft in the AFG group caused increases in the length of the affected MRH and MRW and reduced asymmetry in CPD and OPA. Meanwhile, the MDO+AFG group showed a significant increase in the length of affected MBL. Rajan et al.[7] reported a similar improvement in skin pinch thickness in their series of fat-treated HFM groups. Additionally, studies indicated improvements in the affected ramus height, body length, and CPD in mandibular distraction-treated HFM groups.[22,23] We hypothesised that MDO may alter the

mechanical forces acting on different parts of the mandible, influencing the lengthening of the mandible.[24] The distraction process could lead to more stress and remodelling in the body of the mandible,[16] explaining the significant increase in MBL in the MDO+AFG group compared to the AFG group. Previous findings have suggested that MDO primarily targets skeletal reconstruction,[16] while fat grafting focuses on restoring soft tissue volume, refining contours, and possible induction of bone growth, and offering a comprehensive approach to the intricate facial deformities associated with HFM.[16] Additionally, young patients may benefit from fat graft intervention to optimise facial growth and development.[5,13]

Fat grafting may contribute to growth increases in the affected MRH and MBL, but not significantly compared to the unaffected side in the mild group in this study. In the severe group, the growth increase between the affected and unaffected sides was also not significant. In previous reports, the growth change of the affected side is slower than that of the unaffected side in the HFM mandible after MDO treatment.[23,25] A longitudinal study by Kusnoto and associates on mandibular growth pre-MDO treatment reported that the affected and unaffected MRH and MBL grew at the same rate.[22] The difference in the growth responses and outcomes may be due to pre-existing anatomical differences in the MDO+AFG group, which initially had more severe mandibular deformities than the AFG group. Genetics, nutrition, and overall health can influence the body's natural growth process in patients with HFM.[4,5,26]

The increased growth observed after AFG in patients with HFM is likely multifactorial involving indirect and potentially direct effects. AFG in patients with HFM appears to promote mandibular growth through multiple mechanisms. Firstly, it relaxes the tight, restrictive soft tissue envelope surrounding the mandible by restoring volume, thereby reducing mechanical constraints and allowing for improved bone growth. [5] Secondly, fat grafting indirectly stimulates bone growth by enhancing soft tissue vascularity and creating a more favourable biological environment. [5,13] Lastly, ADSCs within the graft may directly stimulate osteogenesis

and angiogenesis through paracrine effects, although this requires further research in HFM. [10] Clinically, fat grafting is a safe, effective option for improving facial symmetry in HFM, often maintaining volume long-term and serving as an alternative or adjunct to more invasive surgeries.

In this study, the severe (MDO+AFG) group presented with functional issues such as obstructive sleep apnoea due to a hypoplastic mandible. To address these functional problems, mandibular distraction osteogenesis (MDO) was performed to lengthen the mandible.[4,27] In contrast, the mild (AFG) group did not experience functional difficulties and did not require mandibular lengthening.[21] MDO converts a severely hypoplastic mandible into a moderately or mildly hypoplastic one.[23,25] However, the distracted mandible may not have reached its full growth potential. Fat treatment can enhance facial symmetry, volume retention and absorption and promote mandibular growth in HFM.[7,28-30] The present study demonstrated no significant difference in outcome between the AFG and MDO+AFG groups. Based on severity, the suggested HFM treatment algorithm in the present study involves fat graft injection subperiosteally to facilitate mandibular osteogenesis in the AFG group (Pruzansky-Kaban Type I and IIA) without functional problems. In contrast, the MDO+AFG group (Pruzansky-Kaban Type IIB) presented with functional issues such as upper airway obstruction, reduced oropharyngeal volume, feeding difficulties, and speech impairment.[21,25,31] The initial treatment modality for these patients is MDO, which allows immediate structural correction, whereas fat grafting requires more time to achieve structural correction.[16,32] The choice of AFG alone as a treatment option aims to augment FA without functional difficulties.[7] Years after the initial distraction, the severely hypoplastic mandible is converted to a milder form, and fat grafting can further improve mandibular growth in patients with HFM.[5]

The limitations of this study include a small sample size due to the prevalence of HFM in the population studied. A large sample size may strengthen the statistical power of the analyses.

The inclusion of the comparative analysis of the measurements of the untreated HFM would have significantly improved the study. More work is needed on this topic, especially from high-volume centres where the fat graft is practised. The MDO+AFG group age range is higher than the AFG group due to the early MDO intervention, which resulted in later fat treatment in this cohort of patients. We recommend future studies that will evaluate groups within the same age range. Additionally, AFG was not performed at the same interval after MDO for each patient, which could have influenced the reported outcomes.

Conclusion

AFG is a useful procedure in the management of HFM. In the AFG group, where MDO is not considered, AFG has significantly improved MRW, MRH, CPD, and OPA symmetry and deformity. In the MDO+AFG group, MDO may be the initial procedure of choice. AFG can be used a few years later to improve symmetry and deformity further, mainly in the MBL. In addition, AFG treatment has significantly improved soft tissue components in patients with HFM. Finally, we recommend that patients with HFM with airway and malocclusion problems undergo MDO, while those without airway problems should only be treated with fat grafting.

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Table 1. Inter-researcher reliability analyses

Parameters	ICC	95% CI
MRHAffected	0.981	0.965-0.997
MRHUnaffected	0.947	0.925-0.964
MRWAffected	0.877	0.815-0.898
MRWUnaffected	0.890	0.806-0.892
MBLAffected	0.807	0.800-0.838
MBLUnaffected	0.823	0.811-0.856
MBHAffected	0.807	0.799-0.880
MBHUnaffected	0.832	0.818-0.871
CPD	0.941	0.925-0.964
OPA	0.927	0.911-0.955

ICC, intra-class correlation; CI, confidence interval.

Table 2A. Measurements of mandibles pre- and post-autologous fat grafting in the AFG (mild) group

Parameters	Affected			Unaffected		
	Before (Mean±SD) mm	**After (Mean±SD) mm**	***p-value*** ***(Paired T-Test)***	**Before (Mean±SD) mm**	**After (Mean±SD) mm**	***p-value*** ***(Paired T-Test***
MRH	34.90±6.88	38.26±6.28	**0.04***	41.13±5.80	43.85±6.63	**0.02***
MRW	22.27±1.13	24.25±1.95	**0.01***	25.21±2.80	27.96±4.66	**0.11**
MBL	52.44±6.60	59.01±9.89	**0.09**	55.34±8.25	61.11±10.09	**0.03***
MBH	18.53±2.54	20.05±2.97	**0.15**	19.51±2.54	21.33±3.52	**0.14**
	Before *(Mean ± SD)* °	**After *(Mean ± SD)*** °	***p-value*** ***(Paired T-Test)***			
CPD	5.23±1.02	4.34±0.75	**0.02***			
OPA	18.12±0.89	17.08±0.72	**0.03***			

MRH: mandibular ramus height, MRW: mandibular ramus width, MBH: mandibular body height, MBL: mandibular body length. Mean ± SD (mm). CPD: Chin Point Deviation, OPA: occlusal plane angle. Mean ± SD (°): degree, **p-value: <0.05 is significant.*

Table 2B. Measurements of mandibles pre- and post-autologous fat grafting in the MDO+AFG (severe) group

Parameters	Affected			Unaffected		
	Before (Mean±SD) mm	**After (Mean±SD) mm**	***p-value*** ***(Paired T-Test)***	**Before (Mean±SD) mm**	**After (Mean±SD) mm**	***p-value*** ***(Paired T-Test***
MRH	25.84±4.84	31.34±8.78	**0.10**	44.85±5.69	51.28±8.17	**0.05**
MRW	21.03±4.43	22.52±4.45	**0.17**	26.21±4.85	30.12±4.35	**0.11**
MBL	58.43±15.04	64.77±17.51	**0.02***	58.87±14.77	65.61±19.94	**0.06**
MBH	22.73±2.37	24.53±3.37	**0.08**	24.58±3.40	26.96±3.75	**0.04***
	Before (*Mean ± SD)* °	**After (*Mean ± SD)* °**	***p-value*** ***(Paired T-Test)***			
CPD	4.55±1.25	3.38±1.22	**0.20**			
OPA	20.2±5.03	21.9±5.95	**0.05**			

MRH: mandibular ramus height, MRW: mandibular ramus width, MBH: mandibular body height, MBL: mandibular body length. Mean ± SD (mm). CPD: Chin Point Deviation, OPA: occlusal plane angle. Mean ± SD (°): degree, **p-value: <0.05 is significant.*

Table 3A. Measurements of the mandible growth change following fat treatment in the AFG (average of 3 years) group

Parameters	**Affected (Mean±SD) mm**	**Unaffected (Mean±SD) mm**	***p-value*** ***(Independent T-Test)***
MRH	3.36±2.70	2.72±1.53	0.66
MRW	1.98±1.01	2.76±2.95	0.60
MBL	6.57±6.81	5.77±3.76	0.82
MBH	1.51±1.88	1.82±1.77	0.79

*MRH: mandibular ramus height, MRW: mandibular ramus width, MBH: mandibular body height, MBL: mandibular body length. Mean ± SD (mm), *p-value: <0.05 is significant.*

Table 3B. Measurements of the mandible growth change following fat treatment in the MDO+AFG (average of 3.4 years) group

Parameters	Affected (Mean±SD) mm	Unaffected (Mean±SD) mm	*p-value (Independent T-Test)*
MRH	5.5±5.83	6.42±5.39	0.80
MRW	1.48±2.02	3.91±4.25	0.29
MBL	6.34±3.77	6.74±5.66	0.89
MBH	1.8±2.15	2.38±1.74	0.65

*MRH: mandibular ramus height, MRW: mandibular ramus width, MBH: mandibular body height, MBL: mandibular body length. Mean ± SD (mm), *p-value: <0.05 is significant.*

Figure 1

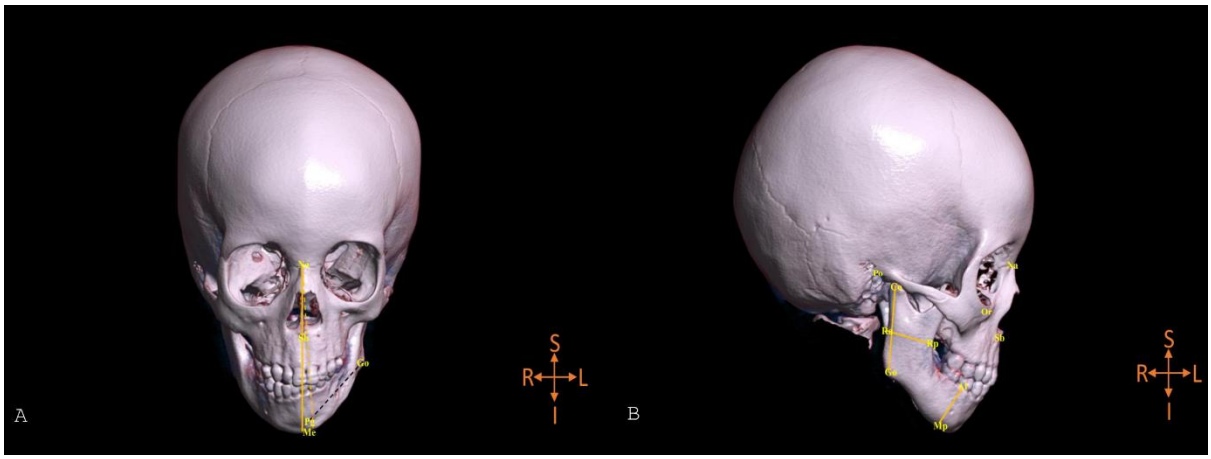
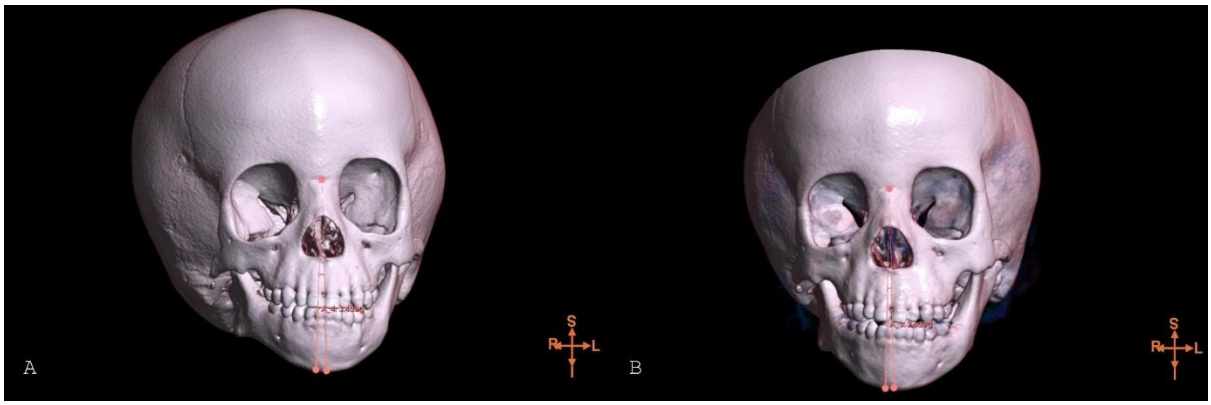


Figure 2



CHAPTER SIX

SYNTHESIS, CONCLUSION, AND RECOMMENDATION

6.1 Synthesis

The research sets out to investigate whether there is a progression in FA or not in patients with HFM, the demographics and clinical presentation of HFM in the South African population, anatomical differences between affected and unaffected MRB and the potential of AFG in the growth of the hypoplastic mandible. This study aims to document the detailed anatomical basis of the hypoplastic mandible in HFM based on its clinical and morphometric presentations. Furthermore, to assess AFG camouflage in facial asymmetry in a South African population. The methodology employed includes a comprehensive systematic search of the databases, an electronic chart review of medical records to document the demographic and clinical features of patients with HFM, an evaluation of the morphological difference between affected and unaffected hypoplastic mandible, an assessment of AFG treatment in HFM and the use of Pruzansky or Pruzansky-Kaban and OMENS+ classifications of HFM through core technologies such as panoramic radiographs and CT.

The main aetiopathogenesis of HFM includes Meckel's cartilage malformation, aberrant migration of CNCC and vascular haemorrhage influenced by multifactorial origin such as gene mutation maternal and environmental factors (Luo et al., 2023). This resulted in multifaceted clinical manifestations of HFM in terms of the severity of the condition (Kaban, 2009). The abnormal mandibular growth influences FA in HFM. When the development of the mandible is restricted, it reduces the vertical growth of the middle and lower face, resulting in a slanted maxillary occlusal plane and asymmetry of the zygoma and orbits (Kaban, 2009, Song et al., 2021). Two theories exist regarding FA as either progressive or non-progressive with age and severity in patients with HFM (Zhang et al., 2023, Atiba et al., 2024). Mandibular asymmetry of ≥4mm is identified as visibly FA, resulting in size, position and volume changes (Silva et al., 2011, Kim et al., 2018). The parameters used to assess the progression of FA in HFM include chin point, occlusal plane angle, gonial/intergonial angle, piriform angle, MRH, TML, and MBL (Kaban, 2009, Renkema et al., 2022b, Shetye et al., 2023). The individual evaluation of FA indicators favoured more non-progressive nature of HFM over a few studies that suggested its progressive nature. Some authors have speculated that early treatment of HFM might promote midfacial growth and facial symmetry (Chen et al., 2020a, Qiu et al., 2021). However, a study by Pluijmers (2019) contradicts the hypothesis of the long-term stability of early treatment in patients with HFM.

Kearns et al. (2000), Shetye et al. (2023), and Zhang et al. (2023) proposed that FA grows more pronounced as individuals age. Yet, other studies did not find supporting evidence for a correlation between FA and the passage of time (Meazzini et al., 2012, Renkema et al., 2022b, Kaprio et al., 2023). The age groups used included dentition age, infancy to childhood, childhood to adolescence and varied age groups (Rune et al., 1981, Polley et al., 1997, Kusnoto et al., 1999, Kearns et al., 2000, Meazzini et

al., 2012, Ongkosuwito et al., 2013b, Ongkosuwito et al., 2013a, Renkema et al., 2022b, Kaprio et al., 2023, Shetye et al., 2023, Zhang et al., 2023). The dentition age and infancy to childhood group used in some studies suggests an increase in mild and severe deformity in relation to age (Kearns et al., 2000, Zhang et al., 2023). In contrast, dentition age used by Meazzini and colleagues and child-to-adolescent group used by Polley and associates (1997) indicated that the asymmetric mandible remains constant throughout growth (Polley et al., 1997, Meazzini et al., 2012, Atiba et al., 2024). While the overall growth pattern pooled for different HFM severities appears not progressive, the data from severe HFM show otherwise (Zhang et al., 2023). This information is relevant to diagnosing and managing patients with HFM (Liu et al., 2022). Also, it is noteworthy that rotations can still increase in one axis and decrease in another even when there are no overall growth changes (Rune et al., 1983). An inherent genetic factor is posited as the probable cause of the asymmetry in these studies (Taiwo, 2020).

Some studies advanced that Pruzansky-Kaban scores are proportional to the severity of the deformity (Kim et al., 2018, Taiwo, 2020). FA in HFM results from both primary malformation of prenatal cause and secondary malformation related to abnormal growth (Kim et al., 2018). The outcome of the deformed mandible's growth potential influences the choice of treatment timeline in HFM. The timeline includes early treatment for severe skeletal deformity. In contrast, late treatment is suggested for mild-to-moderate skeletal defects (Ramanathan, 2021). When considering the treatment timelines to address FA in the hypoplastic mandible, preference must be given to the patient’s specific need (such as obstructive sleep apnoea due to retrognathia, feeding difficulty) in addition to the degree of severity of the deformity (Ramanathan, 2021). There is no relationship between FA and sexual dimorphism in the HFM population. Nagy et al. (2009) reported a similar distribution between sexes and dismissed the concept of prevalence in male patients and laterality to the right side. There is no sexual dimorphism in both progressive and non-progressive FA from the included studies. Therefore, there is no difference in treatment approach to HFM in both sexes.

6.1.1 Demographic and clinical presentation of HFM in South Africa

Mandibular hypoplasia with or without ear deformity is the cornerstone for the phenotypic classification of HFM, distinguishing it from other craniofacial anomalies of first and second pharyngeal arches (Manlove et al., 2022). The phenotypic presentation of HFM exhibits a notable degree of variability. In response to this diversity, several classifications were devised to address the multifaceted disparity observed in HFM (Pruzansky, 1969, David et al., 1987, Kaban et al., 1988, Vento et al., 1991, Horgan et al., 1995, Huisinga-Fischer et al., 2001). The OMENS+ classification was used to assess the clinical presentation of HFM in chapter three. This classification was chosen due to the encompassing nature of the deformity features found in the orbit, mandible, ear, facial nerve, soft tissue, and other associated systemic malformations (Horgan et al., 1995). There are large bodies of literature on HFM; most reports were from the international population, with a few reports from the African continent (Losken et al., 1983, Preston et al., 1985, Allam, 2021, Atiba et al., 2024). South Africa has a multiracial population,

which includes 82% of Black African descent, 7% of White descent, 8% of Coloured descent, and 3% of Indian/Asian descent (Omotoso et al., 2021, Madaree, 2023). The demographic of the South African patients with HFM is 60% Black African, 32% Indian, 4% White, and 4% Coloured. A right-to-left laterality ratio of 1.4:1 and 4% bilateral affectation. 84% of other craniofacial anomalies and 40% of extracraniofacial anomalies in the South African population. Our study recorded no significant difference between the male-to-female ratio and right-to-left-sidedness. Opinions differ about gender and laterality differences in the prevalence of HFM. While some authors have reported that HFM is more present in males to females with a ratio of 3:2, respectively, and right-side laterality preponderance (Cousley and Calvert, 1997), others found no correlation between gender or laterality (Horgan et al., 1995, Xu et al., 2015). The differences reported in our study and the above studies may be due to the disparity in the sample size. This study found that 40% of patients exhibited orbit deformities, consistent with previous HFM research (Rooijers et al., 2020, Renkema et al., 2022a). Ocular defects often coexist, sometimes indicative of Goldenhar syndrome (Singh et al., 2020). The study documented a 20% ocular defect rate, underscoring the importance of early surgical intervention (Renkema et al., 2022a). Mandibular hypoplasia was observed in all cases in this study, presenting complications, including malocclusion, obstructive sleep apnoea, and speech difficulties (Caron et al., 2017, Renkema et al., 2022a). Depending on severity, treatment options range from osteotomy, distraction osteogenesis, and orthognathic surgery (Allam, 2021). Several reports have suggested an increasing association between the severity of the ear and mandibular deformities. In this study, there is a high incidence of ear deformities affecting the external, middle and internal ear structures. Detection of hearing problems in patients with HFM is vital to mitigate learning difficulties, speech development delay, and impaired social functioning (Cohen et al., 2017). Facial nerve palsy affected about 60% of the patients with HFM in this study. The incidence of facial palsy in other studies is 22 % (Zuo et al., 2022) and 23.9% (Li et al., 2018). Soft tissue defects accentuate facial asymmetry in patients with HFM. Soft-tissue reconstruction may influence other types of treatment, such as mandible or ear reconstruction, and should, therefore, be coordinated within a multidisciplinary treatment plan (Sinclair et al., 2019, Renkema et al., 2022a). In previous studies, the prevalence of extracraniofacial anomalies in patients with HFM range from 36 to 85% (Rollnick et al., 1987, Horgan et al., 1995, Barisic et al., 2014, Cohen et al., 2017, Renkema et al., 2019, Allam, 2021). We reported a similar finding of 40% in our study. Respiratory system deformities accounted for the highest occurrence (36%). Renkema and co-authors reported only 3% of respiratory deformities (n=991) in their large population multinational study (Renkema et al., 2019). This present study was associated with severe mandibular, facial nerve, and soft tissue deformities. Renkema et al. (2019) reported a similar association. Some gene mutations are linked to HFM; these include OTX2, PLCD3, Itgb4 and Pde4dip, which are responsible for developmental malformation of the mandible, other facial skeleton, neurocranium, and neck (Chen et al., 2018, Wang et al., 2023). The genetic basis of HFM varies from one individual to another, and not all cases of HFM

have genetic causes. HFM is multifactorial in origin. Currently, research is still ongoing regarding the suggested genetic basis of HFM in South Africa and other parts of the World (Wang et al., 2023).

6.1.2 Anatomical presentation of hypoplastic mandible

We evaluated the anatomical difference between the affected and unaffected MRB in select patients with HFM in South Africa due to the varying presentation of mandibular deformity in patients with HFM. The ramus is the most affected part of the mandible in HFM. The MRB-affected side is shorter than the unaffected side in HFM subjects (Chen et al., 2021b, Renkema et al., 2022b, Zhang et al., 2023), except in the findings of Shetye et al. (2023), where the affected MBL mean value is longer than unaffected.

Regarding the severity grading of HFM in this study, the ramus and body (R-B) index, the A/C ratio and CPD changed insignificantly between the mild and severe groups in patients with HFM, except RatioMBL showed insignificant similarity between severity levels. However, Zhang and colleagues reported a significant change in the mild and severe groups in the A/C ratio in the ramus height and body length (Zhang et al., 2023). A multifactorial origin of HFM in this current study may account for this variation (Chen et al., 2021a).

Age significantly influences the development of HFM's mandibular components, with the affected and unaffected dimensions increasing proportionally with age, except for MBL and CPD. This may result from different osteogenic patterns during prenatal and postnatal development, contributing to the varied features of HFM (Kabak et al., 2019, Chou et al., 2023, Zhang et al., 2023).

In patients with HFM, FA may be masked during infancy by the buccal fat pad but becomes more pronounced in adulthood (Ramirez, 1999, Yousuf et al., 2010). Some studies suggest FA worsens with age and severity grading (Kearns et al., 2000, Chen et al., 2020b, Zhang et al., 2023), while others argue that it remains constant over time (Meazzini et al., 2012, Shetye et al., 2023, Atiba et al., 2024). This study supported the latter, showing non-significant changes in MRB ratios across different age groups and severity levels.

FA's progression and early treatments' stability in HFM remain debated (Padwa et al., 1998, Meazzini et al., 2012, Pluijmers et al., 2014). Surgical interventions like distraction osteogenesis and costochondral grafting often require multiple revisions due to relapse (Nagy et al., 2009, Pluijmers et al., 2014). We hypothesised FA is non-progressive. The peak facial growth in males and females is 16 –18 years and 14–16 years, respectively (Love et al., 1990, Foley and Mamandras, 1992). To ease psychosocial and economic burdens, we advocate for delayed intervention until after mandibular growth completion (Nagy et al., 2009, Pluijmers, 2019). Advanced visualisation techniques like 3D printed operation templates offer potential, but challenges lie in treatment timelines and availability (Igelbrink et al., 2020).

6.1.3 The role of AFG in the hypoplastic mandible in growing patients with HFM

In HFM, disrupted interactions between CNCCs and cephalic myogenic mesodermal cells (CMMCs) during embryonic development led to concurrent hypoplasia of the mandible and masticatory muscles. Hypoplastic muscles fail to provide mechanical stimuli for bone growth, causing asymmetric mandibular underdevelopment. Post-surgical relapse may occur due to muscle atrophy or fibrosis, which limits functional forces on the bone. Abnormal muscle morphology (reduced volume, irregular shape) further disrupts biomechanical equilibrium. Integrated management addressing muscle-bone crosstalk (such as fat grafting, functional therapy, and muscle assessment during skeletal correction) is critical to stabilise growth and improve long-term symmetry in patients with HFM (Heude et al., 2011, Yamaguchi et al., 2017, Luo et al., 2023).

Literature has emphasised the use of AFG in liposculpture of the face and other parts of the body (Tanna et al., 2012, Denadai et al., 2017, Sinclair et al., 2019, Wederfoort et al., 2023). Studies have highlighted other roles of AFG in angiogenesis, osteogenesis, and wound healing (Bellini et al., 2017, Vyas et al., 2020, Herold and Kalucka, 2021). ADSC can potentially promote skeletal growth through their ability to differentiate into bone cells, support tissue regeneration via paracrine signalling, and enhance vascularisation (Yuan et al., 2022). We examined the role of AFG in patients with HFM, both with and without MDO, to address the complex challenges of HFM. While MDO focuses on skeletal reconstruction (Liu et al., 2022), AFG targets soft tissue volume restoration and contour refinement, offering a comprehensive approach to HFM's multifaceted facial deformities (Luo et al., 2023). AFG's minimally invasive nature is particularly appealing for young patients, potentially optimising facial growth and development (Luo et al., 2023, Ma et al., 2023). Children exhibit a better fat retention rate than adults at 67.7% in AFG treatment (Denadai et al., 2017). Due to the inherent mandibular hypoplasia in HFM, AFG may promote mandibular growth, but facial asymmetry is still present after treatment in severe HFM. AFG is used in as a camouflage in severe HFM without initial treatment of affected bone (Yamaguchi et al., 2017, Liu et al., 2022).

According to Rajan et al (2019), AFG is used for soft tissue camouflage and is a versatile, easy, effective, and inexpensive method for obtaining consistent long-term aesthetic goals in mild to moderate cases of HFM. Research indicates AFG's effectiveness in treating soft tissue deficiency in HFM, with some evidence yet its impact on mandibular morphometrics remains insufficiently explored (Sinclair et al., 2019, El Hadidi et al., 2022, Ma et al., 2023). In the present study, fat-treatment in the AFG group significantly increased the length of the affected MRH and MRW and improved symmetry in CPD and OPA. At the same time, in the MDO+AFG group showed a significant increase in the length of the affected MBL. Similar findings were reported in the skin pinch thickness in a group of fat-treated patients with HFM (Rajan et al., 2019). Other studies suggested increases in the affected ramus height, body length, and CPD after mandibular distraction in patients with HFM (Kusnoto et al., 1999;

Meazinni et al., 2012). MDO adds additional structural support by modifying mechanical forces and stress on the mandible, leading to remodelling and lengthening (Du et al., 2021; Liu et al., 2022).

Fat grafting might impact growth increases in the affected MRH and MBL but is not significant enough when compared to the unaffected side in the AFG group. The growth increase between the affected and unaffected sides was also not significant in the MDO+AFG group. In previous studies, the growth change of the affected side of the HFM mandible is slower than that of the unaffected side post-MDO treatment (Ortakoglu et al., 2007, Meazzini et al., 2012, Lewis et al., 2024). Kusnoto and associates reported that the affected and unaffected MRH and MBL pre-MDO treatment grew at the same rate (Kusnoto et al., 1999). The difference between our findings and other studies' growth response and outcome is ascribed to pre-existing anatomical differences in the MDO+AFG group, which initially had a more severe hypoplastic mandible than the AFG group. Other contributing factors are genetics, nutrition, and overall health, which can influence the mandible natural growth process in patients with HFM (Werler et al., 2004; Köstenberger et al., 2022; Luo et al. 2023). The MDO+AFG group, accompanied with obstructive sleep apnoea and other functional impairments due to hypoplastic mandibles, experienced functional and structural improvements after MDO treatment. MDO successfully transformed severely hypoplastic mandibles into moderately or mildly hypoplastic ones, with fat grafting enhancing facial symmetry and promoting growth (Polley et al., 1997; Gui et al., 2011; Sakamoto et al., 2013). For severe (MDO+AFG group) cases with functional issues like obstructive sleep apnoea, MDO was used to lengthen the mandible, converting it from severely hypoplastic to moderately or mildly hypoplastic (Meazzini et al., 2005, Ortakoglu et al., 2007, Meazzini et al., 2012, Köstenberger et al., 2022). The mild (AFG) group did not experience functional difficulties and did not require mandibular lengthening (Huh et al., 2024). This study suggests a treatment algorithm based on HFM severity. For mild cases (Pruzansky-Kaban Type I and IIA), subperiosteal fat grafting is recommended to encourage mandibular growth without functional correction. For severe cases (Pruzansky-Kaban Type IIB), initial treatment with MDO is advised to address functional issues, followed by fat grafting to enhance symmetry and promote further growth (Ortakoglu et al., 2007; Huh et al., 2024). The pluripotent capacity of the human fat tissue may have also contributed to the effectiveness of AFG.

6.2 Conclusion

The study examines FA, hypoplastic mandible parameters, and the effects of AFG treatment in HFM, considering factors such as age, sex, and severity grading, using the Pruzansky or Pruzansky-Kaban and OMENS+ classification systems. Parameters including chin point, gonial/intergonial angle, piriform angle, mandibular ramus height, mandibular length, and body length are commonly used to assess FA, with a consensus favouring the non-progressive nature of HFM-related asymmetry. While American and European populations have extensively reported on FA progression, less data from Asian

populations exist. Furthermore, the demographic and clinical presentations of HFM in South Africa are unique and have a higher prevalence among females, with the right side more commonly affected. Furthermore, this study reports a higher incidence of facial nerve palsy in patients with HFM. Data from our study suggests FA is non-progressive. Severity grading and age grouping influence the mandibular ramus insignificantly, while the mandibular body remains unaffected by severity grading and age grouping. FA is most conspicuous in patients with HFM aged 13-19 years. The A/C ratio of the MRB does not worsen with age or severity grading, supporting the recommendation to defer surgery until skeletal maturity. Regarding treatment, AFG is a useful procedure in the management of HFM. In severe HFM, MDO may be the initial procedure of choice. AFG can be used a few years later to further improve the symmetry and deformity, mainly in the MBL. In the mild group, where MDO is not considered, AFG has significantly improved MRW, MRH, CPD, and OPA symmetry and deformity. In addition, AFG treatment significantly improves soft tissue components in patients with HFM. The variation in the deformity's characteristics of the mandible, ear, facial nerve, orbit, and soft tissue underscore the need for a multidisciplinary approach to HFM treatment involving specialists like otolaryngologists, orthodontists, geneticists, and surgeons (maxillofacial, plastic and reconstructive).

6.3 Recommendation and future research

Longitudinal data can provide a specific growth model of MRB features in subjects with HFM in future research on HFM. A comparative analysis of the measurements between the hemifacial and control groups is required to assess the distinction between patients with HFM and the general population.

The heterogeneous characteristics of HFM presentation require a distinct understanding of individual-to-individual variation in diagnosing, treating, and managing this deformity. Therefore, a well-structured, tailored interventional approach based on individual needs is recommended. The recommended treatment algorithm for mild and severe cases in HFM is as follows: In Pruzansky-Kaban Type I and IIA cases, subperiosteal fat grafting is recommended to facilitate mandibular growth without functional correction. In Pruzansky-Kaban Type IIB cases, initial treatment with MDO is advised to address functional issues, followed by fat grafting to enhance symmetry and promote further growth. The possible mechanism of the autologous fat graft in the promotion of mandible growth in patients with HFM will be investigated in future research.

The MDO+AFG group age range is higher than the AFG group due to the early MDO intervention, which resulted in later fat treatment in this cohort of patients. We recommend future studies that will evaluate groups within the same age range.

Studies on the prevalence and genetic basis of HFM in South Africa and across African countries are needed to understand better the prevalence of this deformity in Africa.

6.4 Limitations of the study

A few limitations encountered in this study were:

A small sample size due to the prevalence of HFM in the population and a large sample size from multiple health facilities may strengthen the statistical power of the analyses. The lack of subgroup analysis within the particular sex groups would have examined the similarities or differences in the developmental growth of patients with HFM.

The use of orthopantomograms in a part of the study to measure mandibular growth may not cover the true depth of three-dimensional growth of the mandible. CT and other advanced visualisation techniques like 3D printed operation templates offer potential, but challenges lie in treatment timelines and availability.

The prevalence of HFM in South Africa was not established due to its inefficient birth registry system. An electronic archive of birth data will allow easy accessibility of congenital anomalies in the population.

A comparative analysis of the untreated and fat-treated HFM measurements would have significantly improved the study. AFG intervention was not performed at the same interval after MDO for each patient, which could have influenced the reported outcomes.

Summary of findings and contribution to knowledge

The distinction between HFM in South Africa and other international populations includes higher incidence in females and facial nerve palsy with comorbidity of the respiratory system.

FA becomes more pronounced between ages 13-19 years, coinciding with the peak facial growth in both sexes.

The hypotheses stating an increase in severity grading and age is directly proportional to FA in the HFM notion were not found in this study. FA is non-progressive with age in this study.

AFG's role goes beyond liposculpture. It has pluripotent properties that may influence the growth of the hypoplastic mandible in HFM and its effectiveness in the management of mild and severe deformed mandibles.

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APPENDIX A

Ethical Approval

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

11 September 2022

Mr Peterson Atiba (221062115)
School of Lab Med & Medical Sc
Westville

Dear Mr Atiba,

Protocol reference number: BREC/00004225/2022
Project title: An anatomical exploration of fat transfer in Hemifacial Microsomia children in South Africa
Degree: PhD

EXPEDITED APPLICATION: APPROVAL LETTER

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application.

The conditions have been met and the study is given full ethics approval and may begin as from 11 September 2022. Please ensure that any outstanding site permissions are obtained and forwarded to BREC for approval before commencing research at a site.

This approval is valid for one year from 11 September 2022. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2020) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be noted by a full Committee at its next meeting taking place on 11 October 2022.

Yours sincerely,

[redacted]

Prof D Wassenaar
Chair: Biomedical Research Ethics Committee

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

24 July 2023

Mr Peterson Atiba (221062115)
School of Laboratory Medicine & Medical Science
Westville

Dear Mr Atiba,

Protocol reference number: BREC/00004225/2022
Project title: AN ANATOMICAL EXPLORATION OF FAT TRANSFER IN HEMIFACIAL MICROSOMIA CHILDREN IN SOUTH AFRICA
Degree: PhD

RECERTIFICATION APPLICATION APPROVAL NOTICE

Approved:	**11 September 2023**
Expiration of Ethical Approval:	**10 September 2024**

I wish to advise you that your application for recertification for the above study has been **noted and approved** by a subcommittee of the Biomedical Research Ethics Committee (BREC). The start and end dates of this period are indicated above.

If any modifications or adverse events occur in the project before your next scheduled review, you must submit them to BREC for review. Except in emergency situations, no change to the protocol may be implemented until you have received written BREC approval for the change.

The committee will be notified of the above approval at its next meeting to be held on 08 August 2023.

Yours sincerely

[redacted]

Ms A Marimuthu
(for) Prof D Wassenaar
Chair: Biomedical Research Ethics Committee

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

15 July 2024

Mr Peterson Atiba (221062115)
School of Laboratory Medicine & Medical Science
Westville

Dear Mr Atiba,

Protocol reference number: BREC/00004225/2022
Project title: AN ANATOMICAL EXPLORATION OF FAT TRANSFER IN HEMIFACIAL MICROSOMIA CHILDREN IN SOUTH AFRICA
Degree: PhD

RECERTIFICATION APPLICATION APPROVAL NOTICE

Approved:	**11 September 2024**
Expiration of Ethical Approval:	**10 September 2025**

I wish to advise you that your application for recertification for the above study has been **noted and approved** by a subcommittee of the Biomedical Research Ethics Committee (BREC). The start and end dates of this period are indicated above.

If any modifications or adverse events occur in the project before your next scheduled review, you must submit them to BREC for review. Except in emergency situations, no change to the protocol may be implemented until you have received written BREC approval for the change.

The committee will be notified of the above approval at its next meeting to be held on 13 August 2024.

Yours sincerely

[redacted]

Ms A Marimuthu
(for) Prof S Singh
Chair: Biomedical Research Ethics Committee

APPENDIX B

Department of Health Approval

KWAZULU-NATAL PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

DIRECTORATE:
Health Research & Knowledge Management Unit

Postal Address: Private Bag X9050
Physical Address: 330 Langalibalele Str; PM Burg; 3201
Tel: 0333953189/3123/2805 Fax: 033-3943782
Email address: hrkm@kznhealth.gov.za
www.kznhealth.gov.za

NHRD Ref: KZ_202206_031

Dear Mr P Atiba
(UKZN)

Approval of research

1. The research proposal titled **'AN ANATOMICAL EXPLORATION OF FAT TRANSFER IN HEMIFACIAL MICROSOMIA CHILDREN IN SOUTH AFRICA'** was reviewed by the KwaZulu-Natal Department of Health (KZN-DoH).

   The proposal is hereby **approved** for research to be undertaken at Inkosi Albert Luthuli Central hospital.

2. You are requested to take note of the following:
   a. *All research conducted in KwaZulu-Natal must comply with government regulations relating to Covid-19. These include but are not limited to: regulations concerning social distancing, the wearing of personal protective equipment, and limitations on meetings and social gatherings.*
   b. *Kindly liaise with the facility manager BEFORE your research begins in order to ensure that conditions in the facility are conducive to the conduct of your research. These include, but are not limited to, an assurance that the numbers of patients attending the facility are sufficient to support your sample size requirements, and that the space and physical infrastructure of the facility can accommodate the research team and any additional equipment required for the research.*
   c. *Please ensure that you provide your letter of ethics re-certification to this unit, when the current approval expires.*
   d. *Provide an interim progress report and final report (electronic and hard copies) when your research is complete to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za*
   e. *Please note that the Department of Health shall not be held liable for any injury that occurs as a result of this study.*

For any additional information please contact Ms G Khumalo on 033-395 3189.

Yours Sincerely

[redacted]

Dr E Lutge
Chairperson, Health Research Committee
Date: 06/09/2022.

GROWING KWAZULU-NATAL TOGETHER

APPENDIX C

Hospital Approval

KWAZULU-NATAL PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

DIRECTORATE:

INKOSI ALBERT LUTHULI CENTRAL HOSPITAL
OFFICE OF THE MEDICAL MANAGER
Private Bag X03, Mayville, 4058
800 Vusi Mzimela (Bellair) Road, Mayville,4091
Tel: 031 240 1059 Fax: 031 240 1005 Email: Ursula.john@ialch.co.za

5 July 2022

Mr P Atiba (221062115)
School of Laboratory Medicine & Medical Science
Westville

Dear Mr Atiba

Re: Approved Research: Ref No: BREC/00004225/2022: An Anatomical Exploration of fat transfer in hemifacial mirosomia children in South Africa.

As per the policy of the Provincial Health Research Committee (PHRC), you are hereby granted permission to conduct the above mentioned research once all relevant documentation has been submitted to PHRC inclusive of Full Ethical Approval.

Kindly note the following.

1. The research should adhere to all policies, procedures, protocols and guidelines of the KwaZulu-Natal Department of Health.
2. Research will only commence once the PHRC has granted approval to the researcher.
3. The researcher must ensure that the Medical Manager is informed before the commencement of the research by means of the approval letter by the chairperson of the PHRC.
4. The Medical Manager expects to be provided feedback on the findings of the research.
5. Kindly submit your research to:

   The Secretariat
   Health Research & Knowledge Management
   330 Langaliballe Street, Pietermaritzburg, 3200
   Private Bag X9501, Pietermaritzburg, 3201
   Tel: 033395-3123, Fax 033394-3782
   Email: hrkm@kznhealth.gov.za

Yours faithfully

[redacted]
.....
Dr A Harrichandparsad
Clinical Care Manager

GROWING KWAZULU-NATAL TOGETHER

KWAZULU-NATAL PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

DIRECTORATE:

INKOSI ALBERT LUTHULI CENTRAL HOSPITAL
OFFICE OF THE MEDICAL MANAGER
Private Bag X03, Mayville, 4058
800 Vusi Mzimela (Bellair) Road, Mayville,4091
Tel: 031 240 1059 Fax: 031 240 1005 Email: Ursula.john@ialch.co.za

Reference: BREC 00004225/2022
Enquiries: Medical Management

5 July 2022

Mr P Atiba (221062115)
School of Laboratory Medicine & Medical Science
Westville

Dear Mr Atiba

RE: PERMISSION TO CONDUCT RESEARCH AT IALCH

I have pleasure in informing you that permission has been granted to you by the Medical Manager to conduct research on: **An Anatomical Exploration of fat transfer in hemifacial mirosomia children in South Africa.**

Kindly take note of the following information before you continue:

1. Please ensure that you adhere to all the policies, procedures, protocols and guidelines of the Department of Health with regards to this research.
2. This research will only commence once this office has received confirmation from the Provincial Health Research Committee in the KZN Department of Health.
3. Kindly ensure that this office is informed before you commence your research.
4. The hospital will not provide any resources for this research.
5. You will be expected to provide feedback once your research is complete to the Medical Manager.

Yours faithfully

[redacted]
.....
Dr A Harrichandparsad
Clinical Care Manager

APPENDIX D

Data Collection Sheet

Morphometric ***parameters of the mandible in the affected and contralateral sides***

ID	Sex	Pruzansky-Kaban Type	Race	Age	Side	RH Affected	RH Unaffected	RW Affected	RW Unaffected	MNW Affected	MNW Unaffected	CPD	MGA	MBL Affected	MBL Unaffected	MBH Affected	MBH Unaffected	TML

OMENS score grading

	0 (%)	1 (%)	2 (%)		3 (%)
			A	B	
Mandible					
Orbit					
Ear					
Nerve					
Soft tissue					

Percentage distribution of associated craniofacial deformity in hemifacial microsomia patients

Craniofacial deformity	Number of patients (%)
Total	

Percentage distribution of associated craniofacial deformity in hemifacial microsomia patients

Extracraniofacial anomalies	Number of patients (%)
Total	

Measurements of mandibles pre- and post-autologous fat grafting

Parameters	Affected		Unaffected	
	Before () mm	**After () mm**	**Before () mm**	**After () mm**
MRH				
MRW				
MBL				
MBH				
	Before *0 °*	**After** *0 °*	-	-
CPD				
OPA				

APPENDIX E

Informed Consent or Assent

Informed Consent Document

Dear Participant,

My name is Peterson Makinde Atiba (student no: *221062115*). I am a PhD candidate studying at Department of Clinical Anatomy, University of KwaZulu-Natal, Westiville Campus. The title of my research is: "**An anatomical exploration of fat transfer in hemifacial microsomia children in South Africa**"

The aim of the study is *to document a detailed account of facial asymmetry resulting from the presence of a hypoplastic mandible in hemifacial microsomia via clinical and morphometric analyses. Moreover, it aimed to assess autologous fat graft camouflage in facial asymmetry (FA) in a South African population.*

This study was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (Ref No: BREC/00004225/2022) and the Department of Health in the Province of KwaZulu-Natal (NHRD Ref.: KZ_202206_031) to conduct this research.

I seek for your participation in the above-named research.

Please note that:

- The information that you provide will be used for scholarly research only.
- Your participation is entirely voluntary. You have a choice to participate, not to participate or stop participating in the research. You will not be penalized for taking such an action.
- Your information in this study will be presented with de-identifying details.
- The record as well as other items associated with the interview will be held in a password-protected file accessible only to myself and my supervisors. After a period of 5 years, in line with the rules of the university, it will be disposed by shredding and burning.
- The researcher may derive a benefit in the award of an academic qualification from UKZN through the completion of a thesis and the results will be published in scientific journals or a book. However, your confidentiality will be protected as any publications will not include any individually identifiable information.
- If you agree to participate, please sign the declaration attached to this statement (a separate sheet will be provided for signatures).

I can be contacted at the Department of Clinical Anatomy, School of Laboratory Medicine and Medical Sciences College of Health Sciences, University of KwaZulu-Natal, Westville Campus, Private Bag X54001, Durban, 4000, South Africa. Email: 221062115@stu.ukzn.ac.za, Cell: [redacted].

My supervisor is Professor Lelika Lazarus, who is located at the Department of Clinical Anatomy, School of Laboratory Medicine and Medical Sciences College of Health Sciences, Westville Campus, Private Bag X54001, Durban, 4000, South Africa.

Contact details: email ramsaroopl@ukzn.ac.za Phone number: +27 31 260 7899; Cell: [redacted]

The Biomedical Research Ethics Committee contact details are as follows: Ms A. Marimuthu Ximba, University of KwaZulu-Natal, Research Office Westville Campus, Govan Mbeki Building, Postal Address: Private Bag X54001, Durban 400

Phone number +27312604769 Email: brec@ukzn.ac.za

Thank you for your contribution to this research.

DECLARATION

I..... *(full names of participant)* hereby confirm that I understand the contents of this document and the nature of the research project, and I consent to participating in the research project.

I understand that I am at liberty to withdraw from the project at any time, should I so desire. I understand the intention of the research. I hereby agree to participate.

I consent / do not consent to have this interview recorded (if applicable)

SIGNATURE OF PARTICIPANT DATE

.....

Appendix F

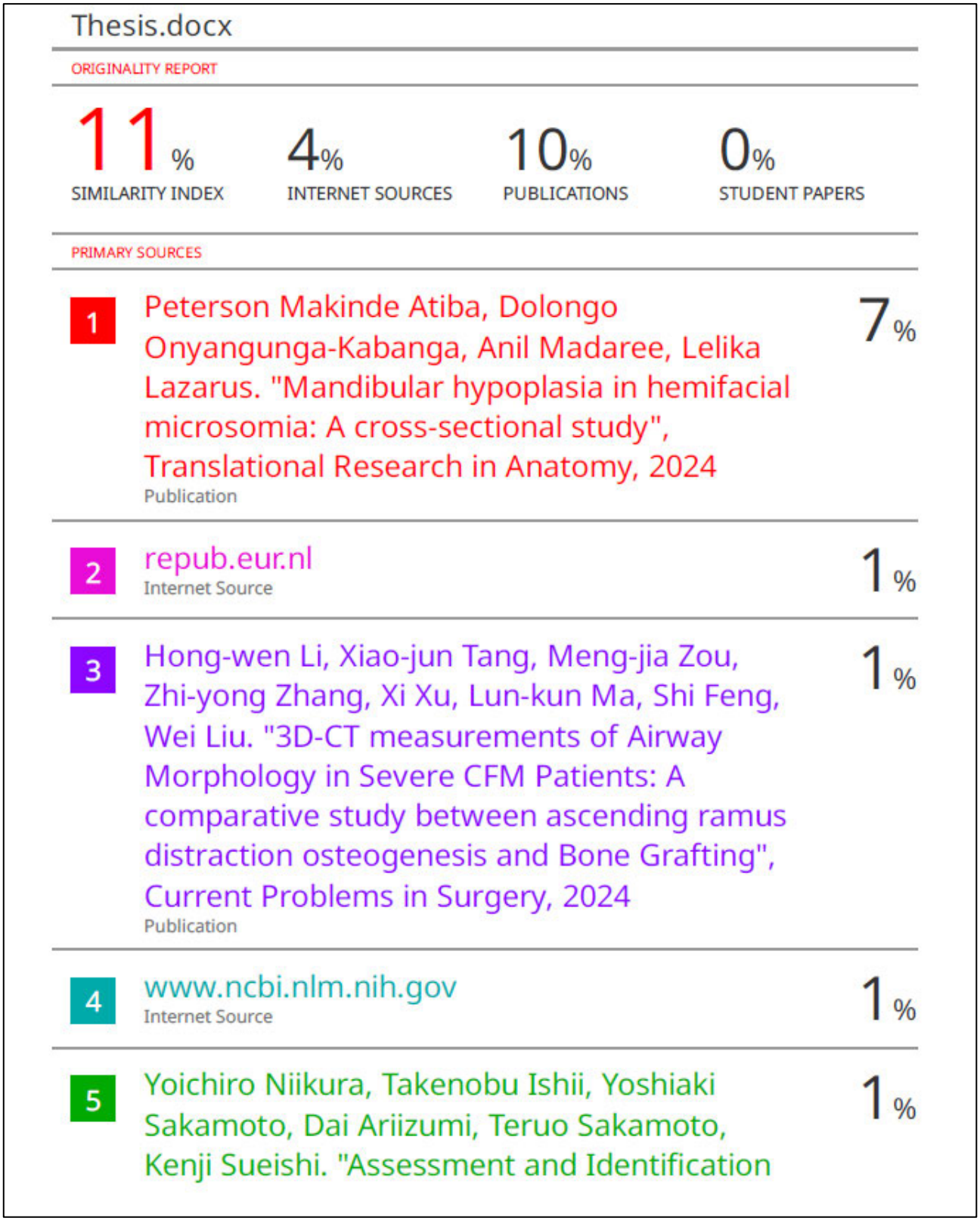
Presentations

Part of the findings observed in this study was presented at the following conferences or symposia:

1. **Atiba, P.M**., Omotoso, B.R., Madaree, A. and Lazarus, L., Hemifacial microsomia: A scoping review progressive facial asymmetry due to mandibular deformity, XXVIII International Symposium of Morphological Sciences (ISMS 2023) August 2023, University of Cape Town, Cape Town, South Africa.
2. **Atiba, P.M**., Omotoso, B.R., Madaree, A. and Lazarus, L., Hemifacial microsomia: A scoping review progressive facial asymmetry due to mandibular deformity, School of Laboratory Medicine and Medical Sciences Research Symposium September 2023, University of KwaZulu-Natal, Durban, South Africa.
3. **Atiba, P.M**., Onyangunga-Kabanga, D., Madaree, A. and Lazarus, L., Mandibular hypoplasia in hemifacial microsomia: A cross-sectional study, College Health Sciences Research Symposium August 2024, University of KwaZulu-Natal, Durban, South Africa.
4. **Atiba, P.M**., Onyangunga-Kabanga, D., Madaree, A. and Lazarus, L., An assessment of autologous fat graft administration in hemifacial microsomia patients with or without distraction osteogenesis: A preliminary study. School of Laboratory Medicine and Medical Sciences Research Symposium September 2024, University of KwaZulu-Natal, Durban, South Africa.

Appendix G

Turnitin Report



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ORIGINALITY REPORT

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SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Peterson Makinde Atiba, Dolongo Onyangunga-Kabanga, Anil Madaree, Lelika Lazarus. "Mandibular hypoplasia in hemifacial microsomia: A cross-sectional study", Translational Research in Anatomy, 2024 Publication	7%
2	repub.eur.nl Internet Source	1%
3	Hong-wen Li, Xiao-jun Tang, Meng-jia Zou, Zhi-yong Zhang, Xi Xu, Lun-kun Ma, Shi Feng, Wei Liu. "3D-CT measurements of Airway Morphology in Severe CFM Patients: A comparative study between ascending ramus distraction osteogenesis and Bone Grafting", Current Problems in Surgery, 2024 Publication	1%
4	www.ncbi.nlm.nih.gov Internet Source	1%
5	Yoichiro Niikura, Takenobu Ishii, Yoshiaki Sakamoto, Dai Ariizumi, Teruo Sakamoto, Kenji Sueishi. "Assessment and Identification	1%