Anatomical classification of Tessier craniofacial clefts number 3 and number 4 in a South African population

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Preface

The study described in this thesis 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 Inkosi Albert Luthuli Central Hospital, Durban, South Africa from February 2017 to November 2019, under the supervision of Prof KS Satyapal, Prof A Madaree, Prof L Lazarus and Dr P Pillay for the award of Doctor of Philosophy Degree in Clinical Anatomy.

Declaration

I, Dr OMODAN, ABIOLA OLUGBENGA declare as follows:

1. That the work described in this thesis, to my knowledge, has not been submitted to UKZN or any other tertiary institution for the purpose of obtaining an academic qualification either by me or any other person.

2. That my contributions to the project were as follows:

   - I was involved in the design and submission of the proposal for ethics approval by the Biomedical Research Ethics Committee.

   - I was wholly responsible for the data collection, collation and analyses.

   - I was responsible under supervision, for writing all the manuscripts and this thesis.

3. This thesis does not contain any other person's writing, data, pictures or other information unless specifically acknowledged as being sourced from other persons or researchers.

   Where other written sources have been quoted then:

   - Their words have been rewritten but the general information attributed to them has been referenced.

   - Where their exact words have been used then it has been properly referenced in the reference section.

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     Signed   **Date**

Dedication

To my parents – Mr James and Mrs Victoria Omodan, you saw me at the very top even when my own vision wasn't too clear. To my unbelievably lovely wife Olayinka, who put her own dreams on hold for me to achieve mine, and to the cutest boys anyone could wish for, Oluwatimilehin and Oluwatomisin who inspire me daily.

Acknowledgement

- I will like to express my sincere gratitude to my supervisors, Prof KS Satyapal, Prof A Madaree, Prof L Lazarus and Dr P Pillay for their never-ending support and open- door policy towards me which they displayed all through my journey of Doctor of Philosophy. I could never have wished for more competent and dedicated supervisors and mentor.

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- Lastly, I would like to appreciate the College of Health Sciences and the Government of South Africa which made a bursary available all through the duration of this doctorate.

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Abbreviations

CFC -   Craniofacial cleft

STO -   Skin, Tissue and Os

PRISMA -   Preferred Reporting Items for Systematic reviews and Meta- analyses

MMAT -   Mixed   Method   Appraisal   Tool

FC -   Facial cleft

Abstract

The craniofacial clefts are rare defects of the face with an incidence of 1.43 to 4.85 per 100,000 live births. In 2016, WHO reported a death rate of 303,000 new-borns before 4 weeks of age due to congenital anomalies of which craniofacial clefts are one. Surviving the defect is associated with long term disabilities which impacts the individual, families, the healthcare system and society. How much we know about these clefts is seriously hampered by the rarity and the variations of these defects, so much so, that its treatment and communication amongst researchers is affected. The understanding of the skeletal defects occurring in the clefts has long been postulated as a key to any successive reconstruction of the face. This study aimed to reveal the extent of our understanding of these clefts, document the anatomical basis for the craniofacial cleft number 3 and number 4 and generating a sub-classification based on this and also document the clinical presentation as well as associated clefts of these craniofacial clefts in our select South African population.

The methods used to achieve these included conducting a scoping review of the literature on patients with Tessier cleft number 3 and number 4 using relevant identified studies from 1976 sourced from PubMed, Medline, EBSCOhost, Google Scholar and the Cochrane libraries. The result of the study was reported using the Preferred Reporting Items for Systematic and Meta-analyses (PRISMA). Likewise, CT scans of patients who had been treated for Tessier clefts number 3 and 4 at Inkosi Albert Luthuli Central Hospital in Durban South Africa between 2003 and 2017 were analysed. Measurements of the expected defects in each cleft were taken and compared with the unaffected side as reference points. Emerging patterns of their analysis were then used to generate a sub-classification for these clefts. Lastly the records of 8 patients who had been treated for either Tessier cleft number 3 or number 4 were reviewed and compared with 9 studies sourced from the literature. In addition to the defects recorded, associated clefts and other congenital malformations were also documented, and findings were compared.

The scoping review had 33 studies that met the inclusion criteria. The majority were conducted in middle income countries (54.5%) while none were recorded in low income countries. Only 12.1% of the included studies reported on anthropometry. In understanding the skeletal defects, the presence of an alveolar cleft, the emerging patterns of comparison of the measurements of the maxilla and the orbits of the cleft side and the non-cleft side as well as absence of the bone were used to arrive at a sub-classification system using (a), (b). (c), (M+ O+), (M- O-), and (0). Clinical presentation of the patients who had been treated as cases of Tessier cleft number 3 and number 4 were compared to the reviewed literature and the different parameters were documented. In addition, associated clefts were also recorded, and this study found that the association pattern noted for Tessier cleft number 4 did not conform to its traditional counterpart.

In conclusion, this study found that the knowledge of Tessier clefts number 3 and number 4 exist albeit not fully documented. Also, the study proposed a sub-classification for Tessier clefts number 3 and number 4 that will allow physicians to anticipate the extent and form of skeletal defect present before even seeing the patient. Lastly, it was concluded that however variable these clefts appear; they have a similar presentation worldwide and also that associated clefts do not conform to the original Tessier classification system.

Introduction

1.1 Background

Congenital craniofacial cleft (CFC) deformity is a partial or total defect of craniofacial tissues (Zhou et al., 2006). The severity of this deformity can range from slight skin excavation, hair loss, to wry mouth, skewed eyes, and absence of the nose and face (Zhou et al., 2006). The incidence of the rare facial clefts is between 1.43 and 4.85 per 100 000 births (Kawamoto, 1976). Paul Tessier in 1976 described an elaborate and comprehensive numerical classification system where numbers 0 – 14 were assigned to each craniofacial cleft relative to the sagittal midline of the face and the orbit (Tessier, 1976). According to the Tessier classification, the craniofacial cleft number 3 (Fig 1.1A) extends from the philtrum of the lip to the medial canthus of the eye, with foreshortening of the distance between the alar base and the medial canthus of the eye (Gunter, 1963). In addition, the cleft affecting the bone occurs on the lateral incisor/ canine area of the alveolus, extending through the frontal process of the maxilla to the medial orbit passing through the lacrimal groove (Thorne et al., 1997). Jackson et al (1982) documented that the superolateral displacement of the alar base is minimal. Madaree et al (1992) also documented a craniofacial cleft number 3 with the alar base and rim pulled towards the eye, with the nostril being considerably enlarged, and the presence of a coloboma of the lower eyelid between the punctum and the medial canthus, which was displaced inferiorly and laterally. They termed this as a typical incomplete CFC number 3. While the number 4 CFC (Fig 1.1B) as described by Tessier (1976), sees the cleft lip arising halfway between the philtral ridge and the angle of the mouth (labial commissure) and arises lateral to the nasal ala and passes on to the cheek and then travels to the lower eyelid lateral to the punctum sparing the lacrimal system and the inner canthus. The bony cleft, just as in the number 3 cleft arises from between the lateral incisor and the canine and passes around the pyriform aperture continuing through the area of the maxillary sinus medial to the infraorbital foramen and ends at the medial end of the inferior orbital rim (Tessier, 1976; David et al., 1989; Winters *et al.,*2016). This cleft exists in a complete form and an incomplete forme fruste type (milder form). The forme fruste- type is characterized by minimal soft and bony tissue deformities while in the complete type the orbital and oral cavities are confluent with the maxillary antrum (Coruh et al., 2005).

The number 3 as well as number 4 CFCs have been reported to be in co-existence with other forms of clefts such as CFCs 0, 4, 7 as well as cranial extensions of CFCs 10 and 11 for CFC number 3 (Allam et al., 2014) and CFCs 5, 7, 9 and 10 for CFC number 4 (Coruh et al., 2005). Both CFCs number 3 and number 4 have been associated with amniotic bands (Alonso et al., 2008; da Silva Frietas et al., 2010; Allam et al., 2014) and choanal atresia (Coruh et al., 2005; Alonso et al., 2008; Allam et al., 2014)
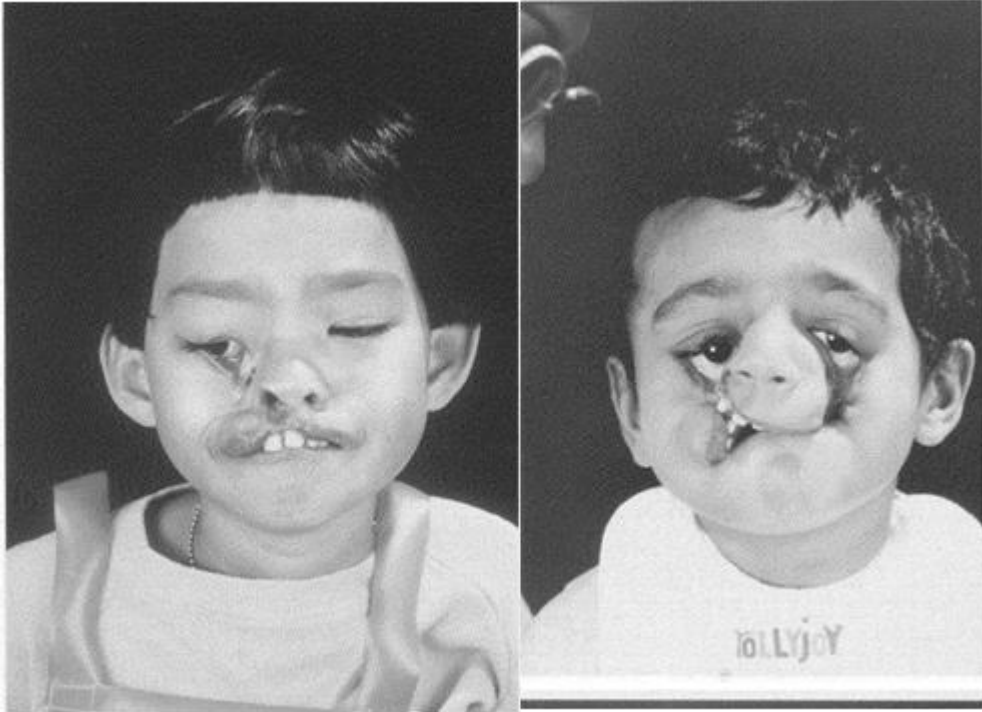
Figure 1.1: A, 7year old with right sided FC 3 cleft. B, 2year old with FC 4 cleft on the left.
(Adapted from David et al, 1989)

Among all the clefts described by Tessier (1976), the number 3 and number 4 CFCs have been documented as two of the most intricate and destructive of all clefts and can often be the most difficult to repair (Tessier, 1976; Alonso et al., 2008). Bony clefts are said to vary in presentations; therefore, understanding the skeletal deformity is basic to any reconstructive surgery of the face (Kawamoto, 1976). Several research studies have emphasized treatment modalities and outcomes (Gawrych et al., 2010; Chen et al., 2012; Allam et al., 2014; Raypeyma et al., 2015); however, there is a paucity of information available on its anatomical basis (i.e. bony and soft tissue landmarks). Hence this study.

1.2 Embryology of the face

The craniofacial structures arise from neural crest cells which arise from a separate pluripotent layer (Sperber, 1989). Neural crest ectomesenchyme has great migratory propensities and is described as the major source of connective tissue throughout the body, because translocated neural crest cells differentiate into bones, cartilages, muscles, ligaments and arteries (Sperber, 1989). Therefore, any disruption in the orderly migration and differentiation of these cells can have severe consequences, manifested by congenital defects (Johnston, 1990). By the 4th week of gestation, the recognizable face begins its development from 5 primordia that surround a central area of depression, the stomadeum (Fig 1.2). The primordia are the single cranially located frontal nasal process and two bilaterally located maxillary processes and mandibular processes. The maxillary and mandibular processes are derived from the first branchial arch (Carstens MH, 2002; Patel et al., 2016). Toward the end of the fourth week, nasal placodes develop bilaterally at the inferolateral corners of the frontonasal process. As the region surrounding the

nasal placodes develops into medial and lateral nasal processes, the deepening nasal placodes are transformed into nasal pits, in time forming the anterior nares. With continued ectodermal development, the nasal placodes become olfactory grooves while the maxillary processes continue to enlarge, encroaching on the stomadeum, to form a primitive oral cavity (Carstens MH, 2004). By the 6th week the medial nasal processes approach each other to form a single globular process that in time gives rise to the nasal tip, columella, prolabium, frenulum, and the primary palate. As this occurs, the frontonasal process collapses inward to form the nasal septum. Continued growth of the maxillary mass below the optic vesicles allows fusion with the lateral nasal process. As fusion occurs, a sinking troughlike epithelial groove demarcates the naso-optic furrow connecting the conjunctival lacrimal sac with the lateral nasal wall. The epithelial groove fuses as a solid epithelial cord and eventually canalizes later in fetal development to become the nasolacrimal duct. Toward the end of the sixth week, the maxillary process fuses with the medial nasal fold of the globular process, forming a true nostril as it gives rise to the lateral lip element (Patel et al., 2016).

By the eighth week, the face has acquired a more human appearance, with complete closure of the lower facial fissures or grooves. The primitive upper and lower jaws are formed with the complete fusion of the maxillary and mandibular processes. The upper lip and lower nasal regions are better defined. As it lengthens vertically, the frontonasal process continues to collapse horizontally, forming a transverse furrow at the nasal bridge (Patel et al., 2016). By whatever causative factor, failure of the lateral maxillary process to fuse with the central globular process is expected to result in a unilateral cleft of the upper lip. Similarly, the median cleft can be explained by incomplete merging of the median nasal processes, and an oblique facial cleft can be explained by persistence of the groove between the maxillary process and the lateral nasal process (medial canthal region to the ala of the nose) (Langman J, 1981). While the occurrence of some facial clefts can be understandable in terms of failure of fusion of the various primordial facial processes, others are not readily explainable in such terms. A cleft that begins lateral to the philtrum and extends to the mid portion of the lower eyelid is difficult to explain. Events prior to the normal process of fusion may lead to localized areas of tissue deficiency, possibly resulting in these atypical clefts (O'Rahilly R, 1996).
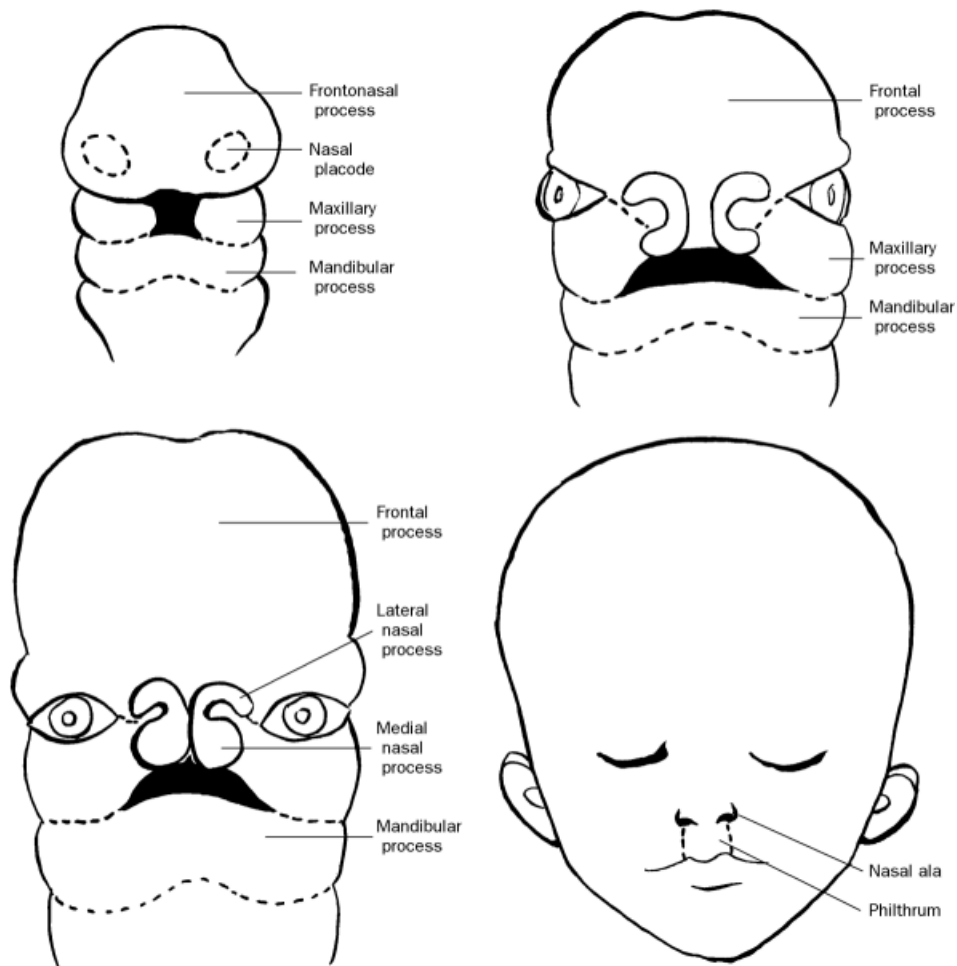
Figure 1.2: Illustration of the development of the face.
(Adapted from Gest, 1999)

1.3 Anatomy of the viscerocranium

Components of the facial skeleton are the frontal bone superiorly, the bones of the midface and the mandible inferiorly (Prendergast, 2012) (Figure 1.3). The midface has the following boundaries viz: superiorly the zygomaticofrontal suture lines, inferiorly the sphenoethmoid junction and the pterygoid plates (Prendergast, 2012). The bones that make up the midface include the maxillae, the zygomatic bones, palatine bones, nasal bones, zygomatic processes of the temporal bones, lacrimal bones, ethmoid bones and the turbinate bones of the nose (Prendergast, 2012). The facial skeleton also contains four openings viz.: the two orbital openings, the nasal opening and the oral opening. The supraorbital and supratrochlear nerves are transmitted by the supraorbital foramen (or notch) and the frontal notch which are found at the superior border of each orbit, respectively (Prendergast, 2012). The maxillary bone forms a great part of the nasal openings, nasal bridge, maxillary teeth, floor of the orbits and the cheek bones. The infraorbital nerve is transmitted through the infraorbital foramen which lies in the maxilla just

below the infraorbital rim; likewise, the zygomaticofacial nerve is transmitted through the zygomaticofacial foramen which is found inferolateral to the junction where the inferior and lateral orbital rims meet (Prendergast, 2012). The lower part of the face is formed by the mandible, which in the midline has an area called the mental protuberance which gives an anterior projection to the overlying soft tissues. Underlying the masseter muscles laterally is the ramus of the mandible which continues superiorly to articulate with the cranium through the coronoid and the condylar processes of the mandible (Prendergast, 2012). Vertically in line with the infraorbital and the supraorbital nerves is the mental nerve which emerges from the mental foramen on the body of the mandible (Prendergast, 2012). The facial skeleton not only provides support, and protection for the sensory organs such as the eyes; it also serves as areas of attachment for the muscles of mastication as well as those of facial expression (Prendergast, 2012).
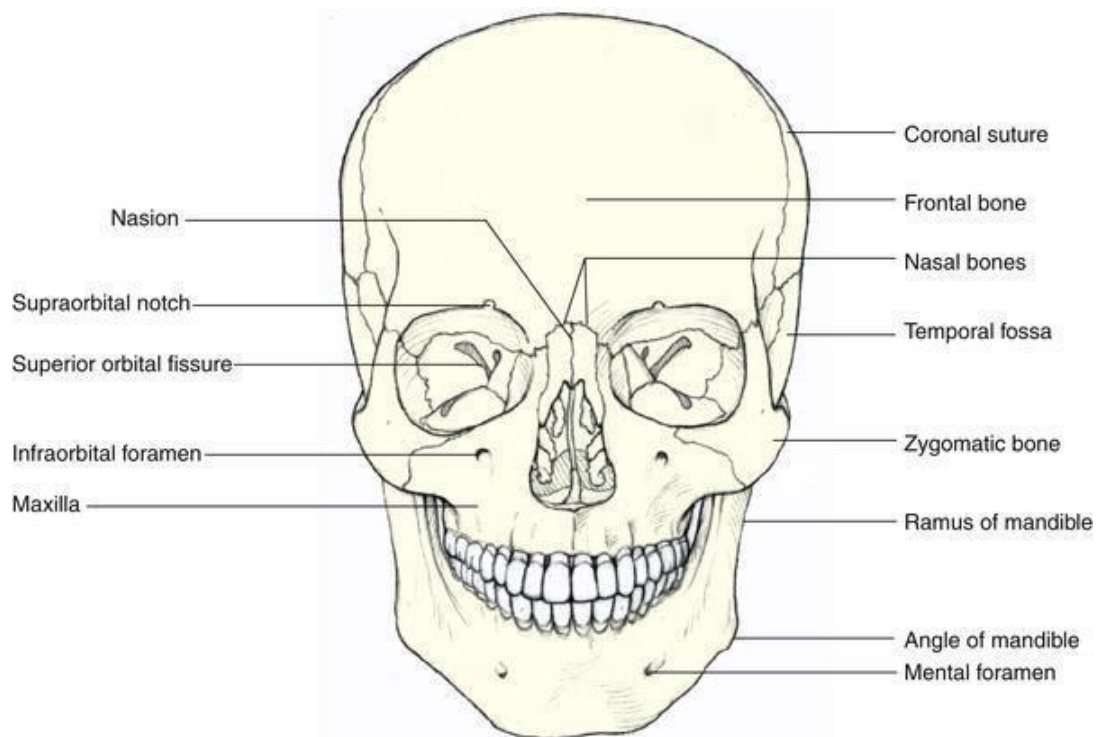

Figure 1.3: Bones of the viscerocranium
(Adapted from Mathers et al., 1996)

1.4 Method of facial cleft classification

The first classification of facial clefts was presented by Morian in 1887. He documented oblique facial clefts which was adopted in 1962 by the Nomenclature Committee of the American Association for Cleft Palate Rehabilitation. This classification divided oblique facial clefts into naso-ocular clefts, which extended from the nostril to the lower eyelid, and the oro-ocular clefts which extended from the lip to the eye (Gorlin et al., 1990; da Silva Frietas et al., 2010). Over the past several years many attempts had been made at formulating several classification methods based on different aspects of the cleft (Tang et al., 2012).

In 1976, Paul Tessier devised a classification for rare CFCs that considered clinical, radiological and surgical observations. This classification is centred around the orbit and each of the clefts is assigned a number in a counterclockwise rotation. Facial clefts (Fig 1.4) are numbered 0 to 7, with 0 being the midline facial cleft while the cranial clefts are numbered 8 to 14, and 14 being the midline cranial cleft (Tessier, 1976). Each of these clefts may involve both the bone and the soft tissue and it is noteworthy that the number does not specify the severity of the tissue involvement, only the location of the cleft on the face and/or skull (Winters, 2016). Recently the Bangalore classification utilized embryological developments as well as clinical presentation of clefts in the head in recommending a classification system (Subramani et al., 2005). The STO (Skin, Tissue and Os) classification made use of skin, soft tissue and craniofacial bone involvement to classify these clefts (Zhou et al., 2006). The Eight Diagrams of China and the Tessier classification were incorporated together to come up with the Spectacle Frame classification that talks about the lacrimal system involvement as well as bony involvements (Tang et al., 2012). Tessier classification appears to be the most popular and clinically accepted due to its simplicity and its ability to improve communication among physicians.
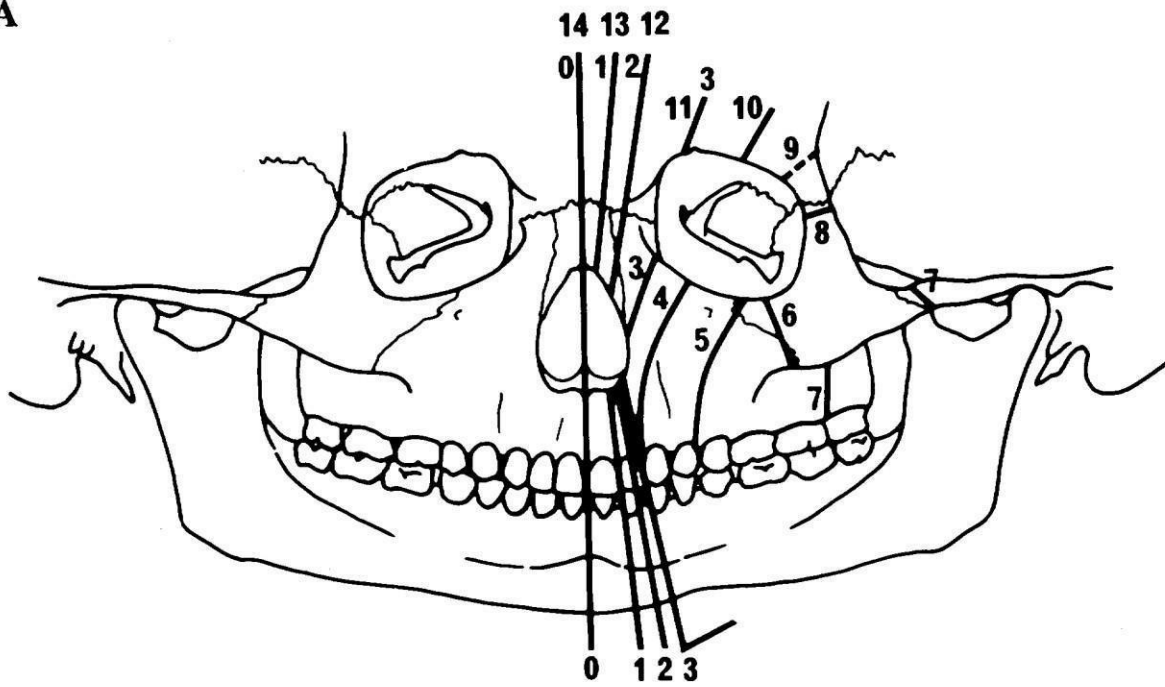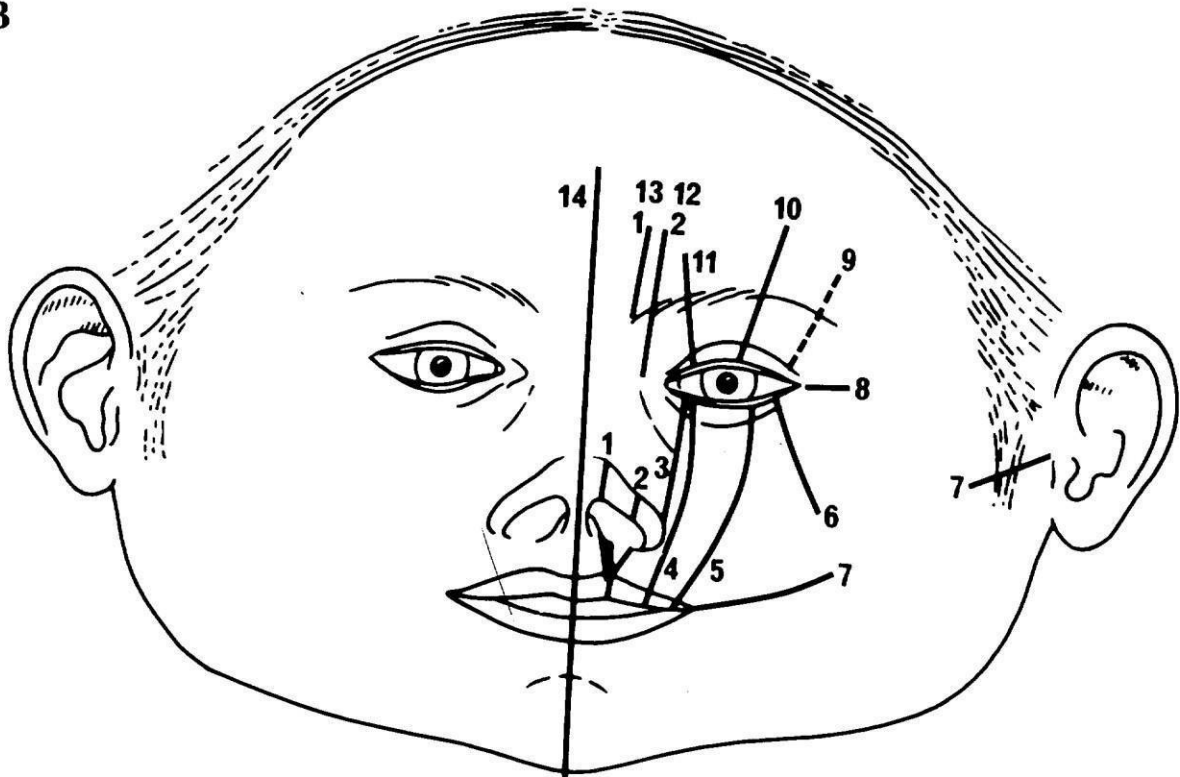
Figure 1.4: Tessier classification of craniofacial clefts. A, skeletal; B, soft tissue
(Adapted from David et al., 1989)

1.5 The number 3 and number 4 clefts

The number 3 CFC extends through the lip in the region of the philtrum. The cleft continues superiorly to the inner canthus and lower eyelid medial to the inferior lacrimal punctum, thereby disrupting the lacrimal system (David et al., 1989; Allam et al., 2014) (Figure 1.4A). Microphthalmia, which is a congenital abnormality where one or both eyeballs are abnormally small, may also be present (David et al.,1989). However, Madaree (1992), in describing an incomplete number 3 CFC recorded a coloboma of the lower eyelid between the punctum and the medial canthus as well. The number 4 cleft ascends from mid-way between the philtral ridge and the corner of the mouth through the cheek and maxillary sinus, medial to the infraorbital nerve to the infraorbital rim and orbital floor (Tessier 1976; Sari et al., 2006; Rahpeyma et al., 2014). The cleft in passing laterally to the lacrimal sac and canalis nasolacrimalis leaves the sac intact (Coruh and Gunay 2005). The eye is usually present and functional although microphthalmic and anophthalmic, which is the absence of one or both eyes, may be present (Coruh and Gunay 2005).

The CFC number 3 is rare and it is said to be responsible for 0.24% of all facial clefts (Gawrych et al., 2010). The number 3 CFC is not frequently encountered, and even surgeons involved in an active craniofacial unit will seldom be called upon to repair such a deformity (Madaree et al., 1992). Worldwide, prior to 2008, there have just been ninety-one (91) cases of the CFC number 4 reported in literature due to being very rare (Alonso et al., 2008) and between 2008 and 2018, about thirty-three (33) were seen documented in English literature. There have been case reports on the number 3 and number 4 CFCs as well as studies looking at treatment outcomes after many years. Chen (2011) compared the outcomes in using the conventional interdigitating skin flaps as treatment modalities against facial units and muscle repositioning in correcting CFC number 3. Allam et al., (2014) reported on a series of 10 number 3 CFCs, all operated on by the same surgeon over a 30- year period, discussing their pathology and treatment modalities. Likewise, the treatment of CFC number 4 and surgical outcome after follow-up have been well documented (Coruh et al., 2005; Alonso et al., 2008; Laure et al., 2010; Rahpeyma et al., 2014).

With regard to sex distribution, Kawamoto (1976), reported for CFC number 3 that there is equal sex distribution while Freitas da Silva et al., (2010), found a female to male ratio of 4:3; whilst Allam et al., (2014), reported a male to female ratio of 2:1 for the CFC number 3 and Alonso et al., (2008) while working with the largest series of CFC number 4 patients (21 cases) also reported a male to female ratio of 2:1.

Regarding association with other clefts, Tessier's nomenclature allows for several different clefts to co-exist (Allam et al., 2014). Allam et al., (2014), reported other facial clefts existed with the number 3

CFC in six patients out of their series of 10. Three patients presented with associations to cleft numbers 0, 4, and 7 while the other three had cranial extensions of cleft numbers 10, 11, and 13 (Allam et al., 2014). Freitas da Silva (2010), also reported a co-existence of CFC number 3 and a number 9 cleft. Importantly, the cranial extension was not always the number 11 cleft, as previously described (Thorne et al., 1992). For CFC number 4, reported associated clefts include numbers 5, 7 and 9 while Alonso (2008) in a series of 21 cases reported only one case with an associated CFC number 10, which hitherto had been described as its cranial extension (Alonso et al., 2008).

With regards to amniotic bands, these are congenital bands which entrap fetal parts while inutero and lead to deformities especially of the extremities. Freitas da Silva et al., (2010) reported six patients that presented with amniotic bands out of 21 cases of number 3 CFCs that were being examined while Alonso et al., (2008), reported four of the twenty- one CFC number 4 cases with associated amniotic bands. Allam (2014), postulated that amniotic bands have an etiologic role in the development of facial clefts.

Choanal atresia was first reported in association with the number 3 CFC in the literature by Dey (1973). Garabedian in 1996 and again in 1999 also reported incidences of choanal atresia and the CFCs number 3 and number 4 (Garabedian et al., 1996, 1999; Atilla et al., 2003) while Allam et al., (2014), had a case of co-existence between the CFC number 3 and choanal atresia in the series they examined. Migration anomalies of the neural crest cells was thought to be a common explanation for these associated craniofacial anomalies (Hengerer et al., 1982; Bonafos et al., 2004).

1.6 Justification for the study

Rare craniofacial clefts due to their variability and complexity have been a significant challenge to the craniofacial surgeon (Chen et al., 2012). The rarity of these defects has also made publications in this field sparse which eventually has created a situation whereby there is no consensus on standardized landmarks, reference measurements and principle of repair (Morgan et al., 2016). Whereas understanding the soft tissue and skeletal deformity is basic to any reconstructive surgical procedure (Kawamoto, 1976), there is little evidence in the literature to suggest that much is being done to address this issue (Omodan et al., 2019). Paul Tessier (1976) with his classification, which appears to be the most popular and clinically accepted, tried to improve communication amongst physicians (Tang et al., 2012). However, in clinical practice the Tessier classification system appeared to present some challenges (Tang et al., 2012). The mere allocation of a number to a Tessier cleft does not give any idea if the cleft is only of soft tissue, bone or a combination and the extent thereof (Tang et al., 2012);hence the need to establish a presentation method that can provide a clear mental image of the patient's condition with the goal of improving communication amongst surgeons.

1.7 Research questions

1. What is the current state of knowledge available regarding CFC number 3 and number 4?

2. What structures in the anatomy of the viscerocranium are affected in CFC number 3 and number 4 and how can they be grouped?

3. What is the spectrum of clinical presentation of CFCs number 3 and number 4 in a South African population?

4. What variations exist outside of the documented combination of CFCs number 3 and number 4 with their cranial extensions in a South African population?

1.8 Aim

To document the detailed anatomical basis of CFC number 3 and number 4 in order to generate a sub-classification for the clefts based on its anatomical presentation in a South African population.

1.9 Objectives

1. To evaluate the current literatures available on the knowledge of CFCs number 3 and number 4.

2. To describe the detailed anatomy of CFCs number 3 and number 4 and possibly generate a sub-classification system for the clefts.

3. To determine the other forms of CFCs that appear in combination with the number 3 and number 4 clefts in a South Africa population.

4. To document the clinical presentation of CFCs number 3 and number 4 with regards to other congenital malformations in a South Africa population

1.10 Materials and Methods

1.10.1 Available knowledge of CFCs number 3 and number 4

The first objective was undertaken by conducting a scoping review of literature on patients who presented with Tessier craniofacial clefts numbers 3 and 4 using the framework from Arksey and O'Malley (2005) for guidance. This framework consists of six steps but adapted to five for this study since the sixth step is optional (Arksey et al., 2005). These steps are (1) identifying the research question, which is generally broad in nature; (2) identifying relevant studies, a process that is as comprehensive as possible; (3) study selection, with the establishment of inclusion/exclusion criteria, based on familiarity with the literature;

(4) charting the data, a stage that includes sifting, charting, and sorting information according to key issues and themes; (5) collating, summarizing, and reporting the results, which provides both a descriptive and numerical summary of the data and a thematic analysis; and (6) a consultation exercise, an additional, parallel step involving key stakeholders to inform and validate study findings (Arksey et al., 2005). Eligible studies from 1976 to 2018 were identified. The following databases were searched for peer-reviewed literature viz., PubMed, MEDLINE, EBSCOhost, Google Scholar, and the Cochrane libraries. The eligibility criteria used for qualifying articles were: if they reported on Tessier craniofacial clefts number 3 or number 4, if they were done in 1976 and later (because the Tessier clefts were proposed then), and if the studies had information on the morphology and anthropometry of Tessier craniofacial clefts numbers 3 or 4. Studies that were not primarily on Tessier craniofacial clefts number 3 or number 4 were excluded (since this index study was on Tessier numbers 3 and 4 primarily) as well as studies done prior to-1976 (since we don't expect the Tessier designation to appear prior to this time). A data table was designed to extract information from the literature. The result of this study was reported using the Preferred Reporting Items for Systematic reviews and Meta- analyses (PRISMA). The quality of the included studies was also assessed using the Mixed Method Appraisal Tool (MMAT).

1.10.2 Detailed Anatomy of CFCs and a sub-classification system generation

The second objective was undertaken using a retrospective study conducted with the approval of the Biomedical Research Ethics Committee of the University of KwaZulu- Natal (BREC Ref No: BE652/17) as well as the Department of Health in the Province of KwaZulu-Natal through the Management of Inkosi Albert Luthuli Central Hospital from January 2003 to December 2017. During this period the Craniofacial Unit recorded 22 new cases of craniofacial clefts. Of these, 10 patients were admitted or presented with Tessier cleft numbers 3 and 4. Three of these patients had no CT scans in their records and therefore were excluded. Of the seven (7) eligible patients for the study, five (5) were Black South Africans and two (2) Indian South Africans, four (4) were male and three (3) were female with ages ranging from one (1) month old to seventeen (17) years old. Two of these patients presented with facial cleft number 3 (FC3) while the remaining five displayed facial cleft number 4 (FC4), one of which was a bilateral FC 4. The data was gathered from digital CT scans and the medical records of the seven patients. Measured parameters from them included age, sex, race, type of cleft, laterality of the cleft, location of the cleft, size of the cleft, absence of the medial maxillary wall, the size (width and height) of the maxilla, the size (width and height) of the orbits, involvement of the inferior orbital rim, nasal septum deviation, associated clefts as well as associated congenital anomalies of all types. This study investigated skeletal defects only. On the unilateral craniofacial clefts, the anatomic landmarks on the cleft side were compared with those on the non-cleft side. However, for the bilateral craniofacial clefts, the comparison was done against a patient of the same age, sex and race with a normal CT scan. The location of the alveolar cleft was measured as the distance from the midline (the vertical line through the tip of the incisal embrasure between the two maxillary central incisors, through the anterior nasal spine, through the vomer passing through the nasion)

to the medial edge of the cleft while the width of the cleft was the distance between the medial and lateral edges of the cleft. The maxillary width was measured as the distance between the zygomaticomaxillary suture to the midline and maxillary height was taken from the fronto-maxillary junction to the inferior border of the alveolar ridge. The orbital width was measured as the distance from the zygomaticofrontal suture to the fronto- maxillary suture and the orbital height was taken from the zygomaticomaxillary suture perpendicular to the inferior border of the supraorbital margin. The views that were used included 3D reconstructed views, coronal and axial sections. All measurements were subjected to both intra and inter observer reliability tests and agreements were calculated.

1.10.3 Clinical presentation of CFCs numbers 3 and number 4 in a South Africa population and associated clefts and other congenital anomalies

The third and fourth objectives of the study were undertaken by collating data from 8 patients with Tessier clefts numbers 3 and 4. These patients had been evaluated and treated over a 15-year period (from 2003 to 2017) at Inkosi Albert Luthuli Central Hospital in Durban, South Africa. Six of these patients had Tessier number 4 cleft while two presented with the number 3 cleft. The parameters of the data collected included age, sex distribution, side of occurrence, clinical presentation as well as associated clefts and congenital anomalies. Regarding the clinical presentation, involvement of the lip, alveolar ridge, nose, maxilla, medial canthus, ocular involvement, lacrimal apparatus involvement, presence of hypertelorism and lower eyelid involvement were assessed. A review of literature was also done, and documentation of these findings were noted for comparison with our documented clinical presentation and associated clefts.

1.10.4 Statistical Analysis

The statistical analysis was conducted using IBM SPSS Statistics, version 25. All measurements taken were subjected to a reliability test with another observer that was trained appropriately and the agreement between the two was calculated using Kappa statistics as well as intra-observer reliability being ensured by taking the measurements three times. A two-sample Wilcoxon rank sum (Mann-Whitney) test was used to compare groups such as cleft type and race as well as laterality and cleft type.

1.11 Publication outcomes

These are the articles that have emanated from this thesis.

Table 1: Summary of the Manuscripts/Publications

Sn	Title	Journal	Remark
1.	Scoping review of the morphology and anthropometry of Tessier craniofacial clefts numbers 3 and 4	Systematic ReviewsJournal (2019) 8:42 https://doi.org/10.1186/s 13643- 019-0951-6	Published
2.	Anatomical classification of Tessier craniofacial clefts numbers 3 and 4	Journal of Craniofacial Surgery Manuscript numb: SCS-19- 01151R1	Accepted for publication
3.	Tessier number 3 and 4 clefts: Clinical Presentation and Associated clefts in a South African population	Journal of Plastics. Reconstructive and Aesthetic Surgery. Manuscript numb: JPRAS-D-19- 01108	Under review

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BRIDGING TEXT
FROM CHAPTER ONE TO TWO

The introduction and literature review from the previous chapter documented the Tessier clefts, the rarity of these clefts as well as efforts hitherto at classifying them. The Tessier classification which is more clinically based was also mentioned and of the numbered types, the number 3 and number 4 were seen as some of the most challenging to the clinician. In addition, it recorded aspects about how the face develops and how these clefts can be formed during its development. The next chapter serves to present a comprehensive literature review which captures in particular the investigations and findings regarding the number 3 and number 4 clefts with a view to revealing where the gaps in the knowledge of these clefts remain.

CHAPTER TWO

MANUSCRIPT ONE

Scoping Review of the Morphology and Anthropometry of

Tessier craniofacial clefts numbers 3 and 4

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Systematic Reviews

Scoping review of the morphology and anthropometry of Tessier craniofacial clefts numbers 3 and 4

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Abstract

Background: In 2016, WHO reported a death rate of 303,000 newborns before 4 weeks of age due to congenital anomalies. Those that survive congenital anomalies may have long-term disabilities which may have significant impacts on the individual, their families, the healthcare system, and societies. Tessier craniofacial clefts numbers 3 and 4 are congenital anomalies that result in a partial or total defect of craniofacial tissues thereby seriously influencing the patient's appearance and impair normal functioning. Therefore, understanding these defects is paramount to relieving the burden caused by this disability. The objective of this review was to examine the literature on the understanding of the knowledge of morphology and anthropometry of Tessier craniofacial clefts numbers 3 and 4 so that areas yet to be fully understood by research can be mapped out for future research.

Methods and analysis: A scoping review for literature on patients who have Tessier craniofacial clefts numbers 3 and 4 was conducted. Relevant studies from 1976 to the present were identified. The following databases were searched for peer-reviewed literature viz., PubMed, MEDLINE, EBSCOhost, Google Scholar, and the Cochrane library. The study selection was guided by the eligibility criteria. A data table was designed to extract information from the literature. The result of this study was reported using the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA). The quality of the included studies was assessed using the Mixed Method Appraisal Tool (MMAT).

Result: Thirty-three studies met the inclusion criteria. The majority of the studies included were conducted in middle-income countries (54.5%) and some in high-income countries (45.5%); none was recorded from low-
income countries. The total available sample size from the studies was 120 with a dominant male population of 67 (55.8%) and female 53 (44.2%). The majority (97%) of the studies reported on the knowledge of morphology while 12.1% of the included studies reported on anthropometry. Of the 33 included studies, 32 scored the
highest quality (76–100%) from the quality assessment.

Discussion: The findings from this review show evidence of the knowledge of morphology and the knowledge of anthropometry of Tessier craniofacial clefts numbers 3 and 4. However, these knowledges have not translated
to universally recognized ways of repairing and documenting these clefts due to the sparse amount of studies on Tessier craniofacial clefts numbers 3 and 4.

Keywords: Craniofacial clefts, Tessier number 3, Tessier number 4, Morphology, Anthropometry

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Background

Congenital craniofacial cleft deformity is a partial or total defect of the soft tissue, bone, or a combination of these tissues in the craniofacial region. The severity of this deformity can range from relatively minor skin and soft tissue deformities to major bony abnormalities or defects of the cranial, orbital, or facial skeleton [1]. Cra- niofacial clefts can occur anywhere in the craniofacial area and may seriously influence the patient's appear- ance and impair normal functioning [1]. The incidence of the rare facial clefts is between 1.43 and 4.85 per 100,000 births [2]. Craniofacial anomalies affect a signifi- cant proportion of society with the ratio varying consid- erably by geographical area and ethnic grouping [3]. The costs of these anomalies in terms of morbidity, health- care, emotional disturbance, and social and workplace exclusion are considerable for affected individuals, their families, and society [3].

According to the World Health Organization (WHO), 303,000 newborns die within the first 4 weeks per year worldwide from congenital anomalies, of which Tessier craniofacial clefts numbers 3 and 4 are included [4]. Since one of the Sustainable Development Goals (SDG) of the World Health Organization (WHO), as well as South Africa, is to ensure healthy lives and promotion of well- being at all ages, knowledge and understanding how to solve this problem are critical for these anomal- ies [5].

Rare craniofacial clefts pose the most significant re- constructive challenge to the craniofacial surgeon today because of their variability and complexity [6]. Facial cleft surgery publications are sparse due to the rarity of the disorders, and consensus has yet to develop on stan- dardized landmarks, reference measurements, and prin- ciples of repair [7]. Understanding the soft tissue and skeletal deformity is basic to any reconstructive surgical procedure of the face [2]. There is little evidence in the literature to suggest that much is being done to address this issue.

Therefore, the objective of this review is to map out evidence of the knowledge of morphology (particular forms in which these clefts present) and anthropometry (description of these clefts using measurements or the use of some form of measurements in their repair) of Tessier craniofacial clefts numbers 3 and 4. Researchers in the field of craniofacial anomalies may benefit from the findings of this review as it highlights areas still un- discovered in the pursuit of understanding the variant anatomy of Tessier craniofacial clefts numbers 3 and 4.

Methods

This study on the knowledge of morphology and the knowledge of anthropometry of Tessier craniofacial clefts numbers 3 and 4 is a part of a larger study looking at "Understanding Tessier craniofacial clefts numbers 3 and 4: A scoping review," which is a part of a study look- ing at the "Anatomical classification of Tessier craniofa- cial clefts numbers 3 and 4 in a select South African population."

A scoping review research method is defined as a "type of research synthesis that aims to map the literature on a particular topic and provide opportunity to identify gaps to guide future studies." [8].

This scoping review began with the establishment of a research team consisting of individuals with expertise in epidemiology and research synthesis [9]. The team ad- vised on the broad research question to be addressed and the overall study protocol, including identification of search terms and selection of databases to search. The methodology for this scoping review was based on the framework outlined by Arksey and O'Malley (2005) and ensuing recommendations made by Levac and colleagues (2010) [9, 10]. The review included the following five key phases: (1) identifying the research question; (2) identifying relevant studies; (3) study selection; (4) chart- ing the data; and (5) collating, summarizing, and report- ing the results. A detailed review protocol can be obtained from the primary author upon request.

Research question

This review was guided by the main question "What types of research on Tessier craniofacial clefts number 3 and 4 have been reported?" and a sub question "In which countries (High, Middle OR low income) are research on Tessier craniofacial clefts number 3 and 4 being reported?". We applied the PCC (Population, Concept and Context) framework to determine the eligi- bility and appropriateness of the primary research ques- tion. The results of the scoping review were reported using the PRISMA (Preferred Reporting Items for Sys- tematic reviews and Meta-analysis) guidelines. See Additional file 1.

Data sources and search strategies

The initial search was implemented on 29 November 2017, in four electronic databases: viz., Google Scholar, EBSCOhost (Academic search complete, Educational source, Health source, Nursing/Academic, Medline with full text, Medline), PubMed, and the Cochrane library. The databases were selected to be comprehensive. No limits were made on language; however, there was a date limit (1976 and above, which is the year that the current accepted classification by Tessier was published). The search query consisted of terms considered by the au- thors to describe the scoping review and its method- ology: Tessier clefts, Tessier number 3, Tessier number 4, Tessier number 3 and number 4 morphology, Treat- ment, Treatment outcome, and anthropometry. The

search query was tailored to the specific requirements of each database. The entire literature search strategy, reflecting dates, database, search terms, and the results were documented.

Citation management

All citations were imported into EndNote X7, and duplicate citations were removed manually with further duplicates removed when found later in the process before they were subsequently used in title and abstract screen- ing and data characterization of full articles.

Eligibility criteria

A set of questions was used to assess the relevance of studies identified in the search. Studies were eligible for inclusion if they reported on Tessier craniofacial clefts number 3 or number 4, if they were done in 1976 and later, and if the studies had information on the morph- ology and anthropometry of Tessier craniofacial clefts numbers 3 or 4. Studies that were not primarily on Tes- sier craniofacial clefts number 3 or number 4 were ex- cluded as well as studies done pre-1976.

Title, abstract, and full-article relevance screening

For the first level of screening, one member of the team screened the titles from the databases and exported eligible articles to an Endnote library ready for abstract screening. For the second level, an ab- stract relevance screening form was developed by the authors and reviewed by the research team. Two members of the research team (AO and DK) inde- pendently screened the abstracts. Any disagreements at this level of the research necessitated both re- viewers to meet for discussion until a common con- sensus was reached. All citations deemed relevant after title and abstract screening were procured for subsequent review of the full-text article.

For articles that could not be obtained through institutional holdings available to the authors, attempts were made to contact the source author or journal for assist- ance in procuring the article. The third level of screening involved creating a full-article screening form, and two members of the team (AO and TS) independently screen the full articles. Disagreements at this stage were how- ever resolved by involving a third reviewer (TMT). The degree of agreement for the full-article screening was calculated with the overall kappa being 0.989, where a kappa of greater than 0.8 is considered to represent a high level of agreement [11] (see Additional file 1). Re- viewers met throughout the screening process to resolve conflicts and discuss any uncertainties related to study selection [9].

Quality assessment of individual studies

All the 33 included primary studies underwent methodo- logical quality assessment using the Mixed Methods Appraisal Tool (MMAT)—version 2011 [12] (see Additional file 2). A form was designed by the authors, and it was then piloted by the research team before it was used on the articles. The studies were assessed in the fol- lowing domains: the clarity of the research question, rele- vance of the sampling strategy to the research question, appropriateness of the measurements, and appropriate representation of the population under study. An overall quality percentage score for each of the included studies was calculated, and the scores were interpreted as low quality ($\leq 50\%$), average quality (51–75%), and high quality (76–100%).

Data characterization

A form was developed by the authors to confirm rele- vance and to extract study characteristics such as author and date, title, main objective, knowledge of morph- ology, knowledge of treatment, knowledge of treatment outcome, knowledge of clinical spectrum, knowledge of anthropometry, most significant outcome, study design, other significant findings, country of the study, and high- or middle/low-income country. Other information such as the percentage of male or female and age range of the population was extracted. The research team reviewed this form and slight modifications were made before use.

Data summary and analysis

The data were compiled in a single spreadsheet and imported into Microsoft Excel 2010. Content analysis of each emerging theme was done. The emerging themes identified for this paper included the knowledge of an- thropometry and the knowledge of morphology. These themes were extracted from all studies that were included.

Patient and public involvement

Patients were not involved in this study.

Results

The original search conducted in November 2017 yielded 5529 potentially relevant citations. After dedupli- cation and relevance screening, 44 citations met the eli- gibility criteria based on the title and abstract and the corresponding full-text articles were procured for review. After data characterization of the full articles, 33 studies remained and they were included in the analysis (see Additional file 2). The flow of articles through identifica- tion to final inclusion is represented in Fig. 1.

Of the 11 articles excluded at full-article screening, five articles could not be procured and thus were not

Fig. 1 PRISMA flowchart of study selection process
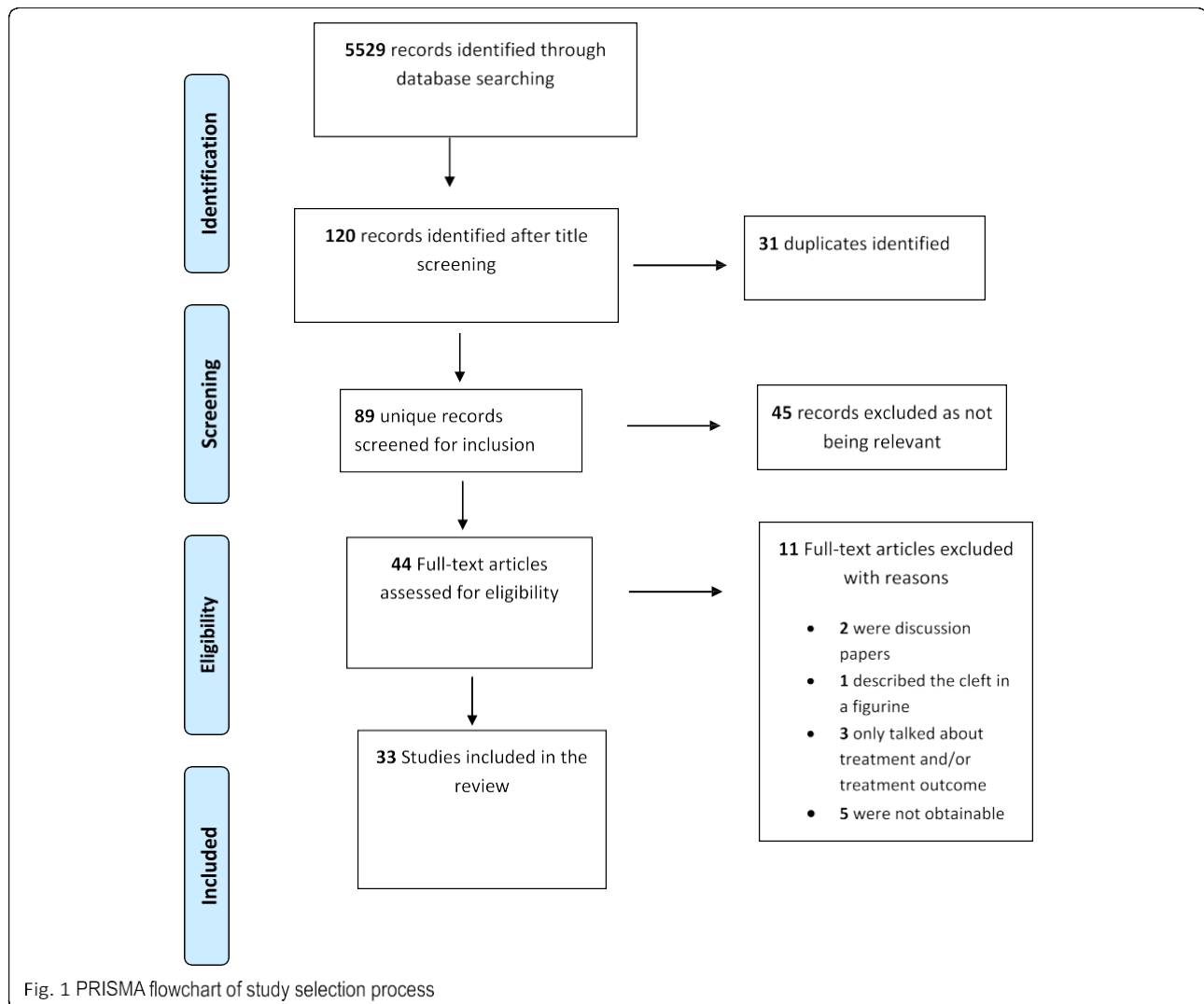
included in the review [13–17]. Two articles were discussion papers [18, 19]. Bartlett discussed the study of [6] which is one of the included studies, while Resnick and Kawamoto discussed the morphology and treatment. Three articles were not relevant as they did not illustrate evidence of the knowledge of anthropometry nor the knowledge of morphology which are the themes for this paper [20–22]. Aleman and Martinez described the cleft in an ancient figurine [23].

Characteristics of included studies
Table 1 shows the characteristics of the included studies while Fig. 2 shows a graphical representation of the advent of the knowledge of morphology and anthropom- etry in literature pertaining to Tessier craniofacial clefts number 3 and number 4. The majority (54.5%) of the in- cluded studies were done in middle-income countries [24–41], 45.5% in high-income countries [6, 7, 42–54], and none

was carried out in low-income countries. All

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included studies were published between 1980 and 2017. The total available sample size from the studies was 120 with a dominant male population of 67 (55.8%) and female 53 (44.2%). All the included studies were either case reports or case series. The majority (97%) of the studies reported on the knowledge of morphology [7, 24–54] while 12.1% of the included studies reported on anthropometry [6, 7, 40, 45].

Quality of evidence from included primary studies
All the 33 primary studies underwent methodological quality assessment using the Mixed Methods Appraisal Tool (MMAT)—version 2011 [12]. The studies were assessed based on all the categorized domains. Of the 33 included studies, 32 scored the highest (76–100%) [24–51, 53, 54]. The last one was not assessed further after scoring a "No" in the first question determining if there was a clear research question [52].

Table 1 Characteristics of articles included

Author/date	Percentage (male)	Percentage (female)	Age of population	Type of cleft	Aim of study	Main outcome
Ahmad Muhsin Mohammad Nor, 2016	100% multidisciplinary		1 day old	FC 4	The aim of this presentation is to report the sequence of procedures to manage Tessier number 4 facial cleft	A multi-disciplinary approach in managing such patient is para- mount due to the complexity. Besides the obvious issues, the psy- chosocial aspect of this matter must also be looked into
Shahin Abdollahi Fakhim et al., 2012		100%	6 months old	FC 4 and 5	Was to present a patient with bilateral numbers 4 and 5 Tessier cleft lip with unilateral complete cleft palate and surgical approach on her	We recommended early repair using autogenous tissues and as minimal disposal of the healthy tissues as possible
Akoz et al., 1995	100%		4 months old	FC 4	To report a case of Tessier no.4 cleft and their surgical approach to repairing it	Using a technique of surgery that preserved maximal amount of soft tissue with conjunctival and lower lid reconstruction utilizing a flap from the medial cleft ridge
Allam et al., 2014	70%	30%	6 weeks old to 20 years old	FC 3	Considering the rarity of the Tessier number 3 cleft, the objective was to review one of the largest series in the literature describing a single surgeon's experience in treating this complex facial cleft	As these clefts can be variable in presentation, each treatment approach must be individualized to the patient and their needs
Nivaldo Alonso et al., 2008	66.7%	33.3%	1 day old to 25 years old	FC 4	The present article aims to describe different clinical features evidenced in 21 cases of this malformation, discussing a 20-year experience with and evolution of its surgical treatment	According to our reconstructive experience, the great majority of Tessier no. 4 facial clefts may be appropriately treated using local flaps. Classic techniques are extremely useful and can offer good functional and esthetic outcomes
S. M. Balaji, 2017	100%		18 months old	FC 4	This article presents a rare case of an 18-month-old baby with bi- lateral Tessier no. 4 clefts and its successful rehabilitation	Early repair using autogenous tissues and minimal discarding of healthy tissues as much as possible is recommended
F. Bodin et al., 2005		100%	4 months old	FC 3, 7, and 11	We report a case of right associated Tessier no. 3, 7, and 11 craniofacial clefts with cardiac malformation	The case we report is a unique association of severe hemifacial microsomia and complete oro-naso-ocular cleft. To our know- ledge, this association has not been previously reported
Chen et al., 2011	N/A	N/A	N/A	FC 3 and 4	Considering the rarity of the Tessier number 3 cleft, the objective was to review one of the largest series in the literature describing a single surgeon's experience in treating this complex facial cleft	The "midface rotation advancement" concept and technique give rise to esthetically favorable results both in primary and in secondary reconstructions. This technique avoided significant scarring with poor skin color matching and unnatural facial expressions associated with the interdigitating skin flap technique
Atilla	Coruh et al., 2003					Renato da Silva Freitas et al., 2009

	50%	FC 4	This article presents two cases of Tessier no. 4 clefts, one unilateral and the other bilateral, and discusses the problems encountered during their surgical and postoperative managements	If the soft tissue deficiency is severe, conventional techniques using flaps or Z-plasties, which are designed to replace the missing tissues, are far from being ideal. Mustarde cheek flaps for lower eyelid reconstruction may be an alternative for extensive fa- cial clefts		
	50%					
	15 days to			We have treated 21 patients with Tessier number 3 cleft at 2 craniofacial centers. Eyelid, nose, and upper lip deformities should be treated in sequential stages, positioning the medial canthus, ala, and upper lip, using the contralateral side as the reference		
		FC 3	The objective was to review the functional outcome and esthetic results of the different techniques applied for each case			
	43%					
	57%					
	1 day old		to 30 years old			
Mohd Ashraf Darzi et al., 1993	66.7% months	33.3%	3 old to 3 years	FC 3, 4, 5, and 9	To adequately examine the occurrence of oblique clefts, the medical community must be aware of the problem and new cases should be presented. On the basis of clinical radiologic and surgical examinations, soft tissue and skeletal disruptions of three patients with the most rare craniofacial clefts (Tessier 3, 4, 5, and 9) are presented	Kawamoto reported Tessier number 5 cleft to be the least frequently observed oblique facial cleft. Our case three is the third bilateral and overall, the ninth case of Tessier number 5 clefts reported in world literature

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Table 1 Characteristics of articles included *(Continued)*

Author/date	Percentage (male)	Percentage (female)	Age of population	Type of cleft	Aim of study	Main outcome
E. Gawrych et al., 2010		100%	2 weeks old	FC 3	This report presents a patient with a right-sided oblique cleft ex- tending through the upper lip, the alar groove, and the lower pal- pebra accompanied by a left-sided complete cleft lip and palate. Hypertylorism and bilateral microphthalmia as well as flexion wrist contractures were also present	The findings of this report demonstrate the wide variability in the pattern of presentation of oblique facial clefts caused by aberrant tissue bands
Alcir Giglio et al., 2008	25%	75%	5 months to 8years	FC 3 and 4	Considering the rarity of the Tessier number 3 cleft, the objective was to review one of the largest series in the literature describing a single surgeon's experience in treating this complex facial cleft	The rotation and advancement flap of the cheek is a safe technique that may present satisfactory results in the treatment of rare craniofacial nos. 3 and 4 clefts
Ugur Horoz et al., 2016	50%	50%	1 to 12 years old	FC 4	The present study presents a new lip-rescue flap technique as an alternative approach for reconstructing Tessier no. 4 facial clefts	We applied our lip-rescue flap surgically on 4 patients with Tessier no. 4 facial clefts and found that the design rendered adequate tissue support and provided acceptable functional and esthetic re- sults. Because it achieves more tissue support, we recommend using this lip-rescue flap as a reconstruction method in appropri- ate patients of Tessier no. 4 facial clefts
Boris Laure et al., 2009	100%		26 years old	FC 4	We report a case of a complete bilateral Tessier number 4 cleft and our approach to surgical correction. We analyze the patient's treatment plan over a 26-year follow-up period	These rare facial clefts should be treated with the same surgical management principles as the more common lip and palate clefts
Longaker et al., 1996	33.3%	66.7%	2 to 5 months	FC 4 and 1/ 13, 2/12, 3/11	We present two cases of Tessier no.4 clefts and one case of a multiple clefted (Tessier nos. 1/13, 2/12, 3/11) child with the typical contracted oculo-alar and oculo-oral distances. Reconstruc- tion with a superiorly based nasolabial flap transposed 90 degrees under the eye was performed in all three as a primary procedure	The preceding reconstruction approach provided early protection of the eye, better position of the medial canthus, reconstitution of the bony orbit, and immediate improvement in facial appearance
Madaree et al., 1992	100%		6 weeks old	FC 3	A method of correction of an incomplete no. 3 facial cleft in an infant is presented. It is compared with previously described repairs, and its advantages are outlined	We feel that our inferiorly based transposed paranasal flap is a preferable method of filling the defect above the released alar rim
Maeda et al., 2014		100%	1 day old	FC 3 and 4	Here we present the first case of a girl born with a combined anomaly of Tessier clefts 3 and 4 with severe bilateral cleft lip, a displaced premaxilla, and three-dimensional underdevelopment of the hard and soft tissues of the maxilla and zygoma	We report an extremely rare case of a combined anomaly of Tessier clefts 3 and 4, which is, to our knowledge, the first case described in the English literature
Mishima et al., 1996	66.7%	33.3%	N/A	FC 3 and 4	This paper describes three cases of oblique facial cleft, one of which was obviously accompanied by an amnion rupture sequence. Of the other two cases, one was not affected by an amnion rupture sequence, while the other may have been	The cause can be adjudged to embryological development. Among our cases, case 3 displayed conditions typical of the amnion rupture sequence, and an amniotic band attached to an encephalocele was also detected

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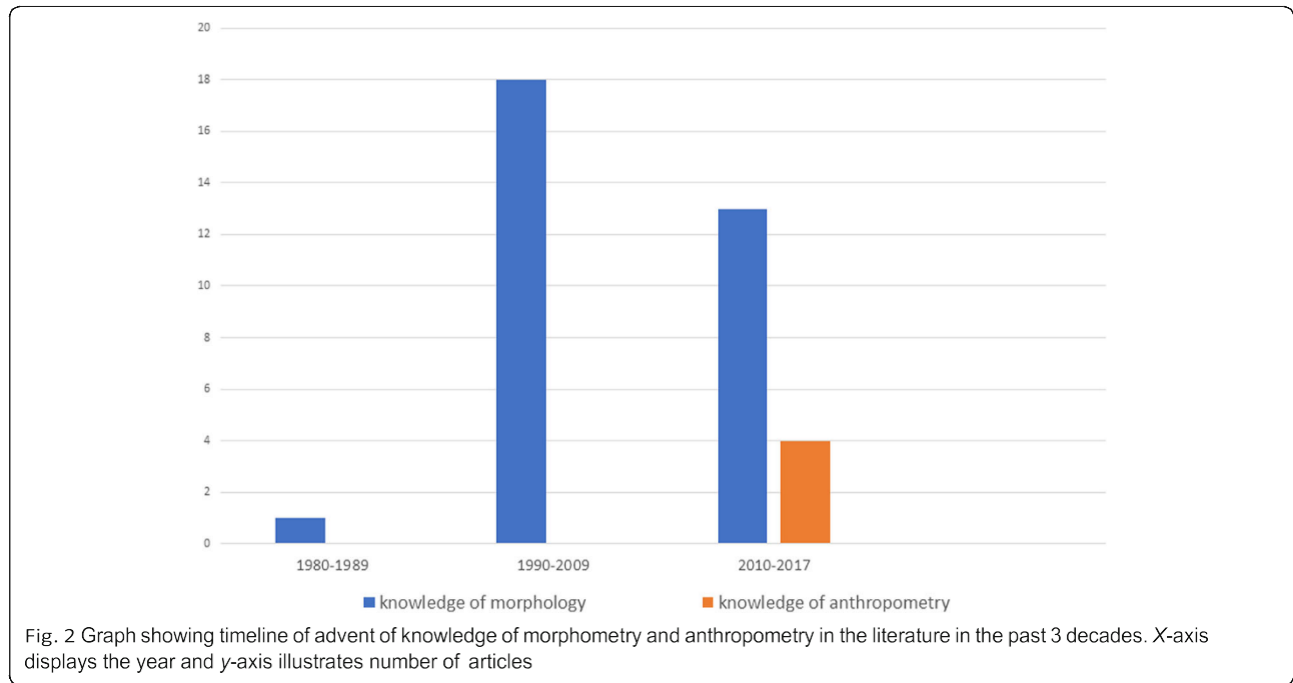| Mishira et al., 2009 | 28.6% | 71.4% | 1.5 to 21 years | FC 3 and 4 | To overcome this problem and provide a ground rule for surgical management of such cases, we propose an easier format with a "split approach" of the affected areas | Also, surgeons are often faced with complexities like the ideal age for surgical intervention and methods to ensure minimal scars in these cases. In this article, we have tried to address these issues and have attempted to provide guidelines to manage such cases effectively on the basis of our experience of seven cases of Tessier cleft types 3 and 4 in their unilateral and bilateral forms |
| Morgan et al., 2016 | 100% | | N/A | FC 3 | The authors describe a method of correcting incomplete unilateral Tessier 3 cleft based on the principles of anthropometrictechniques, based onidentifiablelandmarks and anthropometric measurements that are compared with contralateral unaffected anatomy or population means and | We present a patient with a good long-term postoperative result based on anthropometric methods to reconstruction. We feel this initial technique along with documentation of subsequent proce- dures can help provide a more reproducible form of reconstruc- tion of the soft tissues in this rare patient population |

Table 1 Characteristics of articles included *(Continued)*

Author/date	Percentage (male)	Percentage (female)	Age of population	Type of cleft	Aim of study	Main outcome
					tracked over time to assess impact on growth	
Porttier-Marriet et al., 2008		100%	6 months old	FC 4	We describe the case of a 9-month-old girl with a complete bilat- eral facial cleft. On the right cornea protruded a hard lesion, a cor- neal staphyloma	We describe the case of a 9-month-old girl with a complete bilat- eral facial cleft. On the right cornea protruded a hard lesion, a cor- neal staphyloma. We described the 3 primary surgical steps used to restore the possibility of satisfactory feeding, to promote lan- guage acquisition, and to protect vision in the non-affected eye
Reddy et al., 2014	66.7%	33.3%	2 to 11 years old	FC 2 and 3	We present two surgical options to repair such facial clefts.	We have been able to demonstrate that nasal dorsum rotation flaps were a viable option for treating the nasal defects of Tessier no. 2 facial clefts. Similarly, FENTF were a viable option to treat the nasal defects of Tessier no. 3 facial clefts.
A. Rintala et al., 1980	36.4%	63.6%	1 day old to 58 years old	FC 3, 4, 5, 7, 8, and 9	Explore cases of oblique facial clefts in the center	All patients represent different types of clefts, and in most cases, they are associated either with other facial defects or with defects of other developmental fields. There is a slight over representation of females (7:4)
Sari et al., 2003	100%		8 months old	FC 4	A patient with a Tessier number 4 cleft is presented, whose bony defect was obliterated with autogenous iliac bone graft chips and soft tissue reconstruction was performed with multiple Z-plasty flaps	Postoperative clinical and radiological results demonstrate fine healing and good cosmesis. Although controversy still exists about the treatment of facial clefts with early bone grafts, advantages of performing both bony and soft tissue reconstructions in a single session make this treatment a good alternative with satisfactory clinical and radiological results
Sessena et al., 2011		100%	1 day old	FC 3	The authors present a "step-by-step" solution of the malformation pointing out the limitations of the surgical procedures they used and the goals they wanted to obtain	The authors report an extremely rare case of a Tessier 3 cleft associated with bilateral anophthalmia, which is, as far as they know, the first one described in the English literature
Spolyar et al., 2015	100%		3 to 7 months	FC 3 and 4	Authors propose pre-surgical orthopedic correction for naso- oro- ocular clefts and a novel surgical option for Tessier no. 3 cleft	Presurgical assistance facilitates comprehensive repair of the severe facial clefts, even with single-stage primary defect repair during infancy. Lengthening of the ala base-canthal distance is a key achievement, and it can be addressed by performing a fronto- nasal flap extended with a myocutaneous upper lid flap
Tokioka et al., 2005	50%	50%	1 day old	FC 4	In this report, two cases with Tessier no. 4 cleft, which were treated with the cheek advancement flap technique, are presented	Our results indicated that by using the cheek advancement flap technique, the soft tissue deficiency of the lower eyelid was not satisfactorily reconstructed. It is suggested that any single flap is not enough for the eyelid reconstruction in such a wide cleft as in our cases. Correction with the other local flaps will be planned in the near future. Tissue expansion or free tissue transfer are good alternatives for soft tissue reconstruction

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| Uemura et al., 2004 | 100% | 6 years old | FC 3 | A composite Z-plasty to treat recurrence of cicatricial ectropion of the lower eyelids in Tessier 3 cleft is described | Composite Z-plasty is a convenient surgical method suitable for scar contracture of tissues with free margins, such as the eyelid, nostril rim, and auricular helix, from which support tissue and cov- ering skin tissue must be harvested. Composite Z-plasty should be considered in treatment planning for ectropion |
| Wenbin et al., 2006 | 100% | 1 day old to 2 years old | FC 3 | Tessier 3 cleft with clinical anophthalmia is one of the rarest craniofacial clefts, and hence little has been published about its management and treatment. This article presents two cases of Tessier 3 cleft with clinical anophthalmia | |

Table 1 Characteristics of articles included *(Continued)*

Author/date	Percentage (male)	Percentage (female)	Age of population	Type of cleft	Aim of study	Main outcome
Wu et al., 2012		100%	20 months old	FC 3	A Uighur girl with severe bilateral Tessier 3 clefts and associated orofacial deformities is described here, and a novel protocol for clefts of this severity and rarity is presented. This study focuses particularly on describing the surgical procedures and techniques	The wide facial and palatal clefts were completely closured and the defective nasal ala and the dislocated medial canthi effectively reconstructed. The patient had an acceptable facial appearance with inconspicuous scars and natural facial expression. The outcomes of these operations were functionally and esthetically satisfactory
Xu et al., 2015	100%		1 day old to 6 months old	FC 3	In this paper, we report two extremely rare cases of simultaneous Tessier number 3 cleft, contralateral cleft lip, and signs of amniotic band syndrome	We report two extremely rare cases of Tessier number 3 cleft with contralateral cleft lip and signs of amniotic band syndrome. From these two cases, we may confirm that amniotic bands are the most probable cause of the Tessier number 3 cleft. Treatment of the Tessier number 3 cleft should be individually designed based on the severity of the deformities
Sigler et al., 2004	100% months		6 months old	FC 2, 3, and 7	A unique case of a unilateral partial Tessier no. 7 cleft accompanied by nos. 2 and 3 clefts along with a single median lip pit is presented	After an extensive review of the literature, we found that unilateral transverse facial cleft along with unilateral CL/P and a median LP to our knowledge has never been describe

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Fig. 2 Graph showing timeline of advent of knowledge of morphometry and anthropometry in the literature in the past 3 decades. *X*-axis displays the year and *y*-axis illustrates number of articles

Themes from included studies

Knowledge of anthropometry of Tessier craniofacial clefts number 3 and number 4

Four of the 33 (12.1%) included studies showed varying levels of the knowledge of anthropometry in discussing Tessier craniofacial clefts number 3 and number 4. Two of these studies showed the knowledge of anthropometry in the surgical reconstruction of the defects [6, 7] while the other two displayed the knowledge of anthropometry in defining the clefts and then reconstruction [40,45].

(a) Knowledge of anthropometry in cleft definition and reconstruction

Two of the included studies showed evidence of the knowledge of anthropometry not only in the reconstruction of the defects but also initially in defining the clefts [40, 45]. One of the studies was done in a high-income country (USA) and the other in a middle-income country (China). In their study, Wu et al. aimed at describing a novel proto-col for these clefts and attributed the satisfactory functional and esthetic outcomes to the novelty of the procedure [40]. These studies show a lack of literature on the emerging technique of anthropometry in the correction of defects of Tessier craniofacial clefts numbers 3 and 4.

(b) Knowledge of anthropometry in surgical reconstruction

Two studies showed the knowledge of anthropometry during surgical reconstruction of the defects in Tessier

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craniofacial clefts number 3 and number 4 [6, 7]. Both studies were carried out in high-income countries (Taiwan, USA). In a study by Chen and colleagues aimed at reviewing one of the largest series in the literature describing a single surgeon's experience in treating this complex facial cleft, findings showed that previous treatment options paid little attention to the anatomical repair of the affected facial musculature which has led to suboptimal results with conspicuous facial scars, poor color matching of the cheek and nasal flaps, and unnat- ural facial expression [6]. The study by Morgan et al. described a method of correcting incomplete unilateral Tessier 3 cleft based on the principles of anthropometric techniques showing that consensus has yet to be developed on standardized landmarks, reference measurements, and principles of repair due to sparse publications [7]. Evidence from these studies docu- mented that knowledge of anthropometry is key to a sat- isfactory outcome in the surgical management of these clefts and there is a scarcity of publication on this know- ledge, and this has made arriving at a consensus on stan- dardized landmarks, reference measurements, and principle of repair difficult thus far.

Knowledge of morphology

Thirty-two (97%) of the included studies showed evidence of the knowledge of morphology of Tessier craniofacial clefts numbers 3 and 4 [7, 24–54]. Evidence shows that the knowledge of morphology was expressed by

describing the clefts as complete, while five of the

studies (15.6%) described a form of the cleft as incomplete [26, 27, 33, 34, 41].

(a) Knowledge of morphology of complete clefts

Thirty-one (96.9%) of the studies that showed the knowledge of morphology showed evidence of knowledge of a complete cleft [7, 24–32, 34–54]. Alonso et al., in their study which was on the different clinical features in 21 cases of number 4 cleft, described the complete cleft as consisting of a cleft lip, lateral to the Cupid's bow, which crosses superiorly up to the lower eyelid, decreasing the oro-ocular distance [28]. While Allam et al., in a study reviewing one of the largest series of number 3 clefts in the literature, described the complete number 3 cleft as extending from the philtrum of the lip to the medial canthus of the eye with the fore-shortening of this distance with affectation of the nasal ala [27]. Evidence from these studies show that there is a generally acceptable knowledge of the morphology of a complete cleft of Tessier craniofacial clefts numbers 3 and 4.

(b) Knowledge of morphology of incomplete clefts

Five (12.1%) of the 32 studies that reported on the evidence of the knowledge of morphology showed evidence of incomplete cleft [26, 27, 33, 34, 41]. In their studies, Giglio and colleagues who aimed at reviewing a large collection of the rare cleft number based on a single surgeon's perspective and Madaree et al., whose aim was to describe a method of correction of an incomplete number 3 cleft while comparing with previously documented methods, described the incomplete cleft as sparing the lip [33, 34]. Evidence from these studies show that there is a paucity of literature on the morphology of the in-complete Tessier craniofacial clefts numbers 3 and 4.

Discussion

This study sets out to map out evidence of the knowledge of morphology and the knowledge of anthropometry of Tessier craniofacial clefts numbers 3 and 4. A total of 33 unique articles were found that included the evidence of morphology and anthropometry of Tessier craniofacial clefts numbers 3 and 4. The result of this study shows us that there have been studies on Tessier craniofacial clefts numbers 3 and 4 as far back as 1980 [45]; however, evidence of the knowledge of anthropometry began in the year 2011. In addition, evidence from these studies indicate that the knowledge of anthropometry is key to a satisfactory outcome in the surgical management of these clefts; however, there is a scarcity of publication on this knowledge and this has made arriv-

ing at a consensus on standardized landmarks, reference measurements, and principles of repair difficult thus far. Also, evidence from these studies show that there is a generally acceptable knowledge of the morphology of a complete cleft of Tessier craniofacial clefts numbers 3 and 4; however, there is a sparsity of literature on the morphology of the incomplete numbers 3 and 4 Tessier craniofacial clefts. Although the problem of facial clefts is a global issue [4], this study further revealed that studies on the knowledge of anthropometry of Tessier craniofacial clefts numbers 3 and 4 were mostly done in middle-income countries (54.5%) while 45.5% was carried out in high-income countries, and none were done in low-income countries.

Cizmeci and Kuvat aimed at presenting a treatment option for these rare clefts and also reiterated that little is being published about the treatment and management of these clefts due to its rarity [20].

To the best of our knowledge, this is the first scoping review to map evidence on the knowledge of morphology and the knowledge of anthropometry in Tessier craniofacial clefts numbers 3 and 4. An extensive search strategy, which helped in the identification of a considerable number of studies, was conducted in this study. The study followed clear screening processes using keywords, which were guided by study PCC nomenclature. A thorough data search using Boolean terms was conducted during the literature search to increase the chances of finding eligible studies for inclusion in this review. The degree of agreement between the reviewers was significant (> 0.05) after the full-article screening. The review also included a transparent methodological quality assessment of the included primary studies using the recommended MMAT tool [12].

Despite the reported strength of our study, the limitation we encountered was primarily the inability to retrieve some articles which might have been of benefit to the study [13–17]. This was despite efforts including but not limited to personal letters to the authors. Also, Chen PK-T, et al. did not distinguish male from the female participants in their study [6].

Our review has shown that there is little in the form of research publications on the morphology (especially incomplete clefts) and more importantly on the anthropometry of Tessier craniofacial clefts numbers 3 and 4. We recommend to researchers that not only should more be done in documentation of incomplete clefts but more importantly research should be redirected mostly towards the emerging technique of anthropometry in the understanding and possibly finding a standardized way of managing the rare craniofacial clefts numbers 3 and 4. Also, we recommend that these studies require to be reported in low-resource countries as currently there is no

evi- dence of such studies from these areas.

To surgeons in the management of these complex rare facial clefts, we recommend the use of anthropometric techniques in the way the repairs are carried out as this will prove to be a more reproducible method of repair and will further contribute to having a standardized way of carrying out these complex yet rewarding surgeries.

Conclusion

Our findings suggest that the knowledge of morphology and the knowledge of anthropometry of Tessier craniofacial clefts numbers 3 and 4 exist albeit not fully harnessed. Furthermore, our review highlights the fact that no studies on these clefts are being done in low-income countries despite the global prevalence of this disease. This review also highlights the fact that knowledge of anthropometry is an emerging technique of solving the problem posed to surgeons of not having a standardized way of treating these defects. Further, studies should be encouraged in areas of anthropometry of Tessier craniofacial clefts numbers 3 and 4 as well as other aspects that affect the rare clefts Tessier numbers 3 and 4 such as their treatment, the outcome of this treatment, and possibly the clinical spectrum of their presentation.

Additional files

Additional file 1: PRISMA checklist. (DOC 64 kb)

Additional file 2: Calculation of degree of agreement for full-article screening between the two reviewers. (PDF 86 kb)

Availability of data and materials
All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Authors' contributions
AO and PP conceptualized and designed the study. AO prepared the first draft of the manuscript. PP, LL, AM, and KS critically reviewed the manuscript. All authors reviewed the draft versions of the manuscript and approved the final version of the manuscript.

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Not applicable

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BRIDGING TEXT
FROM CHAPTER TWO TO THREE

The Scoping Review from the previous chapter highlighted the areas of the number 3 and number 4 clefts that have remained gaps in our knowledge despite the clefts being investigated and reported upon. The findings of the previous chapter demonstrated that the morphology and anthropometry of these clefts have been recorded although the full potential of its value is not used being that just one study was identified to have documented the use of anthropometry in the reconstruction of these clefts. It also became apparent that the knowledge of the anthropometry is an emerging technique to resolve the problem of non-standardization of methods of treating these clefts which surgeons face today. The next chapter aims to investigate the use of an anthropometric technique to sub-classify the number 3 and number 4 clefts with the overall aim of attempting to make practice easier for craniofacial surgeons when it comes to documentation and communication within the specialty.

CHAPTER THREE
MANUSCRIPT TWO

Anatomical classification of Tessier craniofacial clefts numbers 3 and 4

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Anatomical classification of Tessier craniofacial clefts numbers 3 and 4

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Abstract

Introduction: Craniofacial clefts are rare occurrences with an incidence of about 1.43 to 4.85 per 100,000 live births. Understanding the skeletal deformity in these clefts is basic to any reconstructive surgery of the face. This study documented the skeletal defects present in Tessier numbers 3 and 4 using anthropometric measurements in order to generate a sub-classification which will aim to improve the means of communication between surgeons managing this anomaly.

Methods: Seven CT scans of patients who had been treated for Tessier 3 and 4 clefts between 2003 and 2017 were analysed. Measurements of the expected defects in each cleft was taken and compared with unaffected side as the reference. Emerging patterns of their analysis was then used to generate a sub-classification for these clefts. The reliability and validity of the measurements were ensured by allowing the data to be examined by both an intra and inter observer.

Results: The presence or absence of an alveolar cleft, the emerging patterns of comparison of the measurements of the maxilla and the orbits of the cleft side and the non-cleft side as well as absence of the bone were used to arrive at a sub-classification system using (a), (b), (c), (M+ O+), (M- O-), and (0).

Conclusion: The study recommends a sub-classification for Tessier clefts numbers 3 and 4 that will allow physicians anticipate the extent and the form of skeletal defects present before even seeing the patient. This can improve the communication amongst surgeons and team members regarding Tessier craniofacial clefts.

INTRODUCTION

The search for a concise, meaningful and comprehensive classification for craniofacial clefts is hindered not only by these clefts being rare but also by the presence of a large variety of them.[1] Paul Tessier published a craniofacial cleft classification that has become widely accepted.[2,3] Tessier used a numbering system to identify the consistent anatomic pathways of soft tissue and skeletal clefts. He described the number 3 cleft (FC3) as passing through the lip in the region of the typical cleft lip involving the ala base and continuing superiorly to the inner canthus and the lower eyelid with disruption of the nasolacrimal apparatus.[2,1] The alveolar cleft emerges between the lateral incisor and the canine, involving the frontal process of maxilla with the possibility of the orbit, maxillary sinus and nose in direct communication.[2,1] The number 4 cleft (FC4) is found midway between the philtral ridge and the commissure of the mouth, continuing upward around the ala base onto the cheek sparing the nasolacrimal apparatus.[2,1] He described the alveolar cleft of FC4 as similar to that found in FC3 and terminates at the medial end of the inferior orbital rim.[2,1] Tessier's classification improved communication amongst carers of craniofacial clefts and by its simplicity aided in appreciating the reconstructive surgery needed to restore normality.[1]

In clinical practice the Tessier classification system appears to present some challenges.[4] The manifestations of craniofacial clefts are very complex and simply allocating them with the Tessier numbering system fails to give a full appreciation of the clinical picture. The physician is not able to mentally visualise a patient diagnosed using the Tessier classification until the patient is seen.[4] The mere allocation of a number to a Tessier cleft does not give any idea if the cleft is of soft tissue only, bone or a combination and the extent thereof. For example, a

patient being diagnosed as a Tessier number 3 cleft cannot be visualised as to the extent of the presenting defects. Hence the need to establish a classification method that can provide a clearer mental image of the patient's cleft. This would improve communications among physicians.[4]

Publications on craniofacial clefts are sparse with a paucity of definitive standardized landmarks, reference measurements and principles of its repair.[5] This problem does not exist with routine cleft lip where the literature is extensive, incorporating anthropometric techniques and measurements.[5] In the quest to understand these clefts better, the appreciation of the skeletal deformities in these clefts play a role in planning the optimal reconstructive procedure.[3] With this in mind we embarked on documenting the skeletal defects present in the patients with Tessier clefts numbers 3 and 4 anatomically using identifiable landmarks and anthropometric measurements that guarantee reproducible methods and outcomes. This led us to a proposal for a new classification system for facial clefts numbers 3 and 4 using the maxillary size (M) and the orbital size (O) in these clefts in a way to give the mental picture hitherto missing in clinical practice. This system will improve communication between surgeons, assist in appropriate referral and influence facial cleft protocols.

METHODS

This was a retrospective study conducted with the approval of the Biomedical Research ethics Committee of the University of KwaZulu- Natal (BREC Ref No: BE652/17) as well as the Department of Health in the Province of KwaZulu-Natal through the Management of Inkosi Albert Luthuli Central Hospital from January 2003 to December 2017. In this period the Craniofacial unit recorded 22 new cases of craniofacial clefts. Of these number 10 patients

were admitted or presented with Tessier cleft numbers 3 and 4. Three of these patients had no CT scans in their records were excluded from this study. Of the seven (7) eligible patients for the study, five (5) were Black South Africans and two (2) Indian South Africans. Four (4) were male and three (3) were female with ages ranging from one (1) month old to seventeen (17) years old. Two of these patients were facial cleft number 3 (FC 3) while the remaining five were facial cleft number 4 (FC4). Of the 5 FC4, one was bilateral. Digital CT scans and the medical records of the seven patients included were retrieved and recorded. The CT scan measurements in this series were from a diverse range of patients and the measurements taken from anatomical landmarks that can be easily reproduced in any patient elsewhere give them a high external validity. The data included age, sex, race, type of cleft, laterality of the cleft, location of the cleft, size of the cleft, absence of the medial maxillary wall, the size (width and height) of the maxilla, the size (width and height) of the orbits, involvement of the inferior orbital rim, nasal septum deviation, associated clefts as well as associated congenital anomalies. This study only looked at the skeletal defects.

On the unilateral craniofacial clefts, the anatomic landmarks on the cleft side were compared with those on the non-cleft side. However, for the bilateral craniofacial clefts, the comparison was done against a normal patient of the same age, sex and race. The location of the alveolar cleft was measured as the distance from the midline to the medial edge of the cleft while the size of the cleft was the distance between the medial and lateral edges of the cleft. Maxillary width was the distance between the zygomaticomaxillary suture to the midline and maxillary height was from the fronto-maxillary junction to the inferior border of the alveolar ridge. Orbital width was measured as the distance from the zygomaticofrontal suture to the fronto-maxillary suture and orbital height as the perpendicular distance from the zygomaticomaxillary suture to the inferior border of the supraorbital margin.

Statistical Analysis

The statistical analysis was conducted using IBM SPSS Statistics, version 25. The measurements were subjected to inter observer reliability test and the agreement between the two was calculated. A two-sample Wilcoxon rank sum (Mann-Whitney) test was used to compare groups such as cleft type and race as well as laterality and cleft type.

RESULTS

Of the seven (7) cases that were analysed, five were FC4 while two were FC3. These were made up of five Black South Africans and two Indian South Africans. Three were male and the female were four. Their ages ranged from 0.23months (1week) to 204months (17years) with an average of 50.89months (70.7). This range of patients is representative of the population of patients affected by these clefts in our environment. Six had unilateral clefts, four of which were FC4 and two being FC3. One had a bilateral cleft (FC4). Four of the patients had soft tissue and bony clefts while three of the cases had only soft tissue clefts. The average location of the bony cleft was 7.3mm (2.2) from the midline and the average size of the clefts was 12.4mm (7.9). These measurements were taken from points of anatomical landmarks that are reproducible in clinical practice anywhere else. Inter observer test was done for the measurements and Kappa was used to check the agreement with an overall score of 0.989. (Figs 1 – 7)

Facial cleft number 3

In our series of patients, there were two (2) with unilateral FC3 clefts. Both clefts were on the right side with one affecting soft tissue only and the other affecting both the bone and soft tissue. The bony cleft present was 9.1mm in size and the maxilla had a width and height that were 1.7% and 2.7% respectively larger on the cleft side as compared to the normal non cleft side. The orbital measurements were 6.1% and 12.1% larger on the cleft side as compared to the non-cleft side for the width and height respectively. The soft tissue cleft only in this series had bony measurements for maxilla which were 8.1% and 14.1% smaller for the width and height respectively as compared to the non-cleft side. The orbital measurements were 3.1% and 11.6% larger on the cleft side as against the non-cleft side. (Table 1)

Unilateral Facial cleft number 4

In the FC4 series, four (4) were unilateral clefts and one (1) was bilateral. In the unilateral group two (2) had both bony and soft tissue clefts and two (2) had only soft tissue clefts. The first of the bony clefts had a cleft with a size of 8.6mm with the measurements of the maxillary width being 4% larger on the cleft side as compared to the non – cleft side while the height was 0.9% smaller. The orbital width was 3.3% smaller on the cleft side while its height was 0.9% larger (Table 1). The other bony cleft patient had a cleft of 26mm in size. The maxillary bone was largely absent on the cleft side and this made the measurements of these parameters impossible. This did not allow for a comparison between the cleft side and the non – cleft side (Table 1). The first of the two (2) soft tissue only clefts had maxillary measurements 3.1% and 12.1% smaller for the width and height respectively on the cleft side as compared to the non – cleft side while the orbits had 11.2% and 3.5% smaller sizes for the

width and height respectively on the cleft side compared to the non – cleft side (Table 1). The second one had maxillary measurements on the cleft side that were 12.5% and 15% smaller for the width and height respectively as compared to the non – cleft side while the orbital width and height were 6.5% and 6% larger on the cleft side than the non – cleft side. (Table 1)

Bilateral Facial cleft number 4

There was one bilateral facial cleft number 4 in the series. There were bony clefts on both sides. The measurements here were compared to a matched patient with a normal facial CT scan of the same age, sex and race. The cleft on the right measured 12.4mm while the left was 5.7mm. The maxilla on the right had a 1.9% and 10.2% smaller width and height respectively compared with the equivalent match while the right orbit had a width and height that were smaller by 9.5% and 7% respectively. The left side cleft measured 5.7mm with a maxillary width that was 4.1% smaller than the equivalent match and a height that was 7.5% larger. The orbital measurements were 14.4% and 6.6% larger in their width and height respectively than the equivalent match. (Table 1)

DISCUSSION

The lack of a standard unified classification has been an issue in the diagnosis, communication and appreciation of the extent of craniofacial cleft deformities.[6] Over the past several years many attempts had been made at coming up with classification methods based on different aspects of the cleft.[4] Recently the Bangalore classification utilized embryological

developments as well as clinical presentation of clefts in the head in recommending a classification system. The STO classification made use of skin, soft tissue and craniofacial bone involvement.[6] The Eight Diagrams of China and the Tessier classification were incorporated together to come up with the Spectacle Frame classification.[4] The Tessier classification appears to be the most popular and clinically accepted due to its simplicity and its ability to improve communication among physicians. The problem with the Tessier classification however is that when it comes to clinical, it lacks the ability to convey the extent of the clinical picture.[4] Surgeons cannot appreciate the extent or the pattern of the FC3 and FC4 defect due to the varying range of affectation. This study improves the understanding of the Tessier classification by making it possible to mentally visualise the form and extent of the cleft prior to seeing a patient.

The study looked at the skeletal defects expected in a number 3 cleft as well a number 4 cleft as described by David et al., 1989. The pattern emerging from measuring the clefts and bone was used as a basis for the sub-classification. The patients either had combined soft tissue and bony clefts or soft tissue only clefts. None of our patients had bony clefts only. The maxilla and the orbits were measured. The documented increase or decrease in the height and width of the maxilla and the orbits are denoted with the positive (+) or negative (-) signs respectively (see Table 2 and Figures 8 and Figure 9).

Using this sub-classification on our sample population, five patterns emerged. The first was a uniform increase in the size of all measurements on the cleft side in comparison to the non-cleft side (Case 2). The second was a uniform decrease of all measurements on the cleft side as compared to the non-cleft side (Case 4). There were additionally two forms of mixed measurements, one being a uniform mix where the maxillary and orbital width and height

had increasing or decreasing measurements on the cleft side as against the non-cleft side (Cases 3 and 5) and the other mixed variant being where the measurements of maxillary and orbital widths and heights were mixed randomly (Cases 1 and 7). The fifth pattern which was identified was a total absence of the maxilla (Figure 10). Therefore, measurement was not possible (Case 6). These were variously represented as indicated below in table 3. The CT scan measurements were taken from anatomical landmarks that make it easy to reproduce clinically on patients with these clefts. These were from a range of patients that were of interest when investigating facial clefts.

This classification gives the clinician more clarity in understanding the clinical picture of patients that are referred.

The study shows that in populations with no bony cleft involvement, the maxilla on the cleft side was always smaller in comparison to that on the non-cleft side despite the non-involvement of the bone. However, this was not the outcome of the orbital measurements in the same population. These anthropometric measurements and the basic nomenclature in this sub-classification could be extended to other Tessier clefts. This will enhance understanding and communication amongst craniofacial team members and could be used as a basis to influence protocols on facial cleft management.

CONCLUSIONS

The understanding of the skeletal deformities of facial clefts is a key factor in determining the best surgical approach to achieve the optimal result. This study used anthropometric

measurements in detailing the presenting skeletal defects of FC3 and FC4 and has the potential to improve communication amongst craniofacial surgeons. The study has enabled us to sub-classify Tessier for clefts numbers 3 and 4.

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Figure legends

Fig 1: (Top left) shows patient during subsequent revision of his surgeries. (Top right) showing amongst others measurement from the midline to the medial edge of the cleft. (Bottom left) shows the measurements of the orbits and the maxilla. (Bottom right) shows the cleft size in measurement

Fig 2: 3-month-old girl with right FC3. (top left) shows the soft tissue cleft. (top right) shows the bony cleft on 3D reconstruction. (Bottom left) shows the right cleft in an axial view

Fig 3: (Top left) shows 8-year-old boy with Right FC3. (Top right) shows the deviation of the nasal septum to the right. (Bottom left) shows the orbital measurements (Bottom right) shows the maxillary measurements.

Fig 4: Left) shows 4-month-old girl with Right FC4. (Right) showing the measurements of the orbits and the maxilla.

Fig 5: (Top left) 4-year-old boy with Left FC4 (Top right) showing orbital measurements (Bottom left) shows the maxillary measurements.

Fig 6: (Top left) Patient with Right FC4 at first presentation. (Top middle) Patient at 17-year-old. (Top right) showing the 3D of the facial bones depicting the absent medial maxillary wall (Bottom left) shows the measurements of the orbits and the present maxilla (Bottom right) shows the size of the alveolar cleft.

Fig 7: (Top left) A week old baby with bilateral FC4. (Top middle) shows the 3D recreation of the facial bone with the right alveolar cleft and medial maxillary wall showing (Top right) shows measurements of the orbits and the maxilla (Bottom left) shows the alveolar cleft sizes.

Fig 8: (A) Illustration of the proposed classification showing a skull with Tessier number 4 cleft and the orbit on the cleft side larger in comparison to the non-cleft side. (B) Shows the orbit on the cleft side smaller in comparison to the non-cleft side.

Fig 9: (A) Illustration of the proposed classification showing a skull with Tessier number 4 cleft and the maxilla on the cleft side smaller in comparison to the non-cleft side. (B) Shows the maxilla on the cleft side larger in comparison to the non-cleft side.

Fig 10: Illustration of the proposed classification showing a skull with Tessier number 4 cleft and a totally absent maxilla.

Figure 1
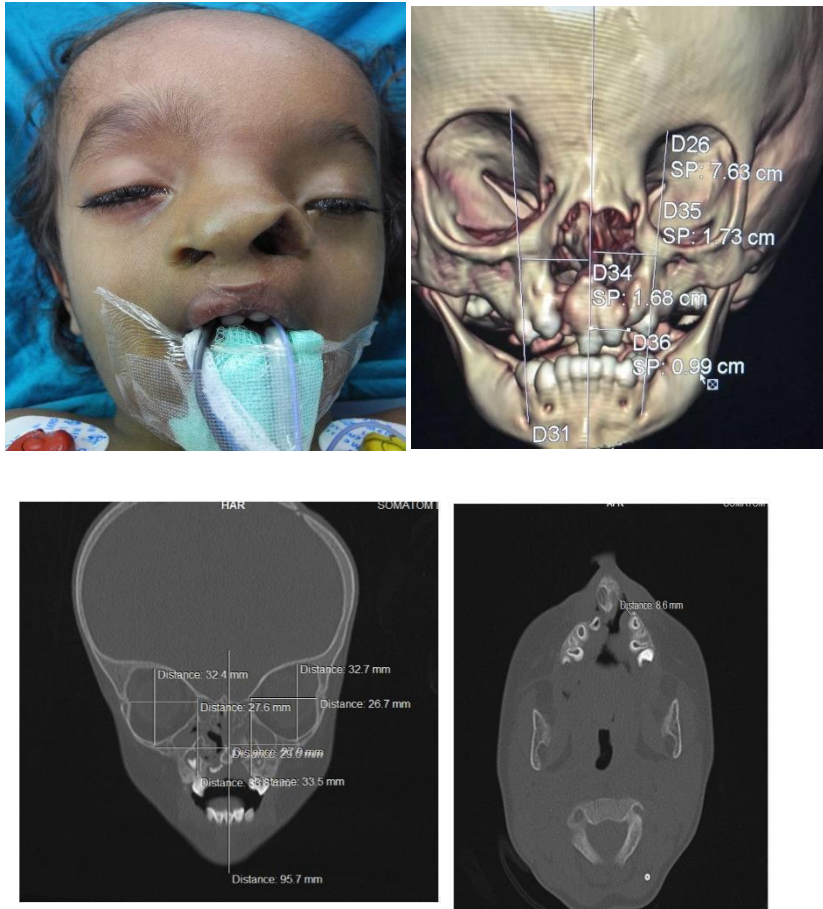
Figure 1

Fig 1: (Top left) shows patient during subsequent revision of his surgeries. (Top right) showing

amongst others measurement from the midline to the medial edge of the cleft. (Bottom left) shows

the measurements of the orbits and the maxilla. (Bottom right) shows the cleft size in measurement.

Figure 2

Figure 2

Fig 2: 3-month-old girl with right FC3. (top left) shows the soft tissue cleft. (top right) shows the bony

cleft on 3D reconstruction. (Bottom left) shows the right cleft in an axial view

Figure 3
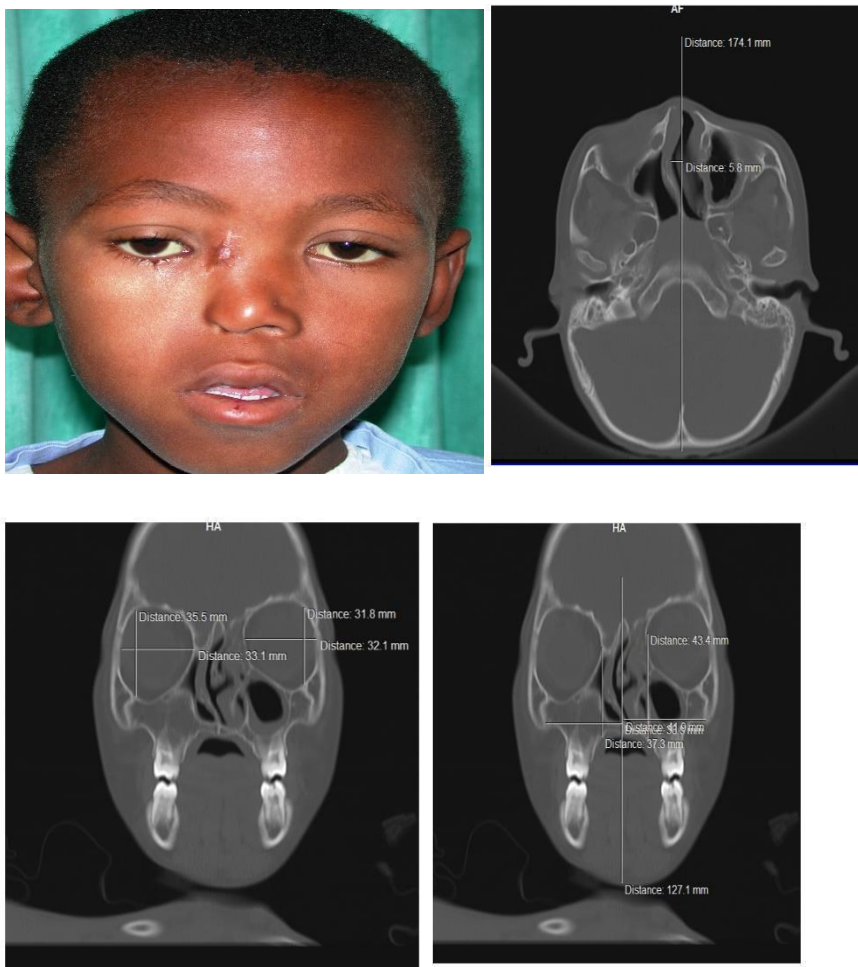
Fig 3: (Top left) shows 8-year-old boy with Right FC3. (Top right) shows the deviation of the nasal

septum to the right. (Bottom left) shows the orbital measurements (Bottom right) shows the

maxillary measurements.

Figure 4

Fig 4: (Left) shows 4-month-old girl with Right FC4. (Right) showing the measurements of the orbits

and the maxilla.

Figure 5

Figure 5

Fig 5: (Top left) 4-year-old boy with Left FC4 (Top right) showing orbital measurements (Bottom left) shows the maxillary measurements.

Figure 6
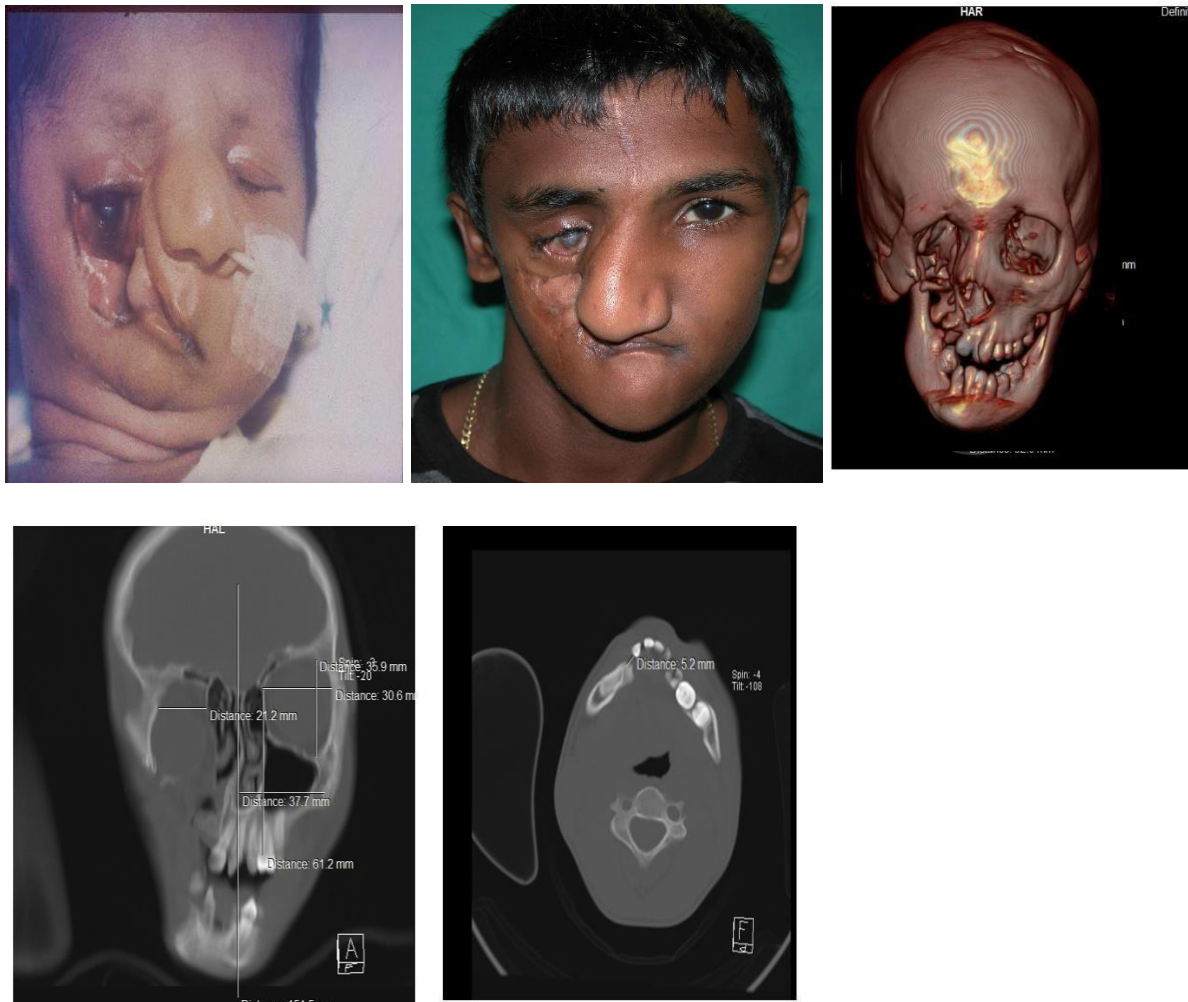
Figure 6

Fig 6: (Top left) Patient with Right FC4 at first presentation. (Top middle) Patient at 17-year-old. (Top right) showing the 3D of the facial bones depicting the absent medial maxillary wall (Bottom left) shows the measurements of the orbits and the present maxilla (Bottom right) shows the size of the alveolar cleft.

Figure 7

Figure 7

Fig 7: (Top left) A week old baby with bilateral FC4. (Top middle) shows the 3D recreation of the facial bone with the right alveolar cleft and medial maxillary wall showing (Top right) shows measurements of the orbits and the maxilla (Bottom left) shows the alveolar cleft sizes.

Figure 8
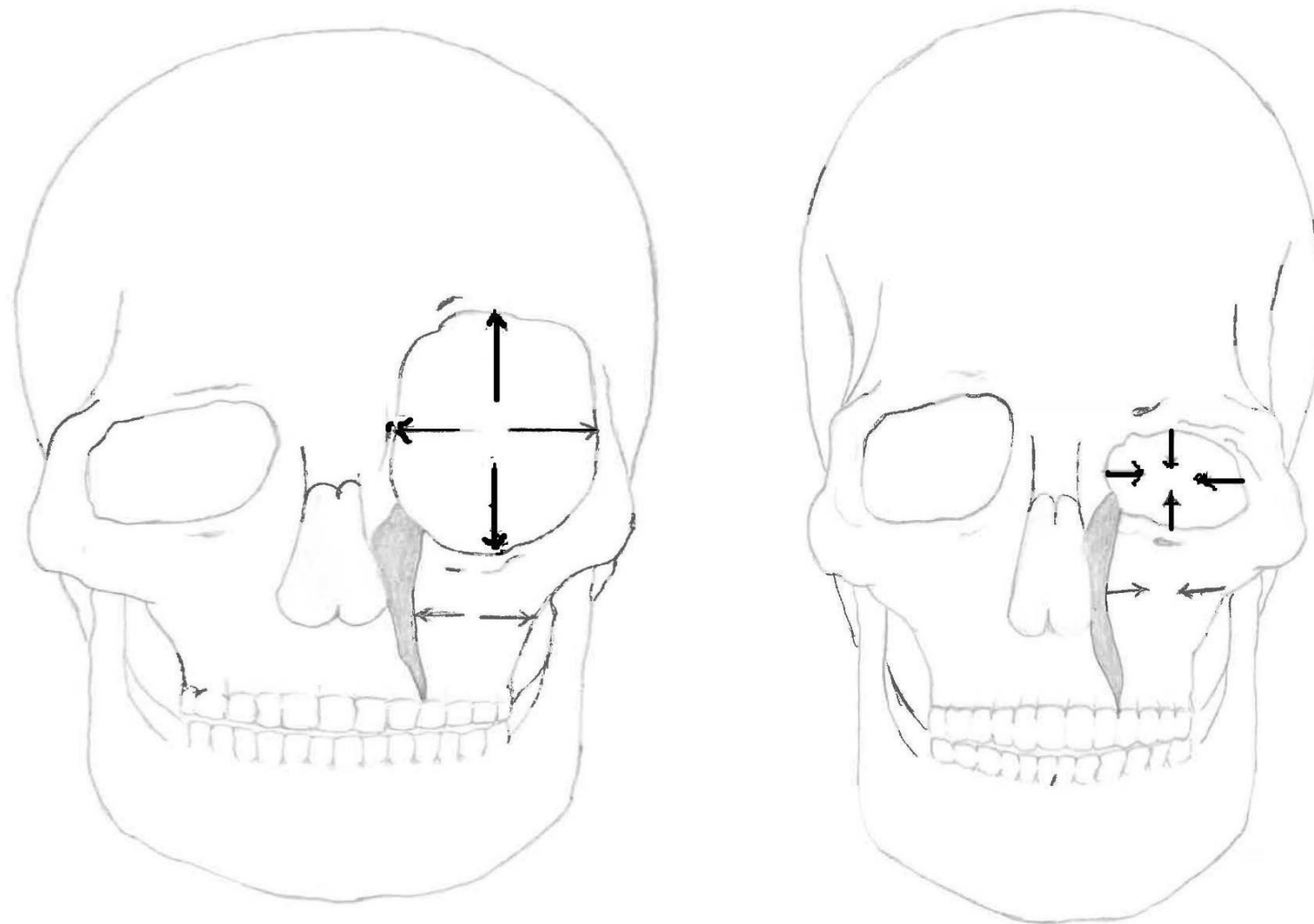
Fig 8a and 8b: Thickened arrows show the orbit on the cleft side. Possible variations include the larger variant (a) and smaller variant (b) in respect to non-cleft side. These can manifest as either uniform increases or decreases with the corresponding maxilla or in a mixed fashion of either increase or decrease with corresponding decrease or increase of the maxilla on the same side.
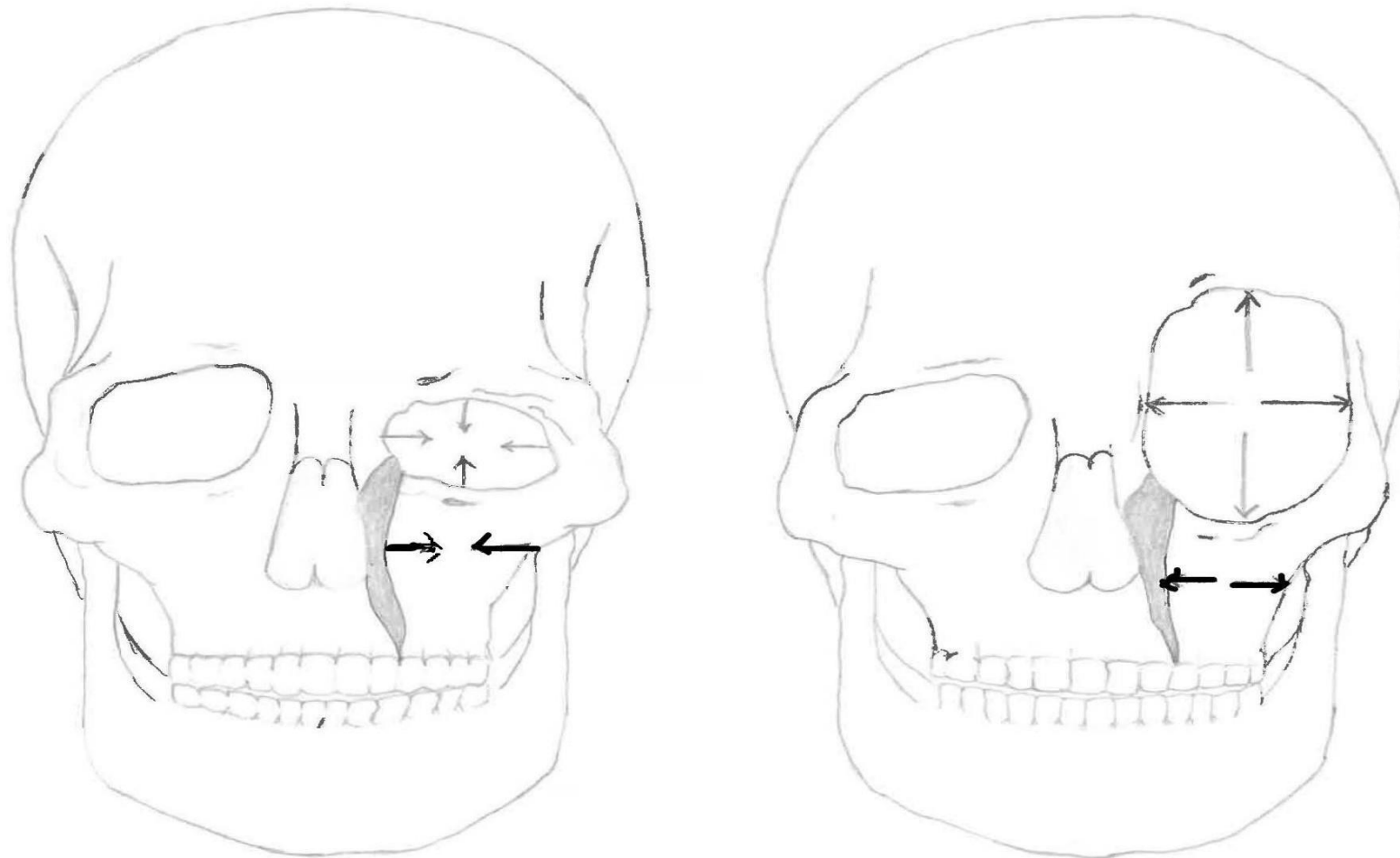
Figure 9

Figure 9a and 9b: Thickened arrows show the maxilla on the cleft side smaller(a) and larger (b) than the non-cleft side. These can manifest as either uniform increases or decreases with the corresponding orbit or in a mixed fashion of either increase or decrease with corresponding decrease or increase of the orbit on the same side.
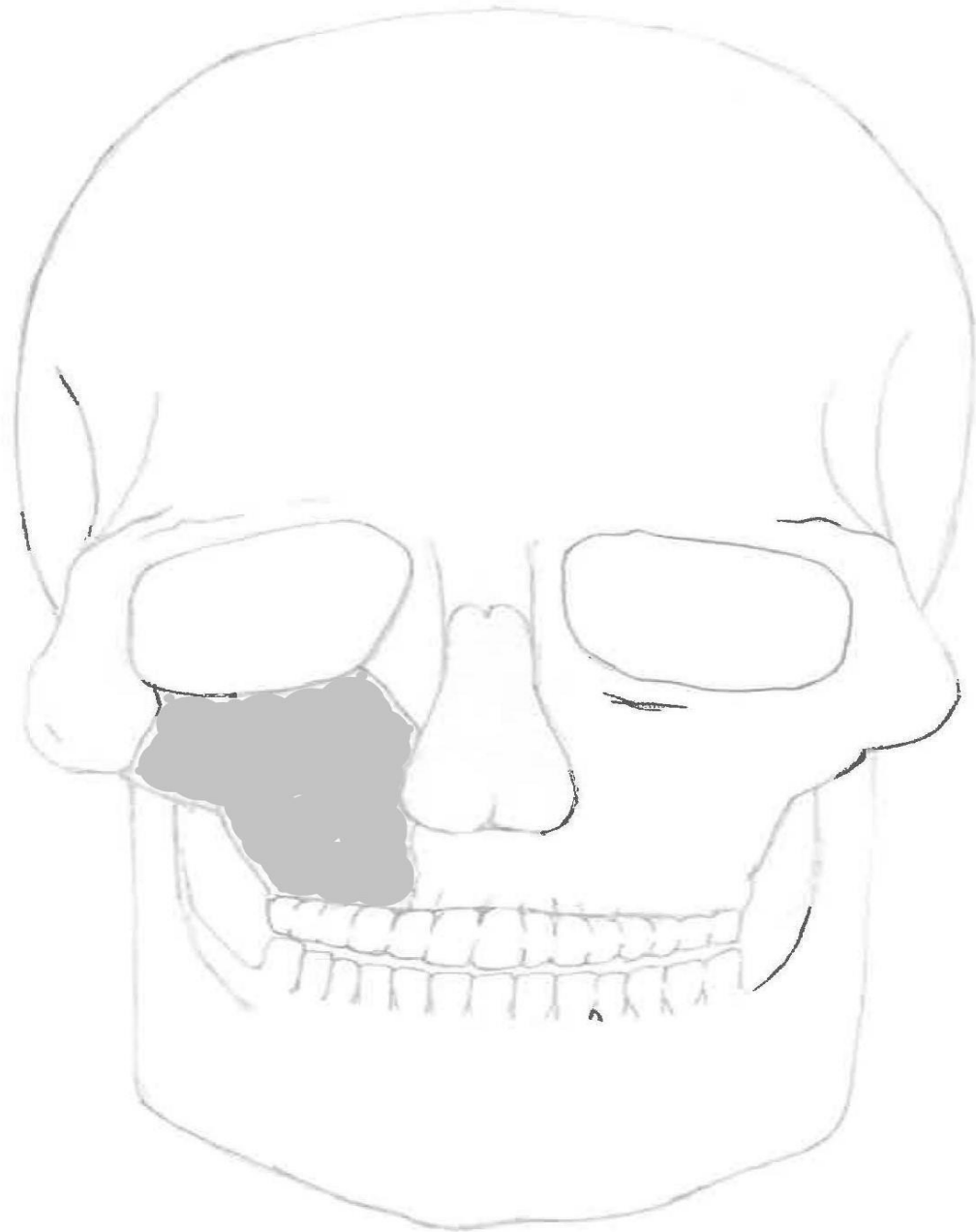
Figure 10

Figure 10: Depicts the skull with the variant where the maxilla is totally absent.

Table 1

Table 1: Bony cleft and measurements of the maxilla and orbits in comparison with the non-cleft side. Encircled measurements depict affected side.

| Case number	Cleft type	Cleft size (mm)	Maxilla (mm)			Orbit (mm)		
			Right Left			Right Left		
1	Left FC4	8.6	**W**27.9 (29.0)	4% bigger		**W**27.6 (26.7)	3.3% smaller	
			H 33.8 (33.5)	0.9% smaller		**H** 32.4 (32.7)	0.9% bigger	
2	Left FC3	9.1	**W**35.9 (36.5)	1.7% bigger		**W**22.8 (24.2)	6.1% bigger	
			H 33.8 (34.7)	2.7% bigger		**H** 26.5 (29.7)	12.1% bigger	
3	Right FC3	No bony cleft	**W**(38.5) 41.9	8.1% smaller		**W**(33.1) 32.1	3.1% bigger	
			H(37.3) 43.4	14.1% smaller		**H**(35.5) 31.8	11.6% bigger	
4	Right FC4	No bony cleft	**W**(23.8) 24.6	3.1% smaller		**W**(20.2) 22.9	11.2% smaller	
			H(18.1) 20.6	12.1% smaller		**H**(19.5) 20.2	3.5% smaller	
5	Left FC4	No bony cleft	**W**36.0 (31.5)	12.5% smaller		**W**30.6 (32.6)	6.5% bigger	
			H 38.8 (38.2)	15% smaller		**H** 31.5 (33.4)	6% bigger	
6	Right FC4	26.0	**absent W**37.7			**W**(21.2) 30.6	30.7% smaller	
			maxilla H 61.2			- 35.9		
7	Bilateral FC4	**R** 12.4	**W**(30.4) 31.0	1.9% smaller		**W**(23.8) 26.3	9.5% smaller	
			H(25.6) 28.5	10.2% smaller		**H**(30.7) 33.0	7% smaller	
		L 5.7	**W**32.0 (30.7)	4.1% smaller		**W**27.0 (30.9)	14.4% bigger	
			H 28.1 (30.2)	7.5% bigger		**H** 33.3 (35.5)	6.6% bigger	

Table 2

Table 2: Shows the sub-classification using the possible forms of presentation of these clefts as well as emerging patterns of the comparison of the measurements of the maxilla and orbits with the normal (non-cleft) side.

Form	Designation
Soft tissue clefts alone	**a**
Soft tissue and bony clefts	**b M+ O+** **M- O-**
Bony clefts alone	**c M+ O+** **M- O-**
Absent bone	**(0)**

Table 3

Table 3: Shows the sub-classification of our population using the proposed new method.

Case	New sub-classification
Case 1 Left FC4 with **randomly mixed** measurements	Left **FC4b M+ O-** **M- O+**
Case 2 Left FC3 with **uniform increase** in measurements	Left **FC3b M+ O+** **M+ O+**
Case 3 Right FC3 with **uniform mix** in the measurements	Right **FC3a M- O+** **M- O+**
Case 4 Right FC4 with **uniform decrease** in the measurements	Right **FC4a M- O-** **M- O-**
Case 5 Left FC4 with **uniform mix** in the measurements	Left **FC4a M- O+** **M- O+**
Case 6 Right FC4 with **absent maxilla** hence measurements were hindered	Right **FC4b (0)**
Case 7 Bilateral FC4 with **randomly mixed** measurements	Bilateral **FC4b M- O- M- O+** **M- O- M+ O+**

BRIDGING TEXT
FROM CHAPTER THREE TO FOUR

Chapter three investigated the use of anthropometry to sub-classify clefts number 3 and number 4. This unique proposed classification will enable a surgeon to have a visual mental picture of a patient's defect. This would help surgeons to refer and communicate in a more precise and efficient manner. Chapter four documents how CFCs number 3 and number 4 may present clinically in a South Africa population as well as the associated clefts that present along with them. It also comments on how such CFCs especially number 3 and number 4 are currently documented in the literature from other parts of the world.

CHAPTER FOUR

MANUSCRIPT THREE

Tessier number 3 and 4 clefts: Clinical Presentation and Associated clefts in a South African population

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Tessier number 3 and 4 clefts: Clinical Presentation and Associated clefts in a South African population

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Abstract

Introduction: The defects found in Tessier clefts number 3 and number 4 come in various forms in different patients. These variations have to a great extent affected not only documentation of these craniofacial defects but invariably its treatment and communication amongst craniofacial researchers. This study has not only documented the clinical presentation of these clefts in a South African population but has also incorporated the clinical presentation of Tessier clefts number 3 and 4 from different regions of the world.

Methods: The records of 8 patients who had been treated for either Tessier clefts number 3 or 4 were reviewed and compared with nine studies from the literature. The defects recorded as well as associated clefts and other congenital malformations were documented, and findings were compared.

Results: The anatomical and clinical presentation of the patients were compared to the the different parameters of these presentations such as involvement of the lip, alveolar, nose, maxilla, media canthus, ocular involvement, lacrimal apparatus involvement, presence of hypertelorism and lower eyelid involvement were documented. In addition, associated clefts, were also recorded in the study – it was noted that the association pattern recorded in Tessier cleft number 4 in this study did not conform to what was previously documented in literature as its counterpart.

Conclusion: This study concluded that the clinical presentations of these clefts, however variable, seem to be similar presentation worldwide. Additionally, associated clefts do not conform to the original Tessier classification system and therefore it is imperative for these patterns to be clearly mapped out.

Keywords: Tessier clefts, The number 3 cleft, The number 4 cleft, Tessier cleft presentation

Introduction

The numbers 3 and 4 clefts as described by Tessier are rare craniofacial malformations whose clinical presentations are extensive (Alonso et al., 2008). The number 3 cleft (FC 3) was described as being a paranasal-medial orbitomaxillary cleft that runs up to the eyelid in the region of the lacrimal groove (Freitas et al., 2010). The defect can affect the entire frontal process of the maxilla as well as the medial wall of the maxillary sinus. It finally crosses to the lip and the alveolus by passing round the nasal ala in the nasolabial groove (Tessier et al., 1977). This cleft comes with varying manifestations from being a complete soft tissue and bony cleft affecting both the face and cranium or minorly expressed as a coloboma in the lower eyelid or a simple notch of the ala base (Freitas et al., 2010). In the number 3 cleft there is a deficiency or absence of the ala. In addition to this, the cranial prolongation of this cleft into the medial third of the upper eyelid and eyebrow onto the forehead is called the number 11 cleft (Kawamoto et al., 1976).

The number 4 cleft (FC 4) follows a similar path; with the soft tissue cleft beginning lateral to the philtrum and crossing to the lower eyelid and in effect decreasing the oro-ocular distance (Alonso et al., 2008). The bony cleft starts from between the lateral incisor and the canine, ascends medial to the infraorbital foramen and may extend to the orbital floor, not affecting the lacrimal duct and sac in the process (Alonso et al., 2008). Also, with the number 4 cleft its corresponding cranial extension is the number 10 cleft which passes through the middle of the upper eyelid and eyebrow (Kawamoto et al., 1976; David et al., 1989). In the number 4 cleft there is no deficiency of the ala. This is usually well formed albeit in a displaced position. The incidence of rare craniofacial clefts is said to be between 1.4 to 4.9 per 100,000 live births with a greater number being sporadic in appearance (Fogh-Anderson, 1965).

A retrospective analysis of patients presenting with Tessier clefts number 3 and 4 were conducted to record their clinical presentation in our facility. These anatomical and clinical parameters were compared to the literature reviewed and documented. Additionally, associated clefts related to Tessier number 3 and 4 clefts were also documented and compared with reported patterns globally.

Materials and Method

The records of 8 patients with Tessier numbers 3 and 4 were reviewed. These patients had been evaluated and treated over a 15-year period (from 2003 to 2017) at Inkosi Albert Luthuli Central Hospital in Durban, South Africa. Six of these patients had Tessier number 4 cleft while two had the number 3 cleft.

Data collected ranged from the age, sex distribution, side of occurrence, clinical presentation as well as associated clefts and congenital anomalies. Regarding the clinical presentation, involvement of the lip, alveolar, nose, maxilla, media canthus, ocular involvement, lacrimal apparatus involvement, presence of hypertelorism and lower eyelid involvement were assessed. The data from our patient series were compared to documented cases in literature of Tessier number 3 and number 4 (Coruh et al., 2003; Tokiota et al., 2004; Bodin et al., 2005; Winbin et al., 2006; Alonso et al., 2008; Portier-Marriet., 2008; Freitas et al., 2009; Gawrych et al., 2010; Spolyar et al., 2015). This study was conducted with the approval of the Biomedical Research ethics Committee of the University of KwaZulu- Natal (BREC Ref No: BE652/17) as well as the Department of Health in the Province of KwaZulu-Natal through the management of Inkosi Albert Luthuli Central Hospital.

Results

In our series, 6 patients were male and 2 were female. Their ages ranged from 1 week to 17 years on the first visit to the hospital. Two (25%) of these were FC 3 clefts and both were unilateral right clefts while 6 (75%) were FC 4 clefts with 3 being on the right, 1 on the left and 2 bilateral clefts.

Cleft upper lip was found in 6 (75%) of the patients with 4 being bilateral cleft lip and 2 were unilateral. Five (62.5%) patients of our series had clefts of the alveolar while 3 (37.5%) had normal alveolar without clefts. All the patients had their noses malpositioned in a superior direction. Three (37.5%) had maxillary hypoplasia while 5 (62.5%) had displaced or absent medial canthi. The canthi were widely displaced inferiorly and laterally. Ocular globe malformations were present in 5 (62.5%) patients with 2 having anophthalmia and the remaining 3 with keratitis due to exposure. The lacrimal apparatus was obstructed in 4 (50%) patients and completely patent in another 1 (12.5%) and normal in 2 (25%) patients. Two (25%) of the 8 patients had hypertelorism while the lower eyelid was clefted in 3 (37.5%)

patients and completely absent in 1 (12.5%) (Table 1).

A review of literature documenting the clinical presentation of these clefts came out with 9 studies cutting across South America, North America, Asia and Europe on clinical presentation of these clefts. Four of these studies were solely on FC 3, four on FC 4 while 1 was both FC3 and FC 4. The sample size of these studies ranged from 1 to 21 patients. All the studies reported on cleft upper lip with the least of the studies reporting 86% of their sample population had cleft upper lip. Alveolar cleft was recorded in 8 of the 9 studies with the study with the least affected population being 81%. Seven studies recorded abnormalities of the nose and the medial canthus; respectively; whilst 3 out of the 9 documented maxillary involvement as well as hypertelorism. All the 9 studies documented involvement of the eye with the study with the least affected population having a 52% involvement. The lacrimal apparatus was seen to be affected in 6 studies while the lower eyelid was recorded to be involved in 8 of the 9 studies (Table 2).

Regarding associated clefts and other anomalies, in the current study the 2 FC 3 clefts had no associated clefts. However, one of them presented with hydrocephalus. Four of the six FC 4 clefts had FC 7, FC 8, FC 9 and FC 10 clefts in association to their clefts while one presented with amniotic bands in the limbs as well (Table 3). Of the 9 studies reviewed, 4 of them reported either associated clefts or other anomalies. Freitas and colleagues (2010) in their study with 21 patients with FC 3 clefts recorded 4 (19%) with FC 11 association, 1 (4.8%) with FC 7, and 3 (14.3%) with FC 9. They also noted that 4 (19%) had hydrocephaly, 1 (4.8%) with encephalocele and 6 (28.6%) had amniotic bands in their limbs. Alonso and colleagues (2008) had 21 patients with FC 4 and recorded 3 (14.3%) with FC 5, 1 (4.8%) with FC7, 1 (4.8%) with FC 10 and 1 (4.8%) with FC 9. Bodin et al. (2005) in the study of FC 3 in 1 patient had both FC 7 and FC 11 associated to the FC 3. Tokioka and colleagues (2004) with 2 FC 4 patients had no associations but recorded amniotic bands in the limbs as well as hydrocephalus (Table 4).

Discussion

Facial clefts numbers 3 and 4 are rare defects and few cases of each are reported in literature (Freitas et al., 2010). For a long time, the terms used to describe these clefts were far from satisfactory, thereby creating divergent views in their classification system (Kawamoto, 1976). However, Tessier's proposed anatomical classification of 1976 helped sanitize the field and has since been commonly used (Tessier, 1976; Van der Muelen, 1985; Alonso et al., 2008).

Due to the variable presentation of these clefts, continued documentation of cases becomes imperative as this will improve communication and invariably surgical techniques used in correcting them. Of all the parameters documented in our series as well as the literature, presence of hypertelorism (Wenbin et al., 2006; Freitas et al., 2009; Gawrych et al., 2010) as well as the involvement of the maxilla (Wenbin et al., 2006; Alonso et al., 2008; Portier-Marriet et al., 2008) were the least recorded with only three studies each documenting their presence and 25% and 38% of patients in our series. All the studies (Coruh et al., 2003; Tokiota et al., 2004; Bodin et al., 2005; Winbin et al., 2006; Alonso et al., 2008; Portier-Marriet., 2008; Freitas et al., 2009; Gawrych et al., 2010; Spolyar et al., 2015) documented the involvement of the upper lip and the eye with the lowest being 86% and 52% of participants, respectively. Our series had an involvement rate of 75% and 63% upper lip and eye, respectively. Eight out of the 9 studies documented the involvement of the lower eyelid (Coruh et al., 2003; Tokiota et al., 2004; Bodin et al., 2005; Winbin et al., 2006; Alonso et al., 2008; Portier-Marriet., 2008; Freitas et al., 2009; Spolyar et al., 2015) and the alveolar (Coruh et al., 2003; Tokiota et al., 2004; Bodin et al., 2005; Winbin et al., 2006; Portier-Marriet., 2008; Freitas et al., 2009; Gawrych et al., 2010; Spolyar et al., 2015), with 67% and 81% occurrence being the lowest amongst studies having more than 2 participants compared to our series with 50% and 63%, respectively for lower eyelid and alveolar affectedness. Seven studies of the 9 had media canthus (Coruh et al., 2003; Tokiota et al., 2004; Bodin et al., 2005; Winbin et al., 2006; Portier-Marriet., 2008; Freitas et al., 2009; Spolyar et al., 2015) as well as lacrimal apparatus (Coruh et al., 2003; Tokiota et al., 2004; Winbin et al., 2006; Alonso et al., 2008; Portier-Marriet., 2008; Freitas et al., 2009; Spolyar et al., 2015) involvement recorded. Amongst these, those studies with more than 2 participants, the lowest rates of involvement were 62% and 71% respectively for Media canthus and lacrimal apparatus which appears in the same range as our study with 63% involvement for both parameters.

The number 11 cleft and the number 10 clefts were described by Tessier as the cranial extensions of the number 3 and the number 4 clefts respectively (Tessier et al., 1981). In our series with 2 FC 3 clefts, there were no associated clefts while there was 1 FC 10 cleft (16%) in the six FC 4 cases that we had. Other associated clefts were FC 7, FC 8 and FC 9. This may suggest FC 4 and FC 10 are not directly associated (Table 3). This finding was also noticed by Alonso et al. (2008) who had just one association in their series as well (Alonso et al., 2008). The other studies reported a total five FC 11, two FC 7 and 3 FC 9 clefts in association with FC 3 clefts while FC 4 clefts had three FC 5, one FC 7, one FC 10 and one

FC 9 associated with them (Table 4). Our study had 1 case of amniotic bands in the limb as well as 1 case of hydrocephalus as other accompanying congenital malformations. The other studies recorded 5 cases of hydrocephalus, 7 cases of amniotic bands in limbs and 1 case of encephalocele (Table 4).

Conclusion

We have documented the clinical presentation as well as associations of FC 3 and FC 4 in our population. This study concluded that the clinical presentations of these clefts, however variable, seem to be similar presentation worldwide. Additionally, associated clefts do not conform to the original Tessier classification system and therefore it is imperative for these patterns to be clearly mapped out.

Conflict of interest, Funding and ethical approval statement

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Table 1

Table 1. Clinical Characteristics of the number 3 and number 4 Facial Clefts

Patient	Sex	Age (y)	Type	Side	Lip	Alveolar	Nose	Maxilla	Media canthus	Eye	Lacrimal involvement	Hypertelorism	Lower eyelid
1	M	8	FC3	R	Normal	Normal	Upward	Hypoplasia	No	Normal	Normal	Yes	No
2	F	0.25	FC3	R	BCL	Clefted	Upward	Normal	No	Normal	Obstruction	No	No
3	M	0.08	FC4	L	BCL	Clefted	Upward	Normal	Dislocated	Normal	Normal	Yes	No
4	M	17	FC4	R	UCL	Clefted	Upward	Hypoplasia	Dislocated	Keratitis	Open	No	Clefted
5	F	0.33	FC4	R	UCL	Normal	Little upward	Normal	No	Anophthalmos	Normal	No	No
6	M	4	FC4	R	Normal	Normal	Upward	Normal	Absent	Anophthalmos	Absent	No	Absent
7	M	0.02	FC4	B	BCL	Clefted	Upward	Hypoplasia	Dislocated	Keratitis, Dystopia	Obstruction	No	Clefted
8	M	0.02	FC4	B	BCL	Clefted	Upward	Normal	Dislocated	Keratitis	Obstruction	No	Clefted

Table 2

Table 2: Clinical characteristics in literature as compared with current study.

Author/year	Country	Cleft type	Sample size	Female (%)	Male (%)	Population age range (yr)	Lip (%)	Alveolar (%)	Nose (%)	Maxilla (%)	Media canthus (%)	Eye (%)	Lacrimal involvement (%)	Hypertelorism (%)	Lower eyelid (%)
Freitas et al., 2009	Brazil	FC3	21	12 (57)	9 (43)	1mo – 17	18 (86)	17 (81)	21(100)	-	13 (62)	11(52)	17 (81)	8 (38)	14 (67)
Alonso et al., 2008	Brazil	FC4	21	7 (33)	14 (67)	0 – 25	21(100)	-	-	13 (62)	-	13 (62)	15 (71)	-	20 (95)
Coruh et al., 2003	Turkey	FC4	2	1 (50)	1 (50)	15day/ 7	2 (100)	2 (100)	2 (100)	-	1 (50)	2 (100)	1 (50)	-	2 (100)
Spolyar et al., 2015	USA	FC3/FC4	2	0	2 (100)	< 1	2 (100)	2 (100)	1 (50)	-	1 (50)	2 (100)	2 (100)	-	2 (100)
Wenbin et al., 2006	China	FC3	2	0	2 (100)	8/14	2 (100)	1 (50)	2 (100)	1 (50)	1 (50)	2 (100)	2 (100)	1 (50)	1 (50)
Tokioka et al., 2004	Japan	FC4	2	1 (50)	1 (50)	11mo/14mo	2 (100)	2 (100)	2 (100)	-	2 (100)	2 (100)	2 (100)	-	2 (100)
Gawrych et al., 2010	Poland	FC3	1	1 (100)	0	11mo	1 (100)	1 (100)	1 (100)	-	-	1 (100)	-	1 (100)	-
Bodin et al., 2005	France	FC3	1	1 (100)	0	4mo	1 (100)	1 (100)	1 (100)	-	1 (100)	1 (100)	-	-	1 (100)
Portier-Marret et al., 2008	Switzerland	FC4	1	1(100)	0	9mo	1 (100)	1 (100)	-	1 (100)	1 (100)	1 (100)	1 (100)	-	1 (100)
Omodan et al., 2019	South Africa	FC3/FC4	8	2 (25)	6 (75)	1week – 17	6 (75)	5 (63)	8 (100)	3 (38)	5 (63)	5 (63)	5 (63)	2 (25)	4 (50)

-, Involvement not documented

Table 3

Table 3: Associated clefts and other malformations in current study

Patient	Cleft type	Associated clefts	Other Anomalies
1	FC 3	Nil	Nil
2	FC 3	Nil	Nil
3	FC4	Nil	Hydrocephalus
4	FC4	Nil	Nil
5	FC4	FC7	Nil
6	FC4	FC9	Nil
7	FC4	FC10	Amniotic bands in limbs
8	FC4	FC8	Nil

Table 4

Table 4: Associated clefts and other anomalies in literature

Author/year	Sample size	Cleft type	Associated clefts	Other anomalies
Freitas et al., 2009	21	FC3	FC 11 (4) FC 7 (1) FC 9 (3)	Hydrocephalus (4) Encephalocele (1) Amniotic bands (6)
Alonso et al., 2008	21	FC4	FC 5 (3) FC 7 (1) FC 10 (1) FC 9 (1)	Nil
Coruh et al., 2003	2	FC4	Nil	Nil
Spolyar et al., 2015	2	FC3/FC4	Nil	Nil
Wenbin et al., 2006	2	FC3	Nil	Nil
Tokioka et al., 2004	2	FC4	Nil	Amniotic bands (1) Hydrocephalus (1)
Gawrych et al., 2010	1	FC3	Nil	Nil
Bodin et al., 2005	1	FC3	FC 7 FC 11	Nil
Portier-Marret et al., 2008	1	FC4	Nil	Nil

CHAPTER FIVE

SYNTHESIS, CONCLUSION AND RECOMMENDATION

5.1 Synthesis

Craniofacial clefts (CFCs) have always been of an enormous cost to the patient in terms of morbidity, healthcare, emotional disturbance, social and workplace exclusion (WHO, 2004). The management and method of repair of these defects is largely centred on the visualisation and appreciation of the extent of the soft tissue and bony defects. Without seeing the patient or images of the patient, appropriate interventions cannot be planned as the numbers alone aren't sufficient. Of these CFCs, particular attention has been drawn to numbers 3 and 4 which have proven to be quite challenging to the surgeon (Alonso et al., 2008). This is further compounded by the fact that there is no consensus on standardized landmarks, reference measurements and methods of repair (Morgan et al., 2016) in addressing these defects. The efforts of several researchers in finding a classification which best describes these clefts to the physician also remain a challenging dilemma (David et al., 1989). The literature on facial cleft surgery appears sparse due to these clefts' rarity and variability (Morgan et al., 2016). All of these factors seem to make it imperative for this field to be widely researched with the aim of enabling better communication amongst surgeons and craniofacial researchers which invariably will translate to a better outcome for the CFC patient.

This study began with an investigation of CFCs number 3 and number 4 with a systematic scoping review of the literature to examine what knowledge of these clefts is currently available. The result of this was that there have been studies on these two cleft types as far back as 1980 (Spolyar et al., 2015). The treatment and management thereof even though being documented were sparsely documented (Cizmeci et al 2011). This might be due to the non-availability of agreed standard mode of surgical correction (Morgan et al., 2016). This study also reported that that despite the burden of this defect being a global one (WHO, 2016), there was nothing being documented in low-income countries (Omodan et al., 2019). This may be attributed to the lack of adequate funding for research in such countries and not that these defects are not being recognised and treated in these countries. The study further established that there existed a sparsity of documentation on the use of the knowledge of anthropometry (which is a novel technique) in solving the problem of non-standardization of treatment modalities being faced by surgeons, with the first appearance of such a study appearing in the literature being 2011 (Omodan et al., 2019). This is despite the postulate, as far back as 1976, by a renowned surgeon Dr Kawamoto, that the understanding of the skeletal defects in craniofacial clefts are basic to any surgical reconstruction of the face (Kawamoto, 1976).

This study demonstrated that with the present documentation and understanding of the craniofacial clefts number 3 and number 4 and how they are currently being used, knowledge of anthropometry

which had earlier been identified as a novel technique may assist surgeons if this aspect is interrogated and further investigated (Omodan et al., 2019). Anthropometry was applied resulting in the creation of a sub-classification of the Tessier craniofacial cleft classification system. The classification of craniofacial clefts had hitherto lacked a standard and unified classification system, and this has been an issue in the diagnosis, communication, and appreciation of the extent of CFC deformities (Zhou et al., 2006). In routine cleft lips the literature is extensive in documenting anthropometric measurements and reference landmarks. This aids in determining the management and methods of repair of these routine cleft lips. In contrast the landmarks, reference measurements and analysis of facial clefts is not well documented (Morgan et al., 2016). Of the several classification systems known for CFCs, the Tessier classification system over time has emerged as the simplest and the most popular clinically. This classification is limited in its ability to convey the extent of the clinical picture to the surgeon (Tang et al., 2012). This study, using anthropometric techniques on Tessier classified patients of CFCs number 3 and number 4 yielded a pattern from the measured clefts and bones of the orbit and maxilla, produced a sub – classification system where the increasing or decreasing proportions of these bones were used. This sub – classification which is depicted by (a), (b), (c), (M+ 0+), (M- O-) and (0), were soft tissue clefts alone, soft tissue plus bony clefts and bony clefts alone are denoted by the a, b, and c lettering, maxilla (M) and orbit (O). The + and – signs illustrate increasing and decreasing proportions, respectively and (O) stands for absent maxillary bone. This sub-classification improves the understanding of the Tessier classification system by making it possible to mentally visualize the form and the extent of the cleft prior to the surgeon seeing the patient. This critically addresses the shortcoming noticed in the clinics with the Tessier classification as it is currently employed (Tang et al., 2012). Importantly, this classification system using measurements of standardized bony landmarks can be replicated in other clefts and also the reference points for the measurements are easily identifiable. The study further revealed a pattern amongst patients with no bony involvement where the maxilla on the cleft side of the face was discovered to be smaller in comparison to the non-cleft side despite the non-involvement of the bone.

In addition, our study investigated the clinical presentations of CFCs number 3 and number 4 in a South Africa population. These clefts have always been known to have extensive clinical presentations (Alonso et al., 2008). The documentation of these clinical presentations in society have become imperative as it was demonstrated earlier that little is being done in low-income countries with regard to documentation of these clefts (Omodan et al., 2019). It is therefore important to investigate the CFC presentations in South Africa and compare and contrast it with those documented in the rest of the world. This is important as it would dictate the types of intervention needed to treat the patient adequately, and identify the correct surgical technique to be used in correcting the defects, as well as to enhance the communication amongst the surgeons and craniofacial researchers in South Africa and the rest of the world. Our study documented that the clinical presentations found in patients

with CFCs number 3 and number 4 in our population in South Africa were similar to the global pattern. This is notable considering that these clefts are known to have various presentations (Alonso et al., 2008). The interventions discovered for the treatment or classification of CFCs anywhere in the world can be translated for implementation in South Africa. Similarly, the sub-classification proposed in this study, based on the patients evaluated in South Africa, can be applied for CFCs world over. The current study also revealed that contrary to the traditionally held view of CFC number 10 being associated with CFC number 4, that this was not the case in our population. This view is also corroborated in the series by Alonso and colleagues (Alonso et al., 2008).

5.2 Conclusions

Researchers of CFCs number 3 and number 4 and the surgeons who treat them need a better and comprehensive understanding of these defects and accurate classification system to facilitate communication in order that the outcome of surgical interventions are improved with better patient outcomes. This study has been able to map out the areas that need to be researched further in the quest to improve our knowledge of these clefts, as well as proposing a sub-classification system based on anthropometry that creates the extent and form of these clefts that the currently popular Tessier classification system lacks. Also, our study has shown that despite the varying presentations of these clefts, there is a similar pattern of clinical presentation in the South African population to that of CFCs number 3 and number 4 globally thereby making application of interventions suggested to relieve this burden easier to introduce anywhere. In conclusion, this study drew attention to the non-correlation of long-standing rules of association of the facial clefts with their cranial extensions.

5.3 Recommendations

In accordance with the findings of this study we recommend that there should be further studies carried out using anthropometric methods so that the problem of standardization of landmarks, reference measurements and principles of repair can be solved in CFCs. We further recommend that radiologists who play an important role in helping physicians in making the diagnosis with CT scans should incorporate simple bone measurements of the maxilla and the orbits into reporting of the images. We recommend the new sub-classification for use amongst surgeons as it helps with mentally visualizing the extent and form of the patient's defect. Furthermore, we recommend that more studies and critical analysis of soft tissue and bone defects of all cranial and facial clefts be embarked upon. This will ultimately improve our understanding of the clefts and definitely influence our strategies, methods and design of surgical repair of these clefts.

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Appendix

18 July 2019

Dr A Omodan 216077058
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Dear Dr Omodan

Protocol: Anatomical Classification of Tessier Craniofacial clefts number 3 and number 4 in a select
South African Population. Degree: PhD
BREC Ref No: BE652/17

RECERTIFICATION APPLICATION APPROVAL NOTICE

Approved: 10 April 2019
Expiration of Ethical Approval: 09 April 2020

I wish to advise you that your application for Recertification received on 08 July 2019 for the above
protocol has been **noted and approved** by a sub-committee of the Biomedical Research Ethics
Committee (BREC) for another approval period. 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 2019.

Yours sincerely

Prof V Rambiritch
Chair: Biomedical Research Ethics Committee

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