# THE COMPARISON OF RADIOGRAPHIC DENTAL CHARACTERISTICS, MID-PALATAL SUTURE MORPHOLOGY AND DEVELOPMENT OF ARTIFICIAL NEURAL NETWORK MODEL IN CHILDREN WITH UNILATERAL CLEFT LIP AND PALATE WITH NON-CLEFT INDIVIDUALS

**MOHAMED ZAHOOR UL HUQH**

**UNIVERSITI SAINS MALAYSIA**

**2024**

# THE COMPARISON OF RADIOGRAPHIC DENTAL CHARACTERISTICS, MID-PALATAL SUTURE MORPHOLOGY AND DEVELOPMENT OF ARTIFICIAL NEURAL NETWORK MODEL IN CHILDREN WITH UNILATERAL CLEFT LIP AND PALATE WITH NON-CLEFT INDIVIDUALS

**by**

**MOHAMED ZAHOOR UL HUQH**

**Thesis submitted in fulfillment of the requirements**
**for the degree of**
**Doctor of Philosophy**

**March 2024**

**ACKNOWLEDGEMENT**

In the name of Allah, the most beneficent, the most compassionate, and the most merciful. All praise be to Allah the almighty for giving me the opportunity, strength, perseverance, and his blessings to complete my research work.

I would like to express my sincere gratitude to my supervisor Dr. Johari Yap Abdullah for his continuous encouragement, skilled supervision, guidance, and keenness throughout my research study, for his patience, motivation, and vast knowledge. His support helped me in all the stages of my research work and the writing of this thesis. I could not have wished for a better supervisor and mentor for my PhD study.

Besides my supervisor, I would like to thank my co-supervisor's Assoc. Prof. Ts. Dr. Wan Muhamad Amir W Ahmad, Dr. Nafij Bin Jamayet, Dr. Matheel Zohair Yousif Alrawas, Prof. Dr Mohammed Khursheed Alam, and Prof Dr Adam Bin Hussein, for their watchful comments and encouragement throughout my study. I also wish to thank my late father, late mother, my sister, my wife, and my dear friends for their affection, care, and moral support. I would like to acknowledge the School of Dental Sciences and office staff for their kind help.

## TABLE OF CONTENTS

## LIST OF TABLES

**LIST OF FIGURES**

## LIST OF ABBREVIATIONS

| | |
|---|---|
| ABG | Alveolar bone grafting |
| AI | Artificial intelligence |
| ANN | Artificial neural network |
| ANS | Anterior nasal spine |
| ACPA | American cleft palate craniofacial association |
| BCLP | Bilateral cleft lip and palate |
| BLR | Binary logistic regression |
| BMI | Body mass index |
| CI | Confidence interval |
| CBCT | Cone beam computed tomography |
| CLAPAM | Cleft lip and palate association of Malaysia |
| CL | Cleft lip |
| CLP | Cleft lip and palate |
| CP | Cleft palate |
| CNN | Convolutional neural network |
| CT | Computed tomography |
| DC | Dental characteristics |
| DICOM | Digital imaging and communications in medicine |
| DL | Deep learning |
| DLM | Deep learning method |
| DNN | Deep neural network |

| | |
|---|---|
| DNA | Deoxyribonucleic acid |
| DO | Distraction osteogenesis |
| EMR | Electronic medical record |
| EP | Electrophysiology |
| FHP | Frankfort horizontal plane |
| GDV | Grey density value |
| GMM | Geometric morphometric method |
| GSTT | Glutathione S-transferase theta |
| HRPZ | Hospital Raja Perempuan Zainab |
| HUSM | Hospital Universiti Sains Malaysia |
| ICC | Intraclass correlation co-efficient |
| ICRP | International commission on radiological protection |
| IIA | Interincisal angle |
| IMPA | Incisal mandibular plane angle |
| JEPeM | Jawatankuasa Etika Penyelidikan Manusia |
| KKM | Kementerian Kesihatan Malaysia |
| kV | Kilovolts |
| L1 | Lower central incisor |
| LCR | Lateral cephalometric radiograph |
| LSTM | Long short-term memory |
| LOP | Lower occlusal plane |
| LR | Linear ratio |
| mA | milliampere |

| | |
|---|---|
| ML | Machine learning |
| MLFFNN | Multilayer feed-forward neural network |
| MP | Maxillary protraction |
| MPS | Mid-palatal suture |
| MPSBD | Midpalatal bone density |
| MREC | Medical research & ethics committee |
| MLE | Maximum likelihood estimation |
| MSE | Mean square error |
| MLP | Multilayer perceptron |
| N | Nasion |
| NAM | Naso alveolar molding |
| NC | Non-cleft |
| NLP | Natural language processing |
| NMRR | National medical research register |
| NN | Neural network |
| NSCLP | Non-syndromic cleft lip and palate |
| NSRME | Non-surgical rapid maxillary expansion |
| OB | Overbite |
| OC | Occlusal canting |
| OJ | Overjet |
| OSNS | Optical surgical navigation system |
| OLR | Ordinal logistic regression |
| PA | Posteroanterior |

| | |
|---|---|
| PMSE | Predicted mean square error |
| PNS | Posterior nasal spine |
| ROI | Region of interest |
| RME | Rapid maxillary expansion |
| RNN | Recurrent neural network |
| SABG | Secondary alveolar bone grafting |
| SD | Standard deviation |
| SMCP | Sub-mucous cleft palate |
| SN | Sella nasion |
| SNP | single nucleotide polymorphism |
| SVM | Support vector machine |
| TPA | Transpalatal arch |
| TSDO | Trans-sutural distraction osteogenesis |
| UCLP | Unilateral cleft lip and palate |
| U1 | Upper central incisor |
| UMMC | University of Malaya Medical Centre |
| UOP | Upper occlusal plane |
| 2D | Two dimensional |
| 3D | Three dimensional |

## LIST OF APPENDICES

# PERBANDINGAN CIRI-CIRI RADIOGRAFI GIGI, MORFOLOGI SERTA PERKEMBANGAN SUTUR PALATAL TENGAH, PEMBANGUNAN MODEL JARINGAN SARAF TIRUAN PADA KANAK-KANAK KLEF BIBIR DAN LELANGIT UNILATERAL DENGAN INDIVIDU TANPA KLEF

## ABSTRAK

Sumbing bibir dan lelangit (CLP) merujuk kepada keadaan yang dicirikan oleh kegagalan penyatuan antara bibir atas dan lelangit. Kecacatan kongenital ini boleh dialami dalam pelbagai perbezaan ketara dari segi bentuk dan tahapnya. Antara jenis CLP yang berbeza, sumbing bibir dan lelangit unilateral (UCLP) adalah yang paling kerap ditemui. Di Malaysia, kadar prevalens keseluruhan CLP dianggarkan satu dalam setiap 611 kelahiran hidup. CLP memberi kesan kepada perkembangan kraniofasial dalam tiga satah: satah sagital, menegak dan melintang. Terdapat beberapa teknik untuk menilai sistem kraniofasial, morfometri maksila, hubungan arkus pergigian, dan ciri-ciri berbeza CLP seperti radiograf sefalometrik, tomografi berkomputer cone-beam (CBCT) dan parameter morfologi maksilofasial. Pada fasa pertama kajian, seramai 100 subjek (50 kes dan 50 kawalan) berumur antara 8-16 tahun telah menyertai kajian dan data diperoleh daripada rekod pesakit di Hospital Universiti Sains Malaysia (Hospital USM) dan Hospital Raja Perempuan Zainab II (HRPZ II). Perisian WebCeph yang didayakan kecerdasan buatan (AI) digunakan untuk membandingkan 14 ciri pergigian antara individu UCLP dan tanpa UCLP. Set data telah dibuat berdasarkan faktor sosio-demografi seperti umur, jantina, jenis sumbing dan kategori maloklusi yang dikaitkan dengan sumbing. Model telah dibangunkan dengan menggabungkan kaedah baharu yang menggabungkan butstrap, rangkaian neural suapan ke hadapan berbilang lapisan (MLFFNN) dan regresi logistik ordinal (OLR) menggunakan sintaks R. Matlamat utama adalah untuk meramalkan pertumbuhan lengkung maksila dan menilai dimensi lengkung maksila pada kanak-kanak dengan UCLP dan tanpa UCLP. Dalam fasa kedua kajian, morfologi jahitan tengah palatal (MPS) melalui ketumpatan tulang dibandingkan antara individu UCLP dan tanpa UCLP. Imej CBCT pesakit CLP yang diperoleh untuk tujuan diagnostik dan juga imej CBCT bagi individu tanpa sumbing dalam kumpulan umur yang sama telah dikumpul; kesemua pesakit ini telah hadir ke klinik pakar sebelum menerima rawatan ortodontik. Dalam fasa ini, strategi lanjutan telah dilaksanakan dalam tiga bahagian, termasuk penciptaan sintaks R untuk pendekatan hibrid biometri yang terdiri daripada butstrap data, MLFFNN, dan regresi logistik binari (BLR). Tujuan membangunkan model BLR adalah untuk meramalkan teknik pengembangan maksila pesat (RME). Penemuan mendedahkan, variasi ketara antara 10 ciri pergigian dalam kumpulan UCLP berbanding kumpulan tanpa UCLP. Model OLR hibrid yang dibangunkan dengan sintaks R telah menunjukkan pemodelan yang luar biasa dengan ketepatan yang lebih besar iaitu 97.53% dalam meramalkan pertumbuhan lengkung maksila. Antara peringkat kematangan MPS yang dinilai daripada populasi kajian, Peringkat E (37%) adalah yang paling lazim, diikuti oleh Peringkat D (27%) dan Peringkat C (20%), manakala Peringkat B dan Peringkat A adalah sama menonjol (8% ). Kaedah hibrid yang dicadangkan dengan BLR menggunakan sintaks R telah menunjukkan prestasi cemerlang model dengan ketepatan yang lebih tinggi iaitu 99.98%. Hasil kajian mencadangkan korelasi yang kuat antara jantina, umur, dan kejadian sumbing. Telah disimpulkan bahawa, CLP dan sumbing lelangit (CP) didapati mempunyai dimensi maksila yang lebih kecil dalam satah sagital dan melintang. Gabungan MPS didapati paling tinggi pada kanak-kanak berumur antara 14-16 tahun. Peratusan gabungan D yang lebih besar (27%) dan E (37%) peringkat MPS, diperhatikan pada kanak-kanak perempuan. Maklumat ini penting bagi doktor dalam membuat keputusan klinikal yang tepat terutamanya dalam menguruskan kanak-kanak dengan UCLP.

# THE COMPARISON OF RADIOGRAPHIC DENTAL CHARACTERISTICS, MID-PALATAL SUTURE MORPHOLOGY AND DEVELOPMENT OF ARTIFICIAL NEURAL NETWORK MODEL IN CHILDREN WITH UNILATERAL CLEFT LIP AND PALATE WITH NON-CLEFT INDIVIDUALS

## ABSTRACT

Cleft lip and palate (CLP) refers to a condition characterized by the lack of union between the upper lip and the roof of the mouth. This congenital defect may present with significant alterations in their shape and extent. Among different types of CLP, unilateral cleft lip and palate (UCLP) was the most frequently observed. In Malaysia, the overall prevalence rate of CLP is estimated to be one in every 611 live births. CLP impacts craniofacial development in three planes: sagittal, vertical, and transverse planes. There are several techniques for assessing the craniofacial system, maxillary morphometry, dental arch relationships, and distinct features of CLP such as cephalometric radiographs, cone-beam computed tomography (CBCT), and maxillofacial morphologic parameters. In the first phase of the study, 100 subjects (50 cases and 50 controls) aged between 8-16 years were recruited; data were obtained from patients' records of Hospital Universiti Sains Malaysia (Hospital USM) and Hospital Raja Perempuan Zainab II (HRPZ II). An artificial intelligence (AI) enabled WebCeph software was used to compare the 14 dental characteristics (DC) between UCLP and NC individuals. A dataset was created based on socio-demographic factors such as age, gender, cleft type, and category of malocclusion associated with the cleft. A model was developed by incorporating a novel method that combines a bootstrap, the multi-layer feed-forward neural network (MLFFNN), and ordinal logistic regression (OLR) utilizing R-syntax. The main goal was to predict the maxillary arch growth and evaluate the maxillary arch dimensions in children with UCLP and NC. In the second phase of the study, the mid-palatal suture (MPS) morphology via its bone densities was compared between UCLP and NC individuals. The CBCT images of the CLP patients which were obtained for diagnostic purposes and also CBCT images of the non-cleft (NC) individuals of the same age group were collected from patients who attended specialist clinics before receiving orthodontic treatment. In this phase, the advanced strategy was implemented in three sections, including the creation of R-syntax for the biometry hybrid approach consisting of data bootstrap, MLFFNN, and binary logistic regression (BLR). The purpose of developing a BLR model was to predict the technique of rapid maxillary expansion (RME). The findings revealed significant variations among the 10 DC in the UCLP group compared to the NC group. The hybrid OLR model developed with R-syntax has shown exceptional modelling with a greater accuracy of 97.53% in predicting the maxillary arch growth. Among the MPS maturation stages assessed from the study population, Stage E (37%) was the most prevalent, followed by Stage D (27%) and Stage C (20%), while Stage B and Stage A were equally prominent (8%). The proposed hybrid method with BLR using R-syntax has demonstrated excellent performance of the model with a higher accuracy of 99.98%. The outcome of the study suggests a strong correlation between sex, age, and cleft occurrence. It has been concluded that patients with CLP and cleft palate (CP) have smaller maxillary dimensions in sagittal and transverse planes compared to healthy individuals. The MPS fusion was found to be highest in children aged between 14-16 years. A greater percentage of fusion D (27%) and E (37%) of MPS stages were observed in female children. This information is vital for clinicians in making precise clinical decisions, especially in managing children with UCLP.

# CHAPTER 1

# INTRODUCTION

## 1.1 Background of the study

Cleft lip and palate (CLP) are one of the most prevalent congenital craniofacial malformations, resulting in a variety of dental defects in early life. The non-union of the upper lip with the roof of the mouth is known as CLP. CLP may cause significant alterations in the form and extent of congenital abnormalities. CLP prevalence varies depending on characteristics such as race, ethnicity, geographical location, socioeconomic lifestyle, and the type of cleft. The Asian and American populations have the greatest incidence rate (1 in 500) (Dixon *et al*., 2011). Among various types of CLP, the most prevalent type seen was unilateral cleft lip and palate (UCLP). It has been found that UCLP is often left-sided when compared to the other side and more common in males compared to females with a ratio of 2:1 (Chawla *et al.*, 2015; Yilmaz *et al*., 2019). The prevalence rate of Cleft lip (CL) in Malaysia with or without Cleft palate (CP) was 1 in 1000, and children with CL showed 1 in 3000 (IPDTOC Group, 2011; Gopinath *et al*., 2017). The overall prevalence rate of CLP in Malaysia is approximately 1 out of every 611 newborns (Lau *et al*., 2021).

The etiology of non-syndromic cleft lip and palate (NSCLP) is still poorly understood. However, the origin of CLP is multifactorial, both environmental and genetic factors play a crucial role at certain points during the growth of the face (Schutte & Murray, 1999; Murray, 2002; Cobourne, 2004; Chawla *et al*., 2015). Patients with CLP may suffer from a variety of esthetic and functional problems like deficiency of the midface, restricted maxillary arches, congenitally malformed and missing teeth, and dental abnormalities such as crowding, malposition, rotation, and impacted teeth. There are also common orthodontic problems like aberrant dental arch relationships (Agrawal *et al*., 2019).

There are limited studies in the literature on the growth and development of the upper dental arch and occlusion in children with CP. The diameters of the dental arches were found to be smaller in the CP group than in the control group (Sajovic *et al*., 2023)

Many researchers have evaluated the craniofacial dimension of CLP patients after the completion of the growth phase, however, only a few studies have indicated a facial growth deficiency before the end of the growth stage (Heidbuchel & Jagtman, 1997; Del Guercio *et al*., 2010; Gopinath *et al*., 2017). CLP influences craniofacial development in three planes: sagittal, vertical, and transverse plane. The concave facial profile exhibited in cleft individuals is caused by a sagittal midface deformity that progresses from childhood to maturity (Silva & Calvano, 2001). Previous studies have found a considerable difference in morphologic characteristics between CLP and normal children (Gopinath *et al*., 2017; Power & Matic, 2017).

There are several techniques for assessing the craniofacial system, maxillary morphometry, relationship of the dental arch, and CLP characteristics (Alam *et al*., 2008; Asif *et al*., 2016; Haque *et al*., 2017). Previous studies have demonstrated individual CLP measurements and assessed the range of parameters such as dental arch relationship (Haque *et al*., 2018), cephalogram (Alam *et al*., 2019; Batwa *et al*., 2018; Alam & Alfawzan, 2020), maxillary morphometry (Haque *et al*., 2020), and cone-beam computed tomography (CBCT) (Parveen *et al*., 2018).

Traditional aspects of dentistry are being modernized by artificial intelligence (AI). In dentistry, AI-based systems are often used to create automated software programs that streamline diagnosis and data management (Schleyer *et al*., 2006). The AI models can be used as a tool for accurate diagnosis, decision-making in clinical practice, and automatic identification of cephalometric landmarks (Khanagar *et al*., 2021). Alam & Alfawzan (2020) have described a novel method to differentiate dental characteristics (DC) in various types of CLP with non- CLP patients using AI-driven cephalometric analysis. The DC measurements include overjet, overbite, upper incisal display, interincisal angle, the relative position of maxillary and mandibular anteriors with respective basal bone, occlusal canting, and angle between the long axis of upper and lower incisor with occlusal plane. The findings revealed significant variation in DC of different types of CLP compared with non-cleft (NC) individuals. Among different types of CLP, bilateral CLP exhibits maximum alteration in distinct DC.

The aims of the treatment for children with CLP are harmonious development of the maxilla, correct speech difficulties, maintaining adequate inter-arch relationships, and finally, optimal aesthetics. To achieve this, children from the day of birth to their age of maturity must be under the care of a multidisciplinary team of specialists. The preliminary part of the treatment is mainly the surgical repair of the lip followed by surgical repair of the palate. This stage of treatment is crucial for the long-term success of maxillary development. The timing of the surgery differs as per the protocols of the individual cleft centers (Sinko *et al*., 2008; Koskova *et al*., 2016).

The mid-palatal suture (MPS) is abnormally lateral to the midline in complete UCLP, and the cleft side segment has no sutural relation with the NC side maxilla. Few studies were done to see whether it was possible to enlarge the maxilla before surgery or after alveolar bone grafting (ABG) (Cavassan *et al*., 2004; da Silva Filho *et al*., 2009). These studies relied on the fact that diastema between maxillary central incisors showed splitting of maxillary processes in premaxillary MPS which demonstrated maxillary opening clinically. It has been suggested that the alveolar cleft crosses the area corresponding to the tooth bud of the maxillary lateral incisor, thereby preventing the development of an intermaxillary suture in the premaxilla region. As a result, there is a possibility that patients with complete alveolar clefts may have an MPS in their premaxilla. Although there is no consensus on whether the premaxillary suture exists in cleft patients, studies demonstrating the lack of a completely independent premaxillary suture have been identified as the "incisive fissure" (Wood *et al*., 1969; Behrents & Harris, 1991; Zahra & Samih, 2017). A thin suture called the Incisive suture is located in the anterior region of the premaxilla and embryologically originated from the primitive palate. However, in children with CLP, the palatal suture system is disrupted. Only a limited number of studies discussed about expansion in complete UCLP patients and the presence or absence of MPS in cleft patients still remains controversial (Zahra & Samih, 2017).

Rapid maxillary expansion (RME) is a widely used technique and is a part of the comprehensive treatment for individuals with CLP (Pan *et al*., 2007; Lypka *et al*., 2012; Yang *et al*., 2012). The maxillary expansion is required due to their limited transverse growth (Thompson, 1952; Ferguson, 1995; Yang *et al*., 2012). Hence, maxillary expansion is a routine procedure in CLP patients to align the maxillary and mandibular width differences (Holberg *et al*., 2007; Pan *et al*., 2007; Gautam *et al*., 2011).

RME can be achieved successfully without the need for surgery in children with pre-adolescent to adolescent age group due to non-fusion of the MPS. The resistance to expansion increases in adulthood due to ossification of circummaxillary and MPS. In routine clinical practice, chronological age is a typical predictor used to identify whether traditional non-surgical RME or surgically assisted RME is more appropriate (Celebi & Akbulut, 2020). However, there is no strong agreement between the authors in the literature on the age at which surgically assisted rapid maxillary expansion (SARME) should be performed (Angelieri *et al*., 2016). SARME is a reliable approach to adult orthodontic therapy when maxilla expansion is required (Bortolotti *et al*., 2019). The literature has reported various surgical methods that when combined with conservative measures can be used to release the resistant areas of the maxilla to provide stable outcomes (Vilani *et al.*, 2012; Loriato & Ferreira., 2020). All techniques involve the prior placement of a fixed expander to open the MPS following surgery. Expanders can be tooth-borne such as Hyrax with or without an acrylic splint (Kurt *et al*., 2010; Magnusson *et al*., 2009); tissue-tooth-borne as described by Haas (2009) or bone-borne expanders applying temporary skeletal anchoring devices known as miniscrew-assisted rapid maxillary expanders (Petrick *et al*., 2009).

The change in dental morphological traits such as the shape and size of the teeth are an important factor related to the etiology of malocclusion. It is essential to evaluate facial growth during the mixed dentition stage due to the potential for enhanced outcomes resulting from early orthopedic and orthodontic interventions. In Malaysia, currently, there is insufficient data regarding the facial profile and maxillary arch dimension of individuals diagnosed with CLP.

Hence, the primary objective of this study was to compare the DC and to develop a neural network logistic regression model to predict the maxillary arch growth in both UCLP and NC individuals.

Another aim of this study was to determine the MPS maturation stages and compare its bone densities between UCLP and NC children and to develop a logistic regression model to predict the possibility of RME or SARME.

## 1.2 Problem statement

An epidemiological survey conducted on the incidence of CLP in the Malaysian population has revealed 1:1300 for CL and 1:1500 for CP (Gopinath *et al*., 2017). Whereas, the international perinatal database of typical oral cleft has shown an overall prevalence rate of CL with or without CP was 9.92/10,000, CL 3.28/10,000 and that of CLP was 6.64/10,000 (IPDTOC group, 2011).

Oral clefts are often associated with soft tissue, skeletal, and dental abnormalities. Discontinuity of the lip, alveolar process, missing or malformed teeth, and skeletal deformity in three planes are examples of such defects (anteroposterior, vertical, and transverse) (Shetye *et al*., 2016). Individuals with CLP may have congenitally or developmentally missing teeth (Al Kharboush *et al*., 2015). This type of dental anomaly differs in accordance with gender, ethnicity, and type of cleft (Aizenbud *et al*., 2005; Al Jamal *et al*., 2010; Pegelow *et al*., 2012; Paranaiba *et al*., 2013; Mikulewicz *et al*., 2014).

Improper oral hygiene in CLP patients is due to the anatomy of the cleft area, the presence of scar tissue resulting from previous surgical procedures, reduced interest of CLP patients in achieving adequate oral hygiene, and the uneasiness that CLP patients have when brushing their teeth adjacent to the cleft area (Parapanisiou *et al.*, 2009; Rocha *et al.*, 2017). The scar tissues in the palatal area of CLP patients not only affect oral hygiene but also alter the transverse and sagittal growth of the maxilla (Shetye & Evans, 2006; Rocha *et al.*, 2017). As a result, there is a subsequent decrease in the transverse dimension of the arch, especially in the anterior region (Rocha *et al.*, 2017).

The cleft disturbs the structural integrity of the palate, causing the minor portion of the maxilla to rotate mediolingually. The collapsed minor segment is a characteristic feature in patients with UCLP, and it is thought to be caused by the molding effect of the surrounding facial soft tissues which often results in a constricted palatal arch and severe anterior crossbite with or without posterior crossbite on the cleft side (Kuroe *et al*., 2003; Lee *et al*., 2016). This decrease in the transverse dimension of the arch strongly suggests RME in the upper arch of CLP patients (Hazza'a *et al*., 2011; Rocha *et al*., 2017).

The growing patients with Class III malocclusions have been mentioned as ideal candidates for RME and opening the MPS with RME if there is a constriction of the maxillary arch and posterior crossbite. In complete UCLP, the MPS is positioned abnormally lateral to the midline, and the segment on the cleft side has no sutural attachment to the NC side maxilla (Zahra & Samih., 2017). It has been suggested that the alveolar cleft traverses the area corresponding to the maxillary left lateral incisor tooth bud while not obstructing the growth of an MPS in the premaxilla region. However, there is a possibility of intermaxillary suture in children with complete UCLP (Lisson & Kjaer, 1997; Zahra & Samih, 2017; Yang *et al*., 2012). There is insufficient information related to the malocclusion characteristics of CLP patients or a lack of data that could represent the facial growth of CLP patients in the local population and different management approaches locally. This study data will shed light on the current management routine for further advancement in the accurate diagnosis and treatment plan with the application of AI-enabled programming software that could be an eye-opener for health policy makers to provide more funds and high-end technology equipment for quick, better, and absolute treatment outcomes.

### 1.3 Justification of the study

It is necessary to determine the skeletal and DC in CLP children from childhood to adulthood as individuals with oral clefts often require a multidisciplinary approach and proper care for any skeletal and dental variations. There is limited evidence regarding the malocclusion characteristics of patients with various types of CLP in the Malaysian population. However, dental defects as well as deficiencies in horizontal and vertical facial growth caused by surgical procedures affect subjects with various oral clefts in different ways. As a result, subjects with different oral clefts are likely to have different malocclusions. The findings will be used to differentiate various DCs among Malaysian ethnicities which enables the clinicians to have accurate diagnosis and treatment planning.

It is well known that there are various facial deformities associated with congenital CL after primary surgical repair. Therefore, it is critical for CLP patients to normalize their facial morphology with primary and subsequent surgeries. Because of the severity of the initial abnormality and any previous surgical repairs, the degree and manner of these facial deformities varies from patient to patient. Several researchers have advocated the use of subjective checklists to measure the severity and form of facial anomalies. The development of standardized methods for evaluating the morphological features of the cleft facial form, palate, lip, and alveolus may make orthodontic diagnosis and treatment planning much easier, resulting in optimized treatment outcomes.

RME is a routine technique and a comprehensive treatment part for CLP patients. As these patients exhibit limited transverse growth, they often require maxillary expansion to balance the width discrepancies between the maxilla and mandible. The assessment of non-CLP patients revealed significant variation regardless of the orthopedic forces exerted on the intermaxillary sutures. The articulation between the maxilla and the pterygoid plate of the sphenoid bone is the limiting factor in the amount of expansion required.

AI is increasingly being used in the field of orthodontics. It has been proved to be a time-saving method and most reliable in many ways. Since data is the basis of well-constructed models with high quality, a greater accuracy of predictive results and image analysis could be achieved through the machine learning process. The use of AI-enabled automated programming software will improve the clinician's knowledge in making precise decisions.

## 1.4 Objectives of the study and hypothesis

### 1.4.1 General objective

- The main aim of the study was to compare the radiographic DC, MPS morphology between UCLP and NC individuals within the Malaysian population and utilize these datasets to develop logistic regression models with AI machine learning techniques.

### 1.4.2 Specific objective

The specific objectives of the study are:

- To compare the radiographic DC between UCLP and NC children in the Malaysian population.
- To develop an integrated ordinal logistic regression model with a neural network to determine the maxillary arch length using radiographic DC from both UCLP and NC Individuals.
- To compare the MPS suture morphology via suture bone densities between UCLP and NC individuals.
- To develop a binary logistic regression model with mid palatal suture morphology to predict surgical or non-surgical RME between UCLP and NC individuals.

## 1.5 Research questions

- What are the significant differences in radiographic DC between UCLP and NC individuals in the Malaysian population?

- What is the prediction of Maxillary arch growth in UCLP-treated children using the Ordinal logistic regression model?

- What are the significant differences in mid palatal suture morphology between UCLP and NC children?
- What is the prediction of the RME technique between UCLP and NC individuals using a binary logistic regression model?

**1.6 Research hypothesis**

- There is a significant difference in radiographic DC between UCLP and NC individuals in the Malaysian population.
- There is a significant difference in the prediction of Maxillary arch growth in UCLP-treated children using an Ordinal logistic regression model.
- There is a significant difference in mid palatal suture morphology between UCLP and NC children.
- There is a significant difference in the RME technique between UCLP and NC individuals using a binary logistic regression model.

**1.7 Null hypothesis**

- There is no significant difference in radiographic DC between UCLP and NC individuals in the Malaysian population.
- There is no significant difference in the prediction of Maxillary arch growth in UCLP-treated children using an Ordinal logistic regression model.
- There is no significant difference in mid palatal suture morphology between UCLP and NC children.

- There is no significant difference in the prediction of the RME technique between UCLP and NC individuals using a binary logistic regression model.

# CHAPTER 2

# LITERATURE REVIEW

## 2.1 Cleft lip and palate

CLP is the most prevalent congenital malformation. There are chances that the child may suffer from either CL or CP or both simultaneously during birth. This birth defect has important medical, psychological, social, and economic repercussions that exhibit wide regional and ethnic variance. The highest prevalence rate (1 in 500) has been reported in Asian countries like China, Malaysia, India, and the native American population (Dixon *et al*., 2011; Yow *et al*., 2021). The most common autosomal disorder related to CLP or CP is van der Woude syndrome with an occurrence rate of 1 in 70000, seen typically with pitting of the lower lip (Chawla *et al*., 2015).

Males are more likely to have CL than females, but females are more likely to have CP. This is because the union of the palatine shelves occurs 1 week later in a female than a man, which may be one of the major causes of a higher prevalence of CP in females. Numerous epidemiological studies show that there is a 3.2% chance for a child to have a CLP and a 6.8% chance of having CP alone (Grosen *et al*., 2010; Vyas *et al*., 2020). The occurrence of a cleft in one parent and one sibling is related to a 15.8% chance that the next child will have a CLP and a 14.9% chance that the next child will have a CP. Whereas, parents with one child getting affected with a cleft have a possibility of 4.4% with another child being affected with a CLP and 2.5% possibility of having a child affected with CP (Banerjee & Dhakar, 2013).

The impairment of maxillary growth which often presents in patients with Cleft lip and palate can develop into severe skeletal and dental abnormality in all 3 planes of space (transverse, vertical, and horizontal). Class III malocclusion related to anteroposterior maxillary retrusion associated with the unilateral and bilateral collapse of the palate affecting the smaller portion of the maxilla can lead to the formation of a narrow dental arch and it is the most common and demanding problem to deal with (Scolozzi, 2008).

### 2.2 Etiology

The causative factor of non-syndromic CLP and CP is not clear. Both genetic and environmental factors play an important role during the formation of the face (Chawla *et al.*, 2015).

#### 2.2.1 Genetic factors

The non-syndromic CLP is a partially heritable congenital disorder that involves multiple genes and complex interactions between genetic and environmental factors (Zhang *et al*., 2018). Several studies on siblings have been conducted and individuals with a close familial relationship, such as first cousins or even an uncle and niece, are considered to have a strong genetic link. According to estimates, around 10.4% of all marriages include persons who are second cousins or have a closer biological relationship. Furthermore, this strong connection persists across many generations. (Bittles, 2010; Bittles & Black, 2010; Hurkat, 2023). Studies conducted on twins have been very helpful. The monozygotic twins getting affected are in a range of 40% to 60% and dizygotic twins at a much lower rate of 5% (Lakhanpal *et al.*, 2014; Vyas *et al*., 2020). This indicates that genetic factors are not the only reason for the phenotypic occurrence of clefts, but also other environmental risk factors can cause or relate to genetic factors (Kohli and Kohli, 2012).

### 2.2.2 Environmental factors

Numerous factors can lead to the formation of CLP. Some of them have been described below.

1. Smoking during pregnancy period – There is an increased risk of both CLP and CP. This can lead to 30% of a child being affected by CLP. Also, the inactivation of teratogens in tobacco smoke by certain fetal metabolizing enzymes has been suggested. The DNA (Deoxyribonucleic acid) of the fetus may lack both copies of a gene called glutathione S-transferase theta 1 (GSTT1) and is at high risk of acquiring CLP. This is because the gene GSST1 has been related to the detoxification of chemicals in cigarette smoke (Lie *et al*., 2008).

2. Alcohol consumption during pregnancy - Women consuming high levels of alcohol during pregnancy are at high risk of having a child with CLP and fetal alcohol syndrome (Yin *et al*., 2019).

3. Medication – Certain anticonvulsant drugs during pregnancy are reported to cause orofacial clefts. A drug known as Lamictal (lamotrigine) is known to cause birth defects of the oral cleft (Dolk *et al*., 2016). Phenytoin, an anti-seizure drug used during the first trimester has been reported to cause CLP cases and positive associations have been related to the use of corticosteroids during pregnancy (Gedzelman & Meador, 2012).

4. Nutritional deficiencies – Folate and zinc deficiency have been known to cause CP and other deformities. Nutrients like riboflavin and vitamin A have also been associated with the development of orofacial clefts (Agbenorku, 2013).

5. Occupational hazards – Chemicals found in industrial and domestic products called glycol ether, xylene, toluene, and acetone when exposed to pregnant women increase the chances of development of CL (Chawla *et al.*, 2015)

## 2.3 Embryology

Lip development begins in the fourth and seventh weeks of pregnancy (Mossey *et al*., 2009). Frontonasal prominence formation starts in mesenchymal tissue posterior to the forebrain and progresses to the development of medial and lateral nasal prominences (Kirschner & Larossa, 2000). The neural crest cells migrating from the first pharyngeal arch form a set of maxillary and mandibular prominences (Tapadia *et al*., 2005). The premaxilla, or primary palate, develops as a result of the union of the median palatine processes. The unilateral CL occurs due to the failure of fusion between the medial nasal process on one side and the maxillary prominence. The cleft lip extends from the maxillary dentoalveolar area to the incisive foramen, which is formed where the medial palatine processes fail to unite. As the lateral palatine processes merge, the secondary palate develops between the sixth and twelve weeks of gestation. A cleft palate occurs when the medial palatine process of the nasal septum fails to fuse with the lateral palatine processes (Vyas & Warren, 2014). The embryological stages of cleft lip and palate are shown in Figure 2.1.

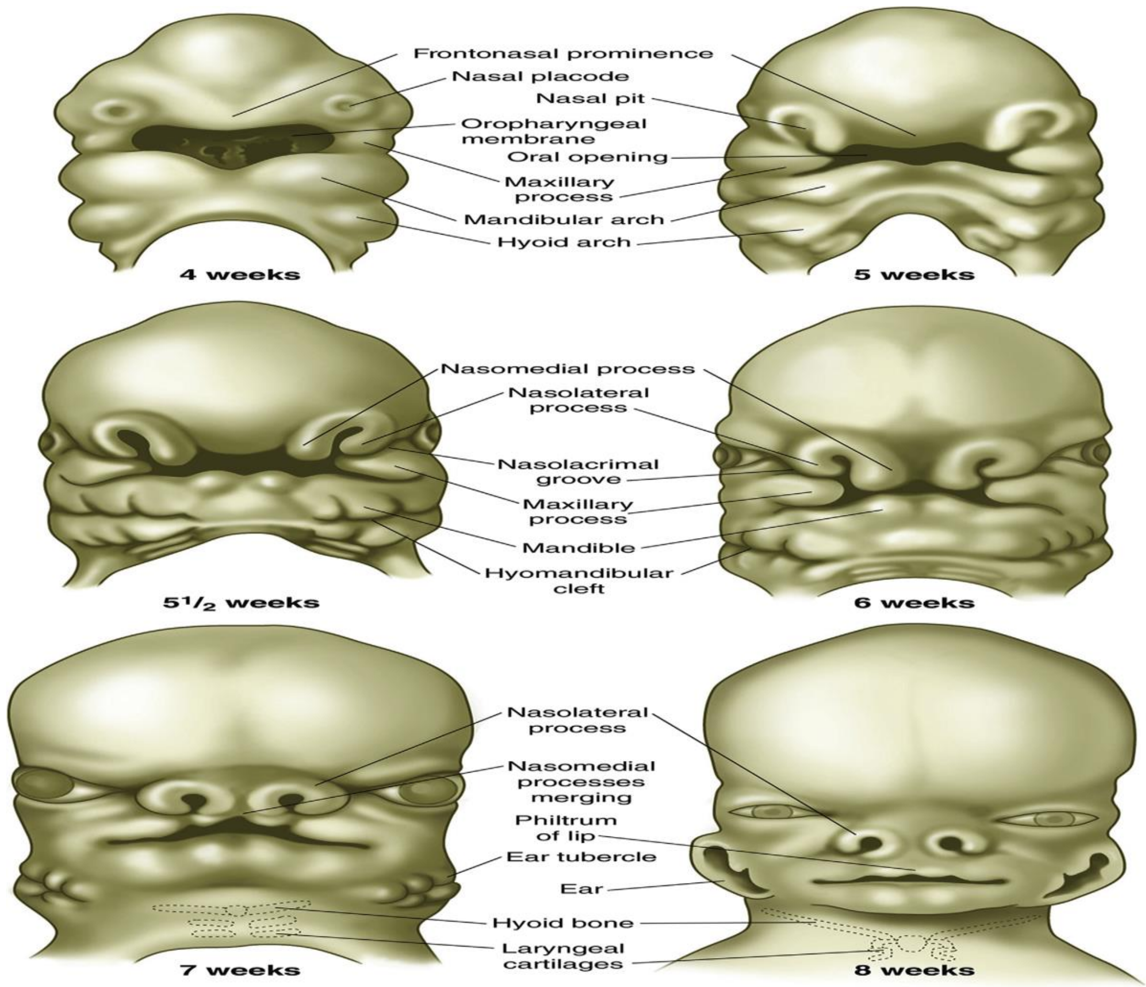


**Figure 2.1:** Embryology of the normal lip-5 prominences of the face: a central frontonasal prominence, paired maxillary prominences, and paired mandibular. During prominences. the fourth week of development, these primordial structures appear and encircle the primitive mouth. The upper jaw, lip (lateral to the philtral column), orbital floor, and inferior portion of the lateral nasal wall arise from the maxillary prominence. The swift growth of the maxillary prominences, along with the medial nasal processes, during weeks 4 to 8 guides a shift of the frontonasal process away from the stomodeum. The medial nasal processes join and give rise to the intermaxillary segment, which finally becomes the philtrum of the lip, the premaxilla, and the primary palate (Vyas & Warren, 2014).

## 2.4 Types of cleft lip and palate

The embryological development of the lip and palate is significant in determining the classification of cleft systems. A CL can be classified as unilateral or bilateral and as complete or incomplete. A complete cleft comprises the entire vertical thickness of the upper lip and is linked to an alveolar cleft and maxillary palatine bone. An incomplete CL consists of a portion of the vertical height of the upper lip with a varying amount of continuity throughout the cleft region. UCLP should be differentiated as right or left depending on the side involved. Palatal clefts are also portrayed as unilateral or bilateral, and their extent may be classified as complete or incomplete (Tolarova *et al*., 1998).

Also, CPs are classified based on their location to the incisive foramen. Clefts of the primary palate appear in front of the incisive foramen and clefts of the secondary palate appear posterior to the incisive foramen. A unilateral cleft of the secondary palate is described as a cleft in which one portion is fused with the nasal septum and the palatal process of the maxilla on one side. There is no site of fusion between the nasal septum and the maxilla in a bilateral complete cleft of the secondary palate (Bernheim *et al*., 2006). CL involves one or both sides of the premaxilla/alveolar arch of the maxillary bone in a full cleft of the entire palate, which encompasses both the primary and secondary palate. An isolated CP usually includes the secondary palate only and has variable degrees of severity. An isolated CP generally affects only the secondary palate and has varying degrees of severity. The submucous cleft palate (SMCP) is the least severe incomplete cleft in which the necessary palatal musculature is absent and incorrectly joined (Banerjee & Dhakar, 2013). Types of Cleft lip and palate have been shown in Figure 2.2.

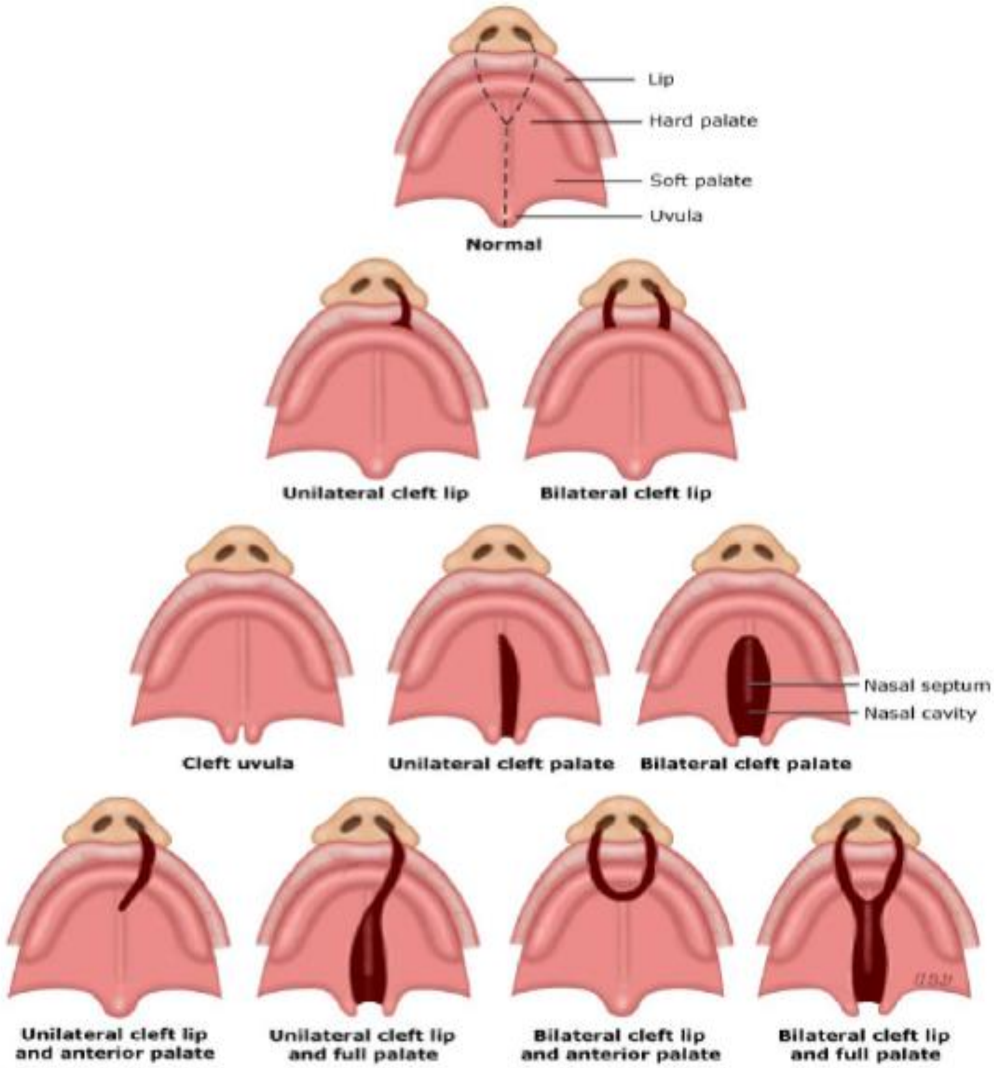


**Figure 2.2:** Different types of unilateral and bilateral cleft lip and palate (Banerjee & Dhakar, 2013)

## 2.5 Classification of Cleft lip and palate

There is no universal agreement on the ideal classification as of now, and several have been proposed and approved across the continent (Table 2.1). The Nomenclature Committee of the American Cleft Palate-Craniofacial Association (ACPA) Rehabilitation has outlined the guidelines to develop the ideal components that a classification should reflect based on three pillars (Harkins *et al.*, 1962): concise clear descriptions of terms, ease of use, and application of clinical research. Although illustrated in 1962, this depiction is still valid as it guides authors to explain new classifications that can stay with the period. Davis and Ritchie (1922) gave the first classification for congenital CLP. This was neither an embryological nor an anatomical classification. Veau's classification was in four groups. It was far from anatomical and is not used today. Later Kernahan in 1971 came up with the "Y" classification in 9 squares with nasopalatine foramen as the focal point. The modified classification of Kernahan signifies the cleft defect exactly as it is present and is very resourceful (Raposo-Amaral *et al.*, 2018).

**Table 2.1**.Classification systems of cleft patients (Raposo-Amaral *et al.*, 2018)

| Classification systems | Description |
|---|---|
| **Davis and Ritchie** | |
| **Group 1** | Clefts of the lip (without the presence of the maxillary alveolus), unilateral, bilateral, or median |
| **Group 2** | Clefts inclusive from the maxillary alveolus to the hard and soft palate |
| **Group 3** | Cleft including the alveolus, unilateral, bilateral, or median being complete or incomplete |
| **Veau** | |
| **Class I** | Cleft of the soft palate |
| **Class II** | Clefts of the hard and soft palates, backward to the incisive foramen |
| **Class III** | Complete unilateral CLP |
| **Class IV** | Complete bilateral CLP |
| **Fogh-Andersen** | |
| **Group I** | Clefts of the primary palate, including lip, alveolus, and incisive foramen |
| **Group II** | Unilateral and bilateral clefts of the lip that extend into the hard palate (complete or incomplete) |
| **Group III** | Midline clefts of the secondary palate, backward to the incisive foramen |
| **Group IV** | Median cleft lip |
| **Kernahan and Stark** | |
| **Group 1** | Cleft altering the primary palate |
| **Group 2** | Cleft altering the secondary palate |
| **Group 3** | Cleft altering primary and secondary palates |
| **ACPA** | |
| **Group 1** | a. Cleft lip, b.cleft alveolus, c. cleft lip, alveolus, and primary palate |
| **Group 2** | a. Cleft of the hard palate, b. cleft of the soft palate, c. cleft of the hard and soft palates |
| **Group 3** | Clefts of the prepalate and palate |
| **Group 4** | a. Cleft of the mandibular process, b. naso-ocular clefts, c. oro-ocular clefts, d. oro-aural clefts |

American Cleft Palate-Craniofacial Association (ACPA)

## 2.6 Prevalence of Cleft lip and Palate

Pereira *et al.* (2018) described the malformations in children associated with clefts in Portugal population of 31 years. This study was conducted to evaluate the occurrence and the type of congenital abnormalities in children with clefts. It was a retrospective study and data was collected from a tertiary referral center in Portugal. A total of 701 patients with orofacial cleft were included in the study based on at least one patient visit between the years 1981 to 2012. The study involved 219 (31.2%) patients out of 701 who had congenital malformations, the incidence of malformation was higher in patients with CP (43.4%) than in patients with CLP (27.5%) and in patients with CL (19.4%). Around 146 (66.7%) cases had multiple congenital anomalies with unknown origin and 73 cases had a known chromosomal defect, monogenic syndrome-related conditions. The most common deformity was from the head and neck region representing around 60.3% of the cases. The authors concluded that nearly 1 among 3 patients with clefts had the prevalence of associated malformation, hence these patients require complete evaluation by a multidisciplinary treatment approach. Further, almost one-third of the cases show a known origin-related congenital anomaly thus early detection and genetic analysis might be very helpful in orofacial cleft management.

Shah *et al*. (2018) evaluated the occurrence of different types of cleft lip and cleft palate in racial groups of Malaysia. A total of 526 CLP patients were included in the study from the registered patients in two tertiary hospitals of Malaysia from August 2007 to March 2009 namely the University of Malaya Medical Centre (UMMC) and Hospital Kota Bharu (HKB). Patients, less than 10 years were excluded. A modified craniofacial registration form was used to collect the data. About 86.7% of total patients were <18 years and females (56.7%) more than males were included in the study.

Results of the study revealed that the right-sided oral cleft was found in about 96.1% of Malay patients, and 3.9% of Chinese patients but the majority with a bilateral oral cleft. Patients with cleft palate were 3.7% Malay, 4.6% Chinese, and 23% Indians. The highest percentage of cleft palate patients among the Indian population may be due to Consanguineous marriages (marriage between blood relatives) (Rajeev *et al.*, 2017). Patients with soft palate clefts were 4% Malay and 7.6% Indian. Both hard and soft palate was found highest in the Malay race constituting about 92%, followed by 95% Chinese and 69% Indian. Management of CLP patients should start early, as the patients and their families undergo lasting financial and psychological stress. Management of CLP patients should involve a multidisciplinary approach. The management of these cases should begin shortly after birth and usually continues till the teenage and involves multiple surgeries and long-term speech therapy combined with orthodontic treatment. The authors concluded that the most commonly affected ethnic group was Malay in this study then Chinese, and Indians among the Malaysian population. Because the highest percentage of UCLP children has been seen in Malay race when compared to other ethnicities.

### 2.7 Treatment of CLP

The management of CLP has evolved extensively over the past decades. The new techniques have been introduced. The timing and age of the children play a very crucial role in treatment planning and CLP management.

The treatment of children with CLP is very challenging. The management of cleft patients begins during intrauterine life and lasts until late adulthood. Because such patients have a