TREATMENT OUTCOME IN CHILDREN WITH NON-SYNDROMIC UNILATERAL CLEFT LIP AND PALATE BASED ON CONGENITAL AND POSTNATAL TREATMENT FACTORS: A MULTI-POPULATION STUDY USING THREE-DIMENSIONAL DIGITAL MODELS

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by

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LIST OF ABBREVIATIONS

ABG	Alveolar Bone Grafting
AD	Arch Depth
AL	Arch Length
AW	Arch Width
BAN	Bangladesh
BCL	Bilateral Cleft Lip
BCLP	Bilateral Cleft Lip and Palate
BT	Bardach Technique
CLP	Cleft Lip and Palate
CG	Control Group
CI	Confidense Interval
CS	Cleft Side
CP	Cleft Palate
CL	Cleft Lip
DAR	Dental Arch Relationship
DC	Deciduous Canine
PC	Permanent Canine
D1M	Deciduous 1st Molar
D2M	Deciduous 2nd Molar
EI	EUROCRAN Index
EMT	Epithelial Cells into Mesenchymal Cells
GOAL	Goteborg (G), Sweden; Oslo (O), Norway; Aarhus (A), Denmark; and Linkoping (L), Sweden
GOSLON	Great Ormond Street, London and Oslo
GSTT1	Glutathione S-Transferase Theta 1
GY	Goslon Yardstick
ICC	Intra-Class Correlation Coefficient
ICW	Inter-Canine Width
IMW	Inter-Molar Width
IPMW	Inter Premolar Width

IRF6	Interferon Regulatory Factor-6
LB	Lower Bound
LS3DM	Laser Scanned 3D Digital Model
MAD	Maxillaryarch Dimension
MAL	Malaysia
MTHFR	Methylene Tetra Hydro Folate Reductase
MD	Mesiodistal
MET	Mesenchymal Cells into Epithelial Cells
mHB	Modified Huddart Bodenham
MSX1	Muscle-Segment Homeobox 1
MT	Millard Technique
MMT	Modified Millard Technique
NAM	Naso-Alveolar Molding
NCS	Non Cleft Side
OFC	Orofacial Clefts
PAKI	Pakistan
PCI	Permanent Central Incisor
PLI	Permanent Lateral Incisor
P1M	Permanent 1st Molar
PCD	Programmed Cell Death
PSOT	Pre Surgical Orthopedic Appliances Treatment
PM	Palatal Morphology
RED	Rigid Extraoral Fixation Device
SATB2	Special At-Rich Sequence Binding Protein 2
SPSS	Statistical Package For Social Sciences
SUMO1	SMT3 Suppressor Of MIF Two 3 Homolog 1
TBX22	T-Box Transcription Factor-22
TGFA	Transforming Growth Factor-Alpha
TGFB3	Transforming Growth Factor-Beta 3
UB:	Upper Bound
UCL	Unilateral Cleft Lip
UCLA	Unilateral Cleft Lip and Alveolus
UCLP	Unilateral Cleft Lip and Palate

VLT	Von Langenbeck Technique
WHO	World Health Organization
3D	Three Dimensional

LIST OF APPENDICES

RAWATAN KANAK-KANAK YANG SUMBING BIBIR DAN LELANGIT UNILATERAL TIDAK SINDROMIK BERDASARKAN FAKTOR RAWATAN KONGENITAL DAN POS NATAL DALAM SATU KAJIAN BERBILANG POPULASI MENGGUNAKAN MODEL DIGITAL TIGA DIMENSI

Kajian keratan rentas ini bertujuan untuk menilai perhubungan arkus pergigian (DAR) dan dimensi arkus maksilari (MAD) kanak-kanak dengan sumbing bibir dan lelangit unilateral tidak bersindrom (UCLP) dan untuk meneroka kongenital (jantina, jenis UCLP, bahagian UCLP, sejarah sumbing keluarga, sejarah maloklusi Kelas III keluarga) dan factor-faktor rawatan posnatal (jenis-jenis keiloplasti dan palatoplasti) yang memberi kesan terhadap hasil rawatan UCLP dalam kalangan kanak-kanak dengan menggunakan model-model digital tiga dimensi yang diimbas dengan laser (LS3DM). Tambahan lagi, kajian ini menilai dan membandingkan saiz gigi mesiodistal (MD) pada sisi rekahan (CS) dan bukan sisi rekahan (NCS) pada maksila dalam kalangan kanak-kanak UCLP lelaki dan perempuan menggunakan LS3DM di samping menilai perkaitan dalam kalangan jantina dan bangsa. Dua ratus dan lima puluh lima plaster tuang pergigian kanak-kanak UCLP sebelum rawatan ortodontik daripada populasi Malaysia, Bangladesh, dan Pakistan, dipilih dalam kajian ini. Purata umur adalah 7.69± 2.46 (purata± sisihan piawai). Kesemua tuang pergigian diimbas dan ditukar kepada LS3M oleh pengimbas laser Next Engine. DAR dinilai oleh dua penilai menggunakan Goslon Yarstick (GY) dan EUROCRAN Index (EI) dan sistem pemarkahan Huddart Bodenham (mHB) yang telah dimodifikasi, dimensi keluasan antara kanin (ICW), antara molar (IMW), kedalaman arkus (AD) dan MD gigi ukur dengan perisian Mimics (Belgium). Hasil rawatan dinilai dalam dua kumpulan; kumpulan pilihan dan bukan pilihan berdasarkan sistem pemarkahan GY,

EI dan mHB. Statistik Kappa digunakan untuk menilai perjanjian dalaman dan antara pemeriksa dan analisis logistik regresi digunakan untuk meneroka faktor yang bertanggungjawab memberi kesan terhadap DAR. Korelasi antara kelas digunakan untuk menilai persetujuan dan analisis regresi linear digunakan untuk menilai hubungan di antara faktor-faktor pelbagai dan MAD (ICW, IMW, and AD) dan dimensi MD saiz gigi maksila. Nilai signifikan diletakkan pada 5%. Skor purata GY adalah 2.97, 3.40 dan 3.09 dalam populesi Malaysia, Bangladesh dan Pakistan. DAR yang bukan menjadi pilihan secara signifikan dikaitkan dengan Teknik Bardach (BT) Palatoplasti (P=0.03) di Malaysia, subjek UCLP lelaki (p=0.03), keiloplasti yang dimodifikasi dengan Teknik Millard (MMT) (p=0.04) dan BT palatoplasti (p=0.04) di Bangladesh dan BT palatoplasti (p=004) di populasi Pakistan menggunakan GY. Markah EUROCRAN adalah 3.07 dan 2.21 dalam populesi Malaysia, 2.66 dan 2.07 d dalam populesi Bangladesh dan 2.56 dan 2.07 dalam populesi Pakistan untuk DAR dan morfologi palatal (PM). Dengan menggunakan analisis regresi logistik, DAR yang tidak menjadi pilihan secara signifikannya dikaitkan dengan sejarah keluarga rekahan yang positif (p=0.3) dan BT palatolasti ($p < 0.001$) dalam kalangan populesi Malaysia, MM keiloplasti ($p = 0.010$) dan BT of palatoplasti ($p = 0.02$) dalam kalangan populesi Bangladesh dan UCLP sebelah kiri ($p = 0.03$), MMT keiloplasti ($p = 0.02$) dan BT of palatoplasti ($p = 0.04$) dalam kalangan populasi Pakistan menggunakan EI. Keseluruhan markah mHB adalah -9.98, -8.76 dan -6.57 dalam populesi Malaysia, Bangladesh and Pakistan. Dengan menggunakan analisis regresi logistik, DAR yang bukan menjadi pilihan dikaitkan secara signifikan dengan sejarah keluarga yang positif dengan rekahan ($p = 0.02$ and $p = 0.04$) dan BT palatoplasti ($p = 0.03$ and $p = 0.01$) dalam populesi Malaysia dan Bangladesh. Purata dimensi ICW adalah 26.88 mm, 26.61 mm dan 26.69 mm dan IMW adalah 45.24 mm, 42.89 mm an 43.33 mm dan AD adalah 29.81 mm, 2906 mm dan 27.06 mm di dalam kalangan dalam populesi Malaysia, Bangladesh dan Pakistan. Perkaitan yang signifikan dilihat di antara keilopasti ICW dan MMT yang lebih sempit. Perkaitan yang signifikan dilihat di antara AD yang lebih pendek dan jenis UCLP (P=0.01) yang penuh dalam populesi Bangladesh. Mengenai saiz gigi asimetri, perbezaan signifikan dilihat di antara dimensi MD kesemua saiz gigi CS dan NCS maksila dalam kalangan lelaki dan wanita dalam kesemua populasi. Kajian pelbagai populasi mencadangkan hasil rawatan berasarkan DAR dan MAD tidak bersindrom dalam kalangan kanak-kanak UCLP tidah di Malaysia, Bangladesh dan Pakistan menunjukkan korelasi dengan beberapa faktor kongenital dan rawatan posnatal menggunakan LS3DM. Kajian ini juga mendapati saiz gigi yang lebih kecil CS berbanding NCS yang berkaitan dengan jantina, dan bangsa dalam semua populasi menggunakan LS3DM.

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ABSTRACT

This cross-sectional study aimed to evaluate dental arch relationship (DAR) and maxillary arch dimension (MAD) of non-syndromic unilateral cleft lip and palate (UCLP) children and to explore the congenital (gender, UCLP type, UCLP side, family history of cleft, family history of Class III malocclusion) and postnatal treatment (types of cheiloplasty and palatoplasty) factors that affect the treatment outcome of UCLP children using laser scanned three-dimensional digital models (LS3DM). Furthermore, the present study evaluated and compared the mesiodistal (MD) tooth sizes on cleft side (CS) and non-cleft side (NCS) of the maxilla among male and female UCLP children using LS3DM as well as evaluated the association among gender and races. Two hundred and fifty-five pretreatment orthodontic plaster dental casts of UCLP children from Malaysia, Bangladesh, and Pakistan populations, 85 from each were selected into this study. The mean age was 7.69± 2.46 (mean± SD). All the dental casts were scanned and converted into LS3DM by Next Engine laser scanner (Santa Monica, USA). DAR was assessed by two raters using GOSLON Yardstick (GY) and EUROCRAN index (EI) and modified Huddart Bodenham (mHB) scoring system. Inter-canine width (ICW), inter-molar width (IMW), arch depth (AD) and MD dimensions of the tooth were measured with Mimics software (Belgium). Treatment

outcome was rated into two groups; favourable and unfavourable groups based on GY, EI and mHB scoring systems. Kappa statistics used to evaluate the intra- and inter-examiner agreements and logistic regression analysis (LRA) used to explore the responsible factor that affect DAR. The intra-class correlation was used to evaluate the intra- and inter-examiner agreements and multiple linear regression analyses used to evaluate the association between multiple factors and MAD (ICW, IMW, and AD) and MD dimension of tooth size of the maxilla. *p-value* was set at 5%. The mean GY score was 2.97, 3.40 and 3.09 in Malaysia, Bangladesh and Pakistan population respectively. Unfavourable DAR was significantly associated with Bardach technique (BT) of palatoplasty (**p = 0.03**) in Malaysian, male UCLP subjects (**p = 0.03**), modified Millard technique (MMT) of cheiloplasty (**p = 0.04**) and BT of palatoplasty (**p = 0.04**) in Bangladeshi and BT of palatoplasty (**p = 0.04**) in Pakistani population using GY. The mean EUROCRAN scores were 3.07 and 2.21 in Malaysia, 2.66 and 2.07 in Bangladesh and 2.56 and 2.07 in Pakistan for DAR and palatal morphology (PM) respectively. Using LRA, unfavourable DAR was significantly associated with positive family history of cleft (**p = 0.03**) and BT of palatoplasty (**p < 0.001**) in Malaysian, MMT of cheiloplasty (**p = 0.010**) and BT of palatoplasty (**p = 0.02**) in Bangladeshi and left sided UCLP (**p = 0.03**), MMT of cheiloplasty (**p = 0.02**) and BT of palatoplasty (**p = 0.04**) in Pakistani population using EI. The total mHB score was -9.98, -8.76 and -6.57 in Malaysia, Bangladesh and Pakistan population respectively. Using LRA, unfavourable DAR was significantly associated with positive family history of cleft (**p = 0.02** and **p = 0.04**) and BT of palatoplasty (**p = 0.03** and **p = 0.01**) in Malaysian and Bangladeshi population respectively, and BT of palatoplasty (**p < 0.001**) in Pakistani population. The mean dimension of ICW was 26.88 mm, 26.61 mm and 26.69 mm and IMW was 45.24 mm, 42.89 mm and 43.33 mm and AD was

29.81 mm, 29.06 mm and 27.06 mm in Malaysians, Bangladeshis and Pakistanis respectively. Significant association was observed between narrower ICW and MMT of cheiloplasty (**$p < 0.001$**) in Malaysian and BT of palatoplasty (**$p = 0.04$** and **$p = 0.02$**) in Malaysian and Bangladeshi population respectively. Significant association was observed between shorter AD and complete type of UCLP (**$p = 0.01$**) in Bangladeshi. Regarding tooth size asymmetry, significant difference observed in MD dimension of all the teeth size of CS and NCS of maxillae among male and female in all populations. This multi-population study suggested that treatment outcome based on DAR and MAD of non-syndromic Malaysians, Bangladeshis and Pakistanis UCLP children was significantly correlated with some of congenital and postnatal treatment factors using LS3DM. The study also revealed significantly smaller teeth size in CS compare to NCS in relation to gender, and races in all populations using LS3DM.

CHAPTER 1

INTRODUCTION

1.1 Background of Study

Any deformities (anatomical or chromosomal) that initiate during pregnancy and their effects detected after birth considered as congenital anomalies (Sekhon et al., 2011). Among them, cleft lip and palate (CLP) is one of the most common and major congenital craniofacial anomalies in human-caused by abnormal facial development during embryogenesis that presents at birth and characterised by partial or complete clefting of the upper lip, clefting of the alveolar ridge or the hard or soft palate (Erverdi and Motro, 2015). A cleft can occur together with cleft lip and cleft palate or individually like isolated cleft lip and or isolated cleft palate. When cleft affecting both lip and palate, it is termed as CLP. The features of CLP ranged in severity with unilateral or bilateral manners. CLP can be syndromic or non-syndromic. Clinically, when CLP appears with other (usually two or more) malformations in a recognisable pattern, it is classified as syndromic CLP. If it appears as an isolated defect or if syndromes cannot be identified, the term non-syndromic CLP is used (Kohli and Kohli, 2012). At least 400 syndromes have been already found associated with CLP (Papadopulos et al., 2005; Dogan et al., 2019). The aetiology of CLP is still controversial. According to previous studies, it is to be thought that both genetic and environmental factors are responsible for CLP (Berkowitz, 2013; Haque et al., 2014; Haque et al., 2015a).

CLP shows significant heterogeneity among different ethnic groups. World Health Organization (WHO) has recognised and included cleft deformities in their Global Burden of Disease initiative. It is estimated that the overall global prevalence of cleft deformities is one affected individual in every 600 newborn babies. An overall global incidence of CLP is 1.43 in 1000 live births (Dixon et al., 2011) and 1.30 in 1000 live births among the Asian population (Cooper et al., 2006).

Common health problems associated with the non-syndromic CLP children are dental anomalies, aesthetic issues, hearing difficulties, speech problems, and psycho-social behavioural issues (Ranta, 1986). The management of a patient with cleft is complex and requires lengthy procedures with the involvement of multi specialities working in tandem to bring out physical, psychological and social rehabilitation. Likewise, maxillary arch constriction (maxillary growth retardation) after the cleft repair, is a common dental problem of CLP patients resulting in concave facial profile, Class III malocclusion, midfacial growth deficiency, congenitally missing and malformed teeth. Orthodontic problems like crowding, rotation and malposition of teeth are also commonly observed (Haque and Alam, 2015a; Haque et al., 2018; Adetayo et al. 2019; Schilling et al. 2019).

Cleft can unilateral or bilateral. Bilateral cleft lip and palate is the most severe of the all common orofacial cleft subtypes (Papadopulos et al., 2005). This study has been carried out on unilateral cleft lip and palate (UCLP).

When a patient born with UCLP, a number of surgeries take place in the first two years of life. Beginning with the pre-surgical orthopaedic feeding plate after birth (Haque and Alam, 2015b), followed by cheiloplasty at 3-6 months old (Haque and Alam, 2014), and palatoplasty at 9-18 months old (Haque and Alam, 2015c). There are excessive scar tissues formation and the undermining of soft tissue are observed after these surgeries which may result in maxillary contracture that finally leads to

Class III malocclusion. Growth retardation of the maxilla is often observed in patients with UCLP (Alam et al., 2008; Kajii et al., 2013).

Many methods for the assessment of the treatment outcome of UCLP children have been described previously such as based on dental arch relationship, maxillary arch dimension, cephalogram etc (Alam et al., 2008; Kajii et al., 2013; Asif et al., 2016; Gopinath et al., 2017; Arshad et al., 2017a; Haque et al., 2018).

Both congenital and postnatal treatment factors are influenced treatment outcome of UCLP. The postnatal treatment factors; such as timing and techniques of cheiloplasty and palatoplasty have been found to influence the outcome of the treatment of UCLP (Kongprasert et al., 2019; Adetayo et al., 2019; Schilling et al., 2019). Moreover, the congenital factors; such as type of UCLP, side of UCLP, family history of cleft and family history of Class III malocclusion also influence the treatment outcome (Alam et al., 2008). A diverse design of studies and findings on the outcome of treatment in children with CLP has led to great diversity in protocols and surgical techniques by various cleft groups' worldwide (Alam et al., 2013). As a result, a comprehensive study which evaluates multi factors in several different populations is required to function as the basis of selection for surgical methods and management.

1.1.1 Evaluating Treatment Outcome Based on Dental Arch Relationship

Cleft deformities remain a significant and interesting challenge for the medical fraternity. An assessment of the dental arch relationship was considered a valuable benchmark of treatment outcome evaluation. Several indices such as the GOSLON (Great Ormond Street, London and Oslo) Yardstick (GY) (Mars et al., 1987), GOAL

(Goteborg (G), Sweden; Oslo (O), Norway; Aarhus (A), Denmark; and Linkoping (L), Sweden) index (Friede et al., 1991), the 5-year-old index (Atack et al., 1997a), Huddart/Bodenham scoring system (Huddart and Bodenham, 1972), modified Huddart Bodenham (mHB) scoring system (Mossey et al., 2003; Gray and Mossey, 2005) the EUROCRAN index (EI) (Fudalej et al., 2011), are used to assess dental arch relationship in patients with CLP.

Treatment outcome based on dental arch relationship has been extensively studied (Schilling et al. 2019; Kongprasert et al. 2019; Hay et al. 2018; Haque et al. 2018; Zin et al. 2017; Arshad et al. 2017b; Chalmers et al., 2016; Zhu et al., 2016; Sasaguri et al., 2014; Dogan et al., 2014; Kajii et al. 2013; Asquith and McIntyre 2012; Dogan et al., 2012; Fudalej et al., 2012; Fudalej et al., 2011; Zaleckas et al., 2011; Alam et al, 2008; Apostol, 2008; Bongaarts et al., 2006). However, none of these studies used three (GY, EI and mHB) indices at a time for the evaluation of dental arch relationship and also considered multiple factors in several different populations using 3D digital modelds.

1.1.2 Evaluating Treatment Outcome Based on Maxillary Arch Dimension

Maxillary arch dimension are previously studied among UCLP subjects (Gopinath et al., 2017; Cassi et al., 2017; Carrara et al., 2016; Russel et al., 2015; dos Santos et al., 2015; Garib et al., 2013; Lewis et al., 2008; Kitagawa et al., 2004). These studies established that UCLP subjects have smaller arch dimensions compared to the normal subjects. In addition to comparison with normal subjects, maxilarry arch dimensions have been used as dependent variable in the study of treatment outcome. Several treatment outcome studies used maxillary arch dimension, however none of the previous studies evaluated the effects of multiple factors on maxillary arch dimension. Additionally, all the studies were in a single population.

1.1.3 Evaluating Tooth Size Asymmetry

The incidence of dental anomalies is markedly increased in children with CLP compared to the general population (Shapira et al., 1999; Alqerban, 2019). Tooth anomalies frequently occur on the cleft side (Camporesi et al., 2007; Alqerban, 2019) due to presence of large gap. Appropriate alignment of tooth can be interfered with tooth size discrepancies between the sides of arch. Before treatment, measuring or recording these asymmetry of tooth may give clues to the clinician to obtain ideal occlusion, overjet and over bite. Remarkable asymmetry of tooth size between cleft side and non-cleft side has been reported by many researchers (Alkofide and Hashim, 2002; Uysal and Sari, 2005; Uysal et al., 2005; Akcam et al., 2014). To the best of our knowledge no reported data to date have been found concerning the measurement of mesiodistal (MD) tooth size of UCLP children in the Malaysian, Bangladeshi and Pakistani populations Thus this study was planned to evaluate tooth size asymmetry including the MD dimension between cleft and non-cleft side in non-syndromic UCLP children of three different populations (Malaysian, Bangladeshi, Pakistani) on 3D digital model.

1.1.4 3D Digital Models

3D digital model and its analyses have been proven to be an accurate and reliable method for UCLP research (Asquith and McIntyre, 2012; Dogan et al., 2012; Russel et al., 2015; Zhu et al., 2016).

Yet, to the best of our knowledge no reported data to date were found on Malaysian, Bangladesh and Pakistani population for evaluation of multiple factors that may influence the treatment outcome by assessing dental arch relationship, maxillary arch dimension and tooth size asymmetry. Thus this study embarked on evaluation of effects of multiple factors among three populations on the treatment outcome of UCLP. Furthermore, this study used 3D digital models for all the measurements.

1.2 Justification of Study

Treatment outcome based on the dental arch relationship is necessary to help surgeons to justify modifications of their techniques, and to provide better understanding on the healing response of growing tissues to surgical repair.

For the first time, this study evaluated treatment outcome based on dental arch relationship and maxillary arch dimension; tooth size asymmetry using laser scanned 3D digital models (LS3DM) in three different populations simultaneously. The dental arch relationship was assessed using GY, EI and mHB scoring systems on UCLP children. The understanding of treatment outcome based on the dental arch relationship and maxillary arch dimension in non-syndromic UCLP children of Malaysian, Bangladeshi and Pakistani populations and the association of multiple congenital and post natal treatment factors may

1. facilitate decision making and treatment planning of CLP.
2. determine to which extent the surgery that could bring those patients to the normal limits.
3. establish a database for further future studies and
4. reduce treatment cost.

1.3 Objectives

1. To determine treatment outcome based on dental arch relationship using GY, EI and mHB scoring system as dependent variable and its association with congenital and postnatal treatment factors in non-syndromic UCLP children of different populations using LS3DM.
2. To determine treatment outcome based on maxillary arch dimension (inter canine width, inter molar width and arch depth) as dependent variable and its association with congenital and postnatal treatment factors in non-syndromic UCLP children of different populations using LS3DM.
3. To determine the tooth size asymmetry on cleft and non-cleft sides of the maxilla among male and female and its association with gender and races in non-syndromic UCLP children of different populations using LS3DM.

1.4 Specific Objectives

1.4.1 Dental Arch Relationship

1.4.1(a) Using GOSLON Yardstick (GY)

1. To determine the treatment outcome based on dental arch relationship in non-syndromic UCLP children of Malaysian, Bangladeshi and Pakistani population using LS3DM.
2. To determine favourable and unfavourable groups of dental arch relationship based on the treatment outcome.
3. To evaluate the association between congenital and postnatal treatment factors and favourable and unfavourable dental arch relationship in non-syndromic UCLP children among Malaysian, Bangladeshi and Pakistani population.

1.4.1(b) Using EUROCRAN Index (EI)

1. To determine the treatment outcome based on dental arch relationship and palatal morphology in non-syndromic UCLP children of Malaysian, Bangladeshi and Pakistani population using LS3DM.

2. To determine favourable and unfavourable groups of dental arch relationship based on the treatment outcome.

3. To evaluate the association between congenital and postnatal treatment factors and favourable and unfavourable dental arch relationship in non-syndromic UCLP children among Malaysian, Bangladeshi and Pakistani population.

1.4.1(c) Using modified Huddart Bodenham (mHB) Scoring System

1. To determine the treatment outcome based on dental arch relationship in non-syndromic UCLP children of Malaysian, Bangladeshi and Pakistani populations using LS3DM.
2. To determine favourable and unfavourable groups of dental arch relationship based on the treatment outcome.

3. To evaluate the association between congenital and postnatal treatment factors and favourable and unfavourable dental arch relationship in non-syndromic UCLP children among Malaysian, Bangladeshi and Pakistani population.

1.4.2 Maxillary Arch Dimension

1.4.2(a) Inter-Canine Width (ICW)

1. To evaluate the mean dimension of ICW of maxilla in non-syndromic UCLP children in Malaysian, Bangladeshi and Pakistani populations.
2. To evaluate the association between congenital and postnatal treatment factors and ICW in non-syndromic UCLP children among Malaysian, Bangladeshi and Pakistani populations.
3. To compare the ICW among three populations.

1.4.2(b) Inter-Molar Width (IMW)

1. To evaluate the mean dimension of IMW of maxilla in non-syndromic UCLP children in Malaysian, Bangladeshi and Pakistani populations.
2. To evaluate the association between congenital and postnatal treatment factors and IMW in non-syndromic UCLP children among Malaysian, Bangladeshi and Pakistani populations.
3. To compare the IMW among three populations.

1.4.2(c) Arch Depth (AD)

1. To evaluate the mean dimension of AD of maxilla in non-syndromic UCLP children in Malaysian, Bangladeshi and Pakistani populations.
2. To evaluate the association between congenital and postnatal treatment factors and AD in non-syndromic UCLP children among Malaysian, Bangladeshi and Pakistani populations.

3. To compare the AD among three populations.

1.4.3 Tooth Size Asymmetry

1. To compare the tooth size (MD) on the cleft and non-cleft sides of the maxilla among male and female non-syndromic UCLP children in Malaysian population.
2. To compare the tooth size (MD) on the cleft and non-cleft sides of the maxilla among male and female non-syndromic UCLP children in Bangladeshi population.
3. To compare the tooth size (MD) on the cleft and non-cleft sides of the maxilla among male and female non-syndromic UCLP children in Pakistani population.
4. To evaluate the association between the tooth size (MD) of the cleft and non-cleft sides of the maxilla and gender and races in non-syndromic UCLP children among the three different populations.

1.5 Research Questions

1.5.1 Dental Arch Relationship

1. Is there any association between favourable and unfavourable dental arch relationship and congenital and postnatal treatment factors in non-syndromic UCLP children in LS3DM using GY, EI and mHB scoring system in Malaysian population?
2. Is there any association between favourable and unfavourable dental arch relationship and congenital and postnatal treatment factors in non-syndromic

UCLP children in LS3DM using GY, EI and mHB scoring system in Bangladeshi population?

3. Is there any association between favourable and unfavourable dental arch relationship and congenital and postnatal treatment factors in non-syndromic UCLP children in LS3DM using GY, EI and mHB scoring system in Pakistani population?

1.5.2 Maxillary Arch Dimension

1. Is there any association between maxillary arch dimension (ICW, IMW and AD) and congenital and postnatal treatment factors in non-syndromic UCLP children in Malaysian population?
2. Is there any association between maxillary arch dimension (ICW, IMW and AD) and congenital and postnatal treatment factors in non-syndromic UCLP children in Bangladeshi population?
3. Is there any association between maxillary arch dimension (ICW, IMW and AD) and congenital and postnatal treatment factors in non-syndromic UCLP children in Pakistani population?
4. Is there any association between maxillary arch dimension (ICW, IMW and AD) and congenital and postnatal treatment factors in non-syndromic UCLP children among the three different populations?

1.5.3 Tooth Size Asymmetry

1. Is there any difference between the tooth size (MD) on the cleft and non-cleft sides of the maxilla among male and female non-syndromic UCLP children in Malaysian population?
2. Is there any difference between the tooth size (MD) on the cleft and non-cleft sides of the maxilla among male and female non-syndromic UCLP children in Bangladeshi population?
3. Is there any difference between the tooth size (MD) on the cleft and non-cleft sides of the maxilla among male and female non-syndromic UCLP children in Pakistani population?
4. Is there any association between tooth size (MD) of the cleft and non-cleft sides of the maxilla and gender and races in non-syndromic UCLP children among the three different populations?

1.6 Null Hypothesis

1.6.1 Dental Arch Relationship

1. There is no association between favourable and unfavourable dental arch relationship and congenital and postnatal treatment factors in non-syndromic UCLP children using GY, EI and mHB scoring system in Malaysian population.
2. There is no association between avorable and unfavourable dental arch relationship and congenital and postnatal treatment factors in non-syndromic UCLP children using GY, EI and mHB scoring system in Bangladeshi population.

3. There is no association between avorable and unfavourable dental arch relationship and congenital and postnatal treatment factors in non-syndromic UCLP children using GY, EI and mHB scoring system in Pakistani population.

1.6.2 Maxillary Arch Dimension

1. There is no association between maxillary arch dimension (ICW, IMW and AD) and congenital and postnatal treatment factors in non-syndromic UCLP children in Malaysian population.
2. There is no association between maxillary arch dimension (ICW, IMW and AD) and congenital and postnatal treatment factors in non-syndromic UCLP children in Bangladeshi population.
3. There is no association between maxillary arch dimension (ICW, IMW and AD) and congenital and postnatal treatment factors in non-syndromic UCLP children in Pakistani population.
4. There is no association between maxillary arch dimension (ICW, IMW and AD) and congenital and postnatal treatment factors in non-syndromic UCLP children among the three different populations.

1.6.3 Tooth Size Asymmetry

1. There is no difference between the tooth size (MD) on the cleft and non-cleft sides of the maxilla among male and female non-syndromic UCLP children in Malaysian population.
2. There is no difference between the tooth size (MD) on the cleft and non-cleft sides of the maxilla among male and female non-syndromic UCLP children in Bangladeshi population.

3. There is no difference between the tooth size (MD) on the cleft and non-cleft sides of the maxilla among male and female non-syndromic UCLP children in Pakistani population.
4. There is no association between tooth size (MD) of the cleft and non-cleft sides of the maxilla and gender and races in non-syndromic UCLP children among the three different populations.

CHAPTER 2

LITERATURE REVIW

2.1 Definition of CLP

A birth defect characterised by one or more clefts in the upper lip resulting from failure of the embryonic parts of the lip to unite termed as cleft lip (CL). On the other hand, a congenital fissure of the roof of the mouth due to a failure of the palatal shelves to come fully together termed as cleft palate (CP). When CL associated with CP termed CLP (Medical Dictionary - Merriam-Webster).

2.2 History of Cleft

CL or CP or CLP are so far the most common of the major congenital facial deformities in human. It is present at birth and may affect the lip, alveolus, hard palate and soft palate in the oral cavity.

The features of CLP ranged in severity, from a small notch in the superficial vermillion border of the lip to a larger cleft extending into the root of the mouth and the nose (Baxter and Shroff, 2011). It can occur in combination or in an isolated manner. Clinically, CLP can be syndromic or non-syndromic. When it is associated with other malformations (usually two or more) in recognizable patterns, it is classified as ‘syndromic ‘CLP (Wong and Hagg, 2004). If it occurs as an isolated defect or no syndrome can be identified, the term ‘non-syndromic ‘CLP is used (Wong and Hagg, 2004).

Historically, although there are no proof and evidences in early description of the clinical pictures or treatments on orofacial cleft, it was believed that the condition had already existed since mankind. History reveals that these unfortunate individuals used to be killed after birth in some culture (Bill et al., 2006).

In 2002, Sandberg and co-workers conducted a study on neonatal CL and CP repair and they found that surgical CL repair has been reported as early as 390 AD in China (Sandberg et al., 2002). In 1816, the surgical treatment of CP was first described by Carl Ferdinand Graefe (Bill et al., 2006) where he refreshed the cleft edges and approximated them using a needle. Other famous surgeon such as Philibert Roux in 1819 and a French dentist, Johann Dieffenbach in 1826 also contributed to this technique (Bill et al., 2006). However, the basic principle of morphological layered closure of the hard and soft palate which was first proposed by Bernhard von Langenbeck in 1861 and Victor Veau in 1931 is still accepted until now (Bill et al., 2006).

2.3 Incidence of CLP

Orofacial clefts are known to be the most common craniofacial defects and one of the most common structural birth defects. These clefts involve the CL or/and CP or isolated clefts of the palate (Mossey and Little, 2002). According to Murray (1997), CLP has been extensively documented as one of the highest occurring hereditary orofacial clefts. It has also been deemed as the most common non-syndromic cranio-facial defect (Cardoso et al., 2013) and the second most common general birth defect (Strong and Buckmiller, 2001).

Incidence is the number of new cases of a disorder or condition identified in a specific time period. Prevalence is the number of individuals who are living with the disorder or condition in a given time period. Multitude epidemiologic studies have been carried out on the incidence and prevalence of CL, CP and CLP worldwide and reported outcome varies between racial groups, type of cleft and sex. Epidemiological estimates of orofacial clefts vary substantially on the basis of a variety of factors, including the sample population, the surveillance methodology, and the clinical classification (International Perinatal Database of Typical Oral Clefts [IPDTOC] Working Group, 2011).

Worldwide, orofacial clefts in any form (i.e., CL, CP or CLP) occur in about one in every 700 live births (World Health Organization [WHO], 2001). Significant heterogeneity among different ethnic group have been reported (Freni and Zapisek, 1991; Schutte and Murray, 1999). An overall incidence ratio of approximately 1.30:1000 among Asian population (both syndromic and non-syndromic) has been published (Cooper et al., 2006).

The incidence reported for several populations are as follows in non-syndromic clefts i.e 1.41:1000 in Japanese, 1.21:1000 in Chinese and 1.25:1000 in other Asian populations (Cooper et al., 2006), 2.1:1000 in African native population (Akintububo et al., 2014), 1.06:1000 in Iran (Kianifar et al., 2015), 0.98:1000 in Indian population (Kharbanda et al., 2014) and 0.34-2.29:1000 on the variety of Caucasian populations (Freni and Zapisek, 1991; Schutte and Murray, 1999; Mossey et al., 2009).

CLP is the second most birth anomalies among newborns in Malaysia after the cardiovascular anomalies. A prevalence rate in Malaysia was 1 per 941 live births reported by Shah et al. (2015). The prevalence in Pakistan is approximately 1 per 523 live births (Elahi et al., 2004). Only one survey was found in literature in 2013 (Ferdous et al., 2013) reported 3.9:1000 live births where more than 5000 CLP patients are born every year in Bangladesh.

Overall, higher rates have been reported in Asians and American Indians (one in 500 births), and lower rates have been reported in African-derived populations (one in 2,500 births) (Dixon et al., 2011). CP is more frequently found in females than in males, at a ratio of 2:1. In contrast, there is a 2:1 male-to-female ratio for CL with or without CP (Mossey et al., 2009).

2.4 Embryology of CLP

CLP is congenital anomalies of lip and palate which ensues during the 1st 3 months of pregnancy. When both sides of upper lip fail to fuse together in the 5/6 weeks of fetal development results to cleft lip. Similarly cleft palate occurs during 8 to12 weeks of fetal development due to failure of formation of roof of the mouth entirely (Langman and Sadler, 2004).

2.4.1 Formation of Upper Lip

During 6th to 7th week of embryonic development, maxillary prominences increase in size, as illustrated in **Figure 2.1A**. These prominences also migrate medially, compressing the mesial nasal prominences in a mesial direction, eventually resulting in fusion of both mesial nasal prominences, as illustrated in **Figure 2.1B**. (Magreni and May, 2015).

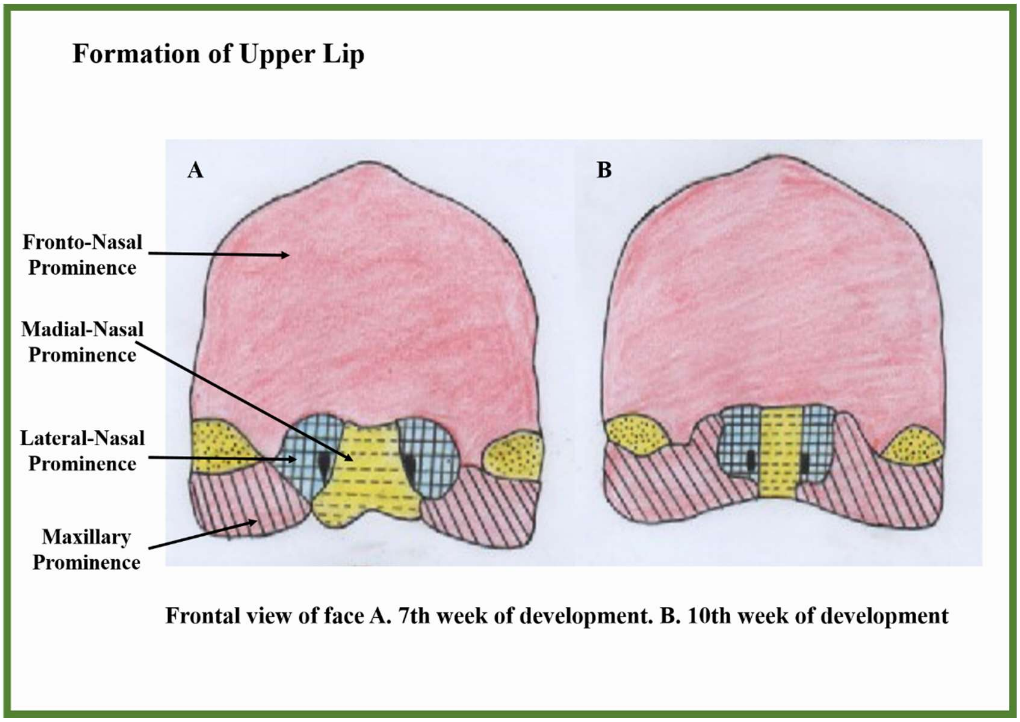


Figure 2.1 Formation of upper lip [redrawn from Sadler (2012)]

2.4.2 Formation of Inter-Maxillary Segment

The fusion of mesial nasal prominences occur at a deeper level, extending horizontally, leading to the formation of intermaxillary segment. This comprises philtrum of lip, upper jaw containing the four incisors and the primary palate as illustrated in **Figure 2.2**. (Magreni and May, 2015).

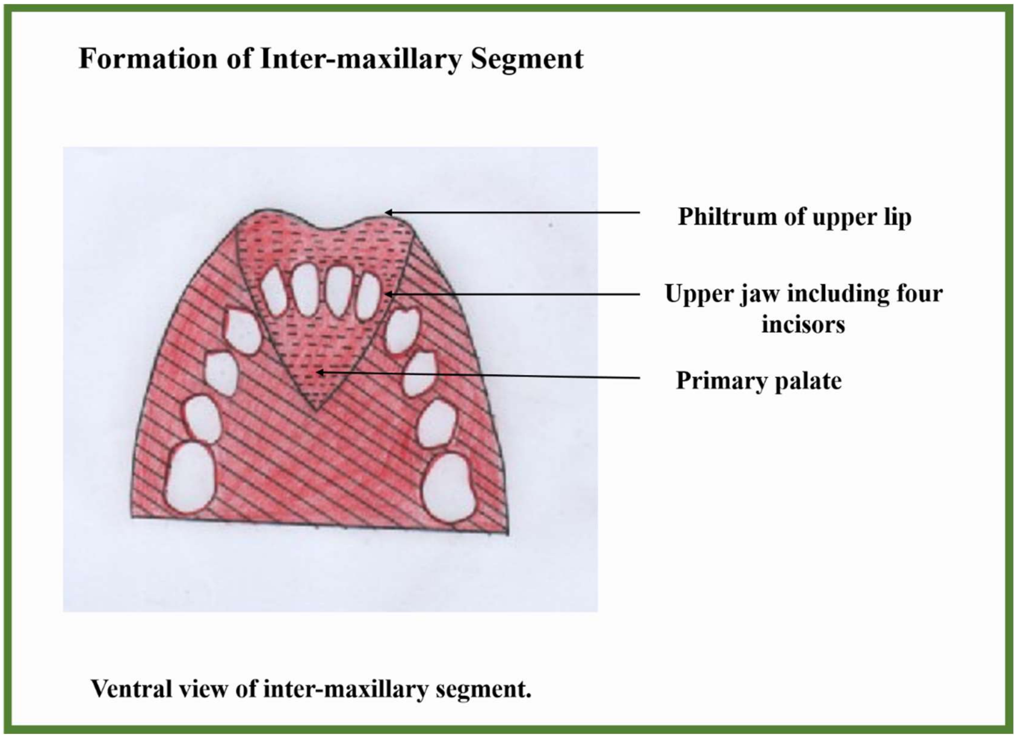


Figure 2.2 Formation of inter-maxillary segment [redrawn from Sadler (2012)]

2.4.3 Formation of Secondary Palate

At the same time, the secondary palate is mainly formed by the two shelf-like outgrowths of the maxillary prominences. During 6th week, the horizontal palatine shelves are directed obliquely downwards on either side of the tongue, as illustrated in **Figure 2.3 A**. (Magreni and May, 2015).

In the 7th week, the palatine shelves attain a horizontal position above the tongue and by the end of 10th week, start to fuse together to form secondary palate, as illustrated in Figure 2.3. Fusion of palatine shelves anteriorly results in the formation of incisive foramen. Incisive foramen is an embryological landmark demarcating the primary and the secondary palate. (**Figure 2.3 B**) (Magreni and May, 2015).

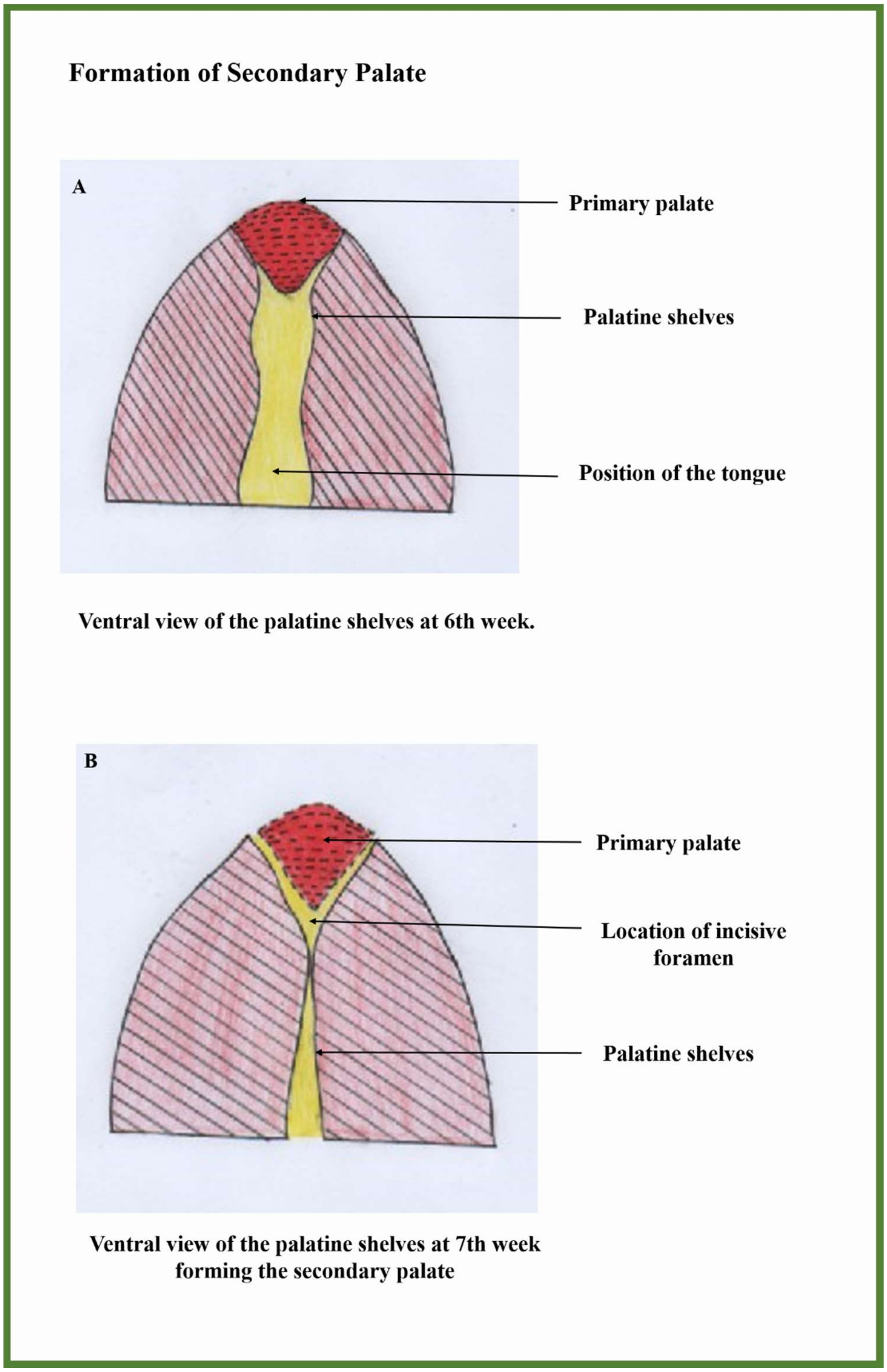


Figure 2.3 Formation of secondary palate [redrawn from Sadler (2012)]

2.4.4 Formation of CLP

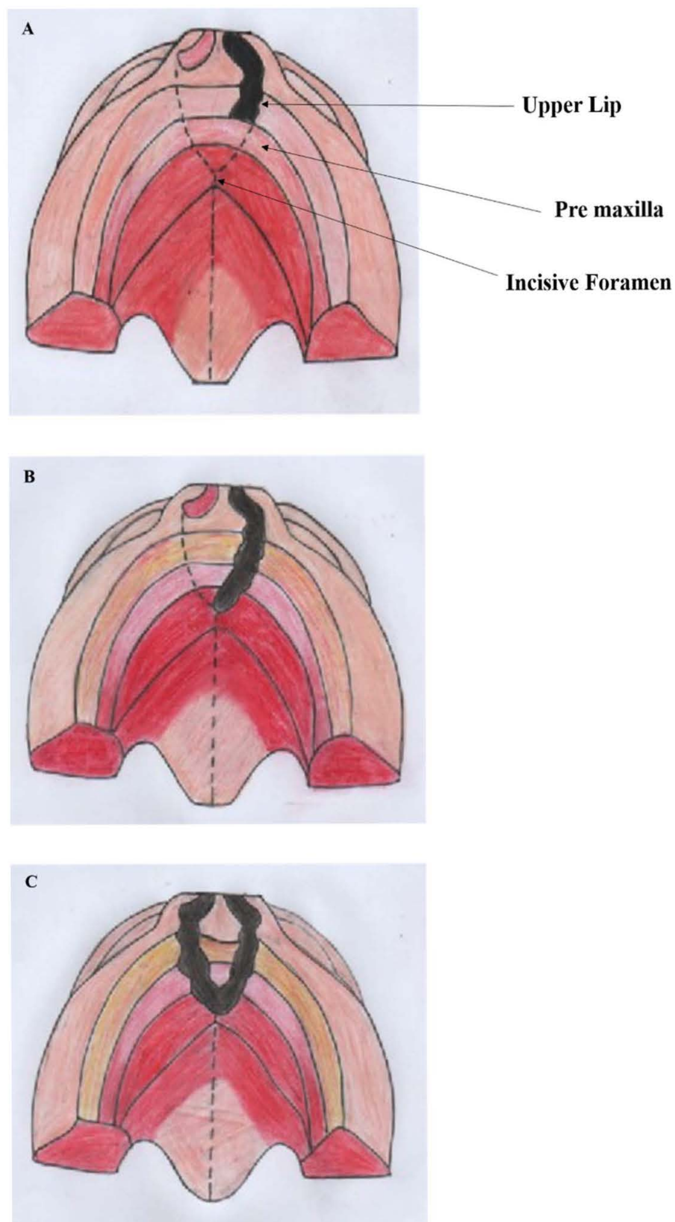
According to Bernheim et al. (2006), some basic terminology of CLP is given as follows

a) Failure of fusion of medial nasal prominences creates a gap or a split termed as cleft, which can extend from the lip up to the primary palate.
b) Failure of fusion of maxillary prominences also results in the formation of a cleft involving secondary palate. This phenomenon of cleft formation can occur in isolation or simultaneously i.e., involving lip, primary and secondary palate.
c) When failure is in isolation it will be termed as “isolated cleft lip” or “isolated cleft palate”. Whereas, in latter case “total cleft lip and palate” is formed.
d) When the failure of fusion is on one side it is termed as “unilateral” but if both sides are involved then the resulting cleft will be termed as “bilateral”.

2.4.4(a) Formation of Cleft of Lip and Primary Palate

CLP occurs due to the failure of fusion between the maxillary processes with the medial nasal prominences at the 5th week of fetal development which generally happens at the connection of central and lateral sides of upper lip on any or both sides. The appearance of the cleft may from slight notching on the lip to a more severe cleft extending up to incisive foramen. Detachment of the philtrum of upper lip from both sides and pre maxilla from the rest of maxillary arch occurs in the bilateral CL (Sadler, 2012).

There are different types of cleft depending on their cleft extension. Those extend up to the primary palate are termed as clefts of alveolus while those involve incisive foramen are termed as clefts of primary palate. Sometimes CL and alveolus may have bands of soft tissue folding across the two sides called ‘Simonart’s bands’ (Sadler, 2012).



2.4 (A) Unilateral cleft lip; (B) Unilateral cleft lip with alveolar involvement; (C) Bilateral cleft lip [redrawn from Sadler (2012)]

2.4.4(b) Formation of Cleft of Lip and Palate (Secondary Palate)

Development of secondary palate is arisen from the palatine shelves. On the 6th week the palatal shelves are vertically positioned at the side of tongue. On the 7th week, the shelves turn horizontal and migrate towards each other. This turning of shelves is made possible if the tongue move downward and accompanied by the growth of mandible. On the 8th week, the fusion of the palatal shelves started anteriorly which lasts until 12/17th week. If the fusion of medial nasal and maxillary prominences is failure, the CLP is protracted further down to the secondary palate and form CLP (Gritli-Linde, 2007; Marazita and Mooney, 2004).

2.4.4(c) Formation of Cleft Palate Only

Due to the failure of partial or total of fusion of the palatal shelves, the CP is formed. It can occur in many ways. CP is different in both embryologically and etiologically from the CLP. The extension of CP may vary from the soft palate alone to secondary hard palate up to incisive foramen. Cleft of soft palate is generally related to ‘Pierre Robin Syndrome’ with a dissimilar U shape while most of the CP are V shaped (Gritli-Linde, 2007; Marazita and Mooney, 2004).

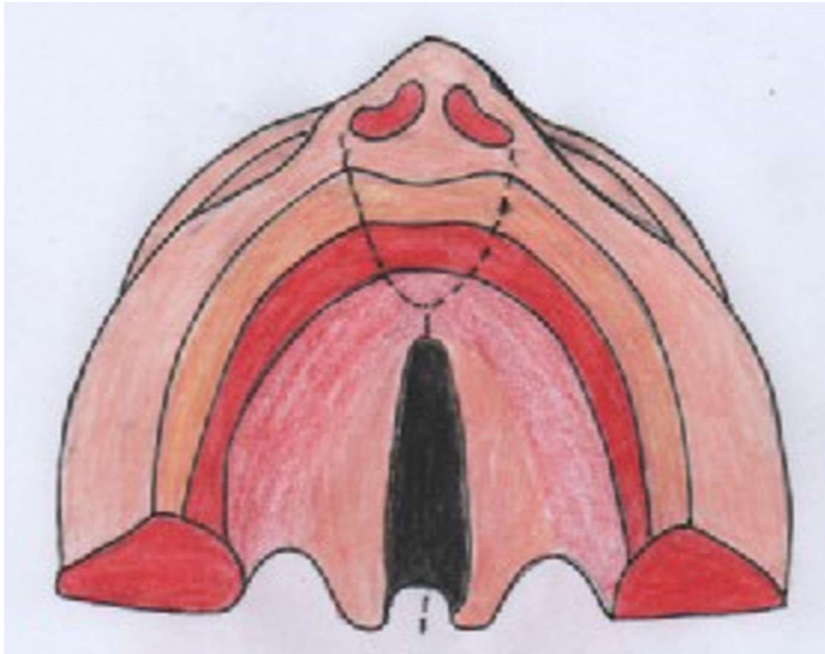


Figure 2.5 Cleft palate only [redrawn from Sadler (2012)]

2.5 Etiology of CLP

CLP is the congenital abnormalities of complex etiology. Many efforts have been made by many researchers in view to understand the etiology of these conditions thus it can help in the prediction of it occurrences and prevent it from occurring in the future but still there is no precise answer (Jones, 1993; Nguyen and Sullivan, 1993; Marazita and Mooney, 2004; Yaqoob et al., 2013; Burg et al., 2016). There are two established causes of CLP namely genetics and environmental influences regardless whether it is syndromic or non-syndromic. Studies of the etiology of non-syndromic clefts pivot on candidate genes associated with craniofacial development, genes influenced by environmental teratogens or deficiencies, and genes associated with syndromic clefts (Haque et al., 2015a; Murray, 2002). The subdivision into non-syndromic and syndromic is important because non-syndromic CLP rarely occur again in the same family (2-6%) and many syndromic cases have a strong association with specific genetic mutations with a higher inheritance risk (passed down with in the families). Non-syndromic CLP is a complex trait with multifactorial etiology, resulting from gene-gene and gene-environmental interactions (Murray, 2002). Identification of key genes contributing to the genesis of orofacial clefts will help in early diagnosis, disease prevention, or possibly developing adjunctive therapies.

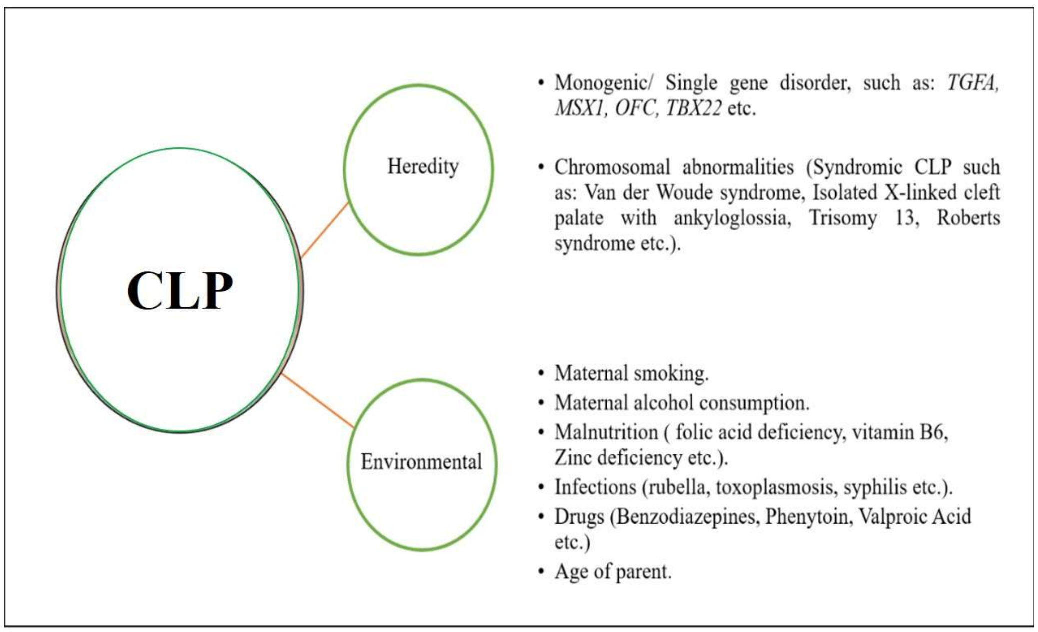


Figure 2.6 An overview of etiology of CLP (Klotz et al., 2010)

2.5.1 Heredity

Heredity is thought that one of the etiologic factors of CLP (Jones, 1993; Nguyen and Sullivan, 1993). Family history of CLP is in a higher risk of having a baby with a cleft in some way. A rate of recurrence of cleft condition is depend on a number of factors that are consistently constant in an individual family including the number of family members with clefts, their relationship to family members with clefts, race and sex of the affected individuals, and the type of cleft (Klotz et al., 2010).

The recurrence risk for first-degree relatives is about 3.3% for CLP and for isolated cleft palate it is 2%. Once parents have a child with a cleft the risk of having a second child with a cleft is about 2–5%, and after two affected children that risk rises to 9–12% (Gunnerbeck et al., 2014; Klotz et al., 2010; Tenconi et al., 1988). If more than one member of a family affected with cleft, the risk of recurrence of cleft is 14-15%. Unaffected siblings of an affected child also have 1% of recurrent risk of the having cleft baby (Gunnerbeck et al., 2014; Klotz et al., 2010; Tenconi et al., 1988). In twins with CLP and those with CP, the concordance is far greater for monozygotic twins than for dizygotic twins. In case of syndromic CLP, the risk of recurrence of cleft as high as 50%. Parents and young adults should be counseled appropriately by a geneticist so that they are in a better position to make decisions about future pregnancies (Gunnerbeck et al., 2014; Klotz et al., 2010; Tenconi et al., 1988).

Table 2.1 Risk of recurrence of cleft (Klotz et al., 2010; Murray, 2002)

	Risk for future children
1. Unaffected parents with one affected child	CLP: 4.4%
	CP: 2.5%
2. One affected parent	CLP: 3.2%
	CP: 6.8 %
3. One affected parent with one affected child	CLP: 15.8%
	CP: 14.9 %

2.5.1(a) Genes Involvement in CLP

The involvement of genetics in clefting was first described by Fogh-Andersen in year 1942 (Fogh-Andersen, 1942) and his theory was confirmed by a segregation analysis done by Mazarita and colleagues in year 1986 (Marazita et al., 1986).

The etiologies of CLP is multifaceted and occupy both major and minor genetic influences with erratic connections from environmental factors (Leslie and Marazita, 2013). Although many studies have investigated to find the genetic pattern of this malformation, there is still no precise answer. It is indispensable to highlight the gene involvement in CLP patients according to literature review.

Orofacial clefts have been associated with numerous genetic syndromes. Non-syndromic clefts are more common and their genetic etiology has been attributed to a single-gene locus mutation at one time or involving multiple sites (Murray, 2002).

To measure the genetic influence and strength of hereditary involvement on occurrence of clefts, concordance rates are assessed. A range of 40-60% in monozygotic twins was quoted in previous studies (Jones, 1993; Nguyen and Sullivan, 1993; Marazita and Mooney, 2004) and 5% in dizygotic twins (Funato and Nakamura, 2017; Leslie and Marazita, 2013; Murray, 2002). A 100% concordance rate is essential to declare genetic mutation as the sole cause of orofacial cleft (Murray, 2002).

The most recent estimates suggest that anywhere from three to 14 genes contribute to CLP. Candidate genes and loci responsible for non-syndromic CLP have been identified on chromosomes 1, 2, 4, 6, 11, 14, 17, and 19. Two genes IRF6 and

MSX-1 now seem to explain about 15% of non-syndromic CLP (Funato and Nakamura, 2017; Leslie and Marazita, 2013).

Mutations in IRF6 lead to Van der Woude and popliteal pterygium syndromes. Mutations in other genes e.g. TBX22, FGFR1, and P63, also contribute to syndromic clefts. Aberrant transforming growth factor beta-3 (TGF-β3) signaling plays a role in the pathogenesis of cleft palate (Kohli and Kohli, 2012).

Syndromic oral clefts may occur as part of a Mendelian disorder (i.e., resulting from a single gene defect) (Kirschner and LaRossa, 2000). It may arise from a chromosomal abnormality as part of a syndrome associated with a known teratogen; or as part of an uncharacterized syndrome (Kirschner and LaRossa, 2000).

Syndromes with the phenotype expression of oral clefts have become an important tool for elucidating the complex genetics of non-syndromic oral clefts. **Table 2.2** represents some major syndromes associated with CLP.

Table 2.2 Some major syndromes associated with CLP (Batra et al., 2003)

	Syndrome
Autosomal dominant	• Van der Woude syndrome (lip pits with cleft lip/palate) • EEC syndrome (ectrodactyl, ectodermal dysplasia and clefting) • Hereditary artho-ophthalmopathy (Stickler syndrome) • Larsen syndrome (originally thought to be recessive) • Retinal detachment, myopia and cleft palate (Marshall syndrome) • Sondyloepiphyseal dysplasia congenital
Autosomal recessive	• Chondrodysplasia punctata (Conradi syndrome) • Diastrophic dwarfism • Smith-Lemli-Opitz syndrome • Meckel syndrome • Orofaciodigital syndrome, type II • Fryns syndrome (with diaphragmatic hernia, limb and facial anomalies) • Roberts syndrome • Velocardiofacial (Shprintzen) syndrome
X-linked	• Orofaciodigital syndrome, type I (dominant, lethal in male) • Otopalatogidital syndrome

	• Isolated X-linked cleft palate with ankyloglossia
Chromosal	• Trisomy 13 • Trisomy 18 • Chromosome 18 deletions • Various other autosomal abnormalities
Non-medelian	• Peirre Robin sequence Clefting with • congenital heart disease • De Lange syndrome

Various researches have been done to find a genetic linkage and researchers found that the occurrence of clefts is influenced by various loci. The findings have been briefly summarised in **Table 2.3**.

Table 2.3 Summary of association of gene from previous studies

Author & Year	Gene	Loci/Locus	Association
Shaw et al., 1998; Mills et al., 1999; Passos-Bueno and Steman, 1999; Shaw et al., 1999; Blanton et al., 2000; Wyszynski and Diehl, 2000; Martinelli et al., 2001a; Martinelli et al., 2001b; Vieira et al., 2005; Chevrier et al., 2007	*SKI/MTHFR*	1p36	Found
Lidral et al., 1997; Tanabe et al., 2000	*TGFB2*	1q41	Not Found
Ardinger et al., 1989; Chenevix-Trench et al., 1992; Holder et al., 1992; Vintiner et al., 1992; Field et al., 1993; Shiang et al., 1993; Feng et al., 1994; Jara et al., 1995; Lidral et al., 1997; Maestri et al., 1997; Mitchell, 1997; Pezzetti et al., 1998; Christensen et al., 1999; Machida et al., 1999; Tanabe et al., 2000; Zeiger et al., 2005; Vieira, 2006	*TGFA*	2p13	Not Found
Lidral et al., 1997; Lidral et al., 1998; Beaty et al., 2001; Beaty et al., 2002	*MSX1*	4p16	Found
Mitchell et al., 1995	*MSX1*	4q31	Found
Scapoli et al., 1997; Pezzetti et al., 1998	*MSX1*	6p23	Found
Sözen et al., 2001	*PVRL1*	11q23	Not Found
Lidral et al., 1997; Lidral et al., 1998; Tanabe et al., 2000; Beaty et al., 2001; Beaty et al., 2002	*TGFB3*	14q24	Not Found
Tanabe et al., 2000; Scapoli et al., 2002	*GABRB3*	15q11	Not Found
Chenevix-Trench et al., 1992; Shaw et al., 1993	*RARA*	17q21	Found

Shaw et al., 1993; Stein et al., 1995	*BCL3*	19q13	Found
Braybrook et al., 2002	*TBX22*	Xq21	
Jugessur et al., 2003	*MSX1*	4p16	Found
	TGFA	2p13	Found
	TGFB3	14q24	Not Found
Zuchero et al., 2004	*IRF6*	1q32.3q41	Found
Marcano et al., 2004	*TBX22*		Found
Carinci et al., 2007	*OFC2*	2p13	Found
	OFC3	19q13.2	
	OFC4	4q21-q31	
	TGFB3	14q24	
	RARA	17q21.1	
Rajion and Alwi, 2007	*TGFA*	2p13	Found
	TGFB2	1q41	Not found
	TGFB3	14q24	Found
	MSX1	4q25	Found
	MTHFR	1q36	Found
	RARA	17q21-q24	Found
Shprintzen, 2008	*TBX1*	22q11.2	Found
Tudose and Bara, 2008	*OFC2-TGFA*	2p13	Found
	OFC1	6p24.3	Not found
Singh et al., 2011	*TGFB3*	14q24	Not found
Kohli and Kohli, 2012	*PVRL1*	11q23	Found
	TGFA	2p13	Found
	MSX1	4p26	Found
	MTHFR	1p36	Found
	TGFB3	14q24	Found

2.5.1(a)(i) Transforming Growth Factor-Alpha (TGFA)

TGFA is a secretory protein that binds to the epidermal growth factor receptor and has been localised to palatal epithelium prior to and during the time of palatal closure (Dixon et al., 1991). It is strongly expressed in the medial edge epithelium of fusing palatal shelves and promotes extracellular matrix biosynthesis

(Dixon and Ferguson, 1992). It was one of the first gene reported and associated with non-syndromic CLP (Ardinger et al., 1989; Dixon et al., 1991). Their finding is strongly supported by studies done by few researchers (Holder et al., 1992; Vintiner et al., 1992; Hwang et al., 1995). Vieira (2006), proposed that TGFA was probably a genetic modifier in clefting in humans which was consistent with the oligogenic model suggested for non-syndromic oral clefts. In addition, Machida and co-workers (1999) found five mutations of the sequenced TGFA gene in a group of non-syndromic cleft lip and palate patients that could be the etiology to orofacial cleft.

In addition, there is a significant interaction between TGFA gene and the environment factors such as maternal smoking and maternal periconceptional vitamin use (Shaw et al., 1996; Shaw et al., 1998; Zeiger et al., 2005; Sull et al., 2009). Maternal smoking among infants with uncommon TGFA phenotype could increase the risk of cleft palate by six to eight times (Hwang et al., 1995) and CLP by two times (Shaw et al., 1996). The relative risk for CLP increased by three to eight times if the multivitamins were not consumed by the mother during the first trimester of pregnancy with the baby carrying the A2 TGFA genotype (Shaw et al., 1998).

2.5.1(a)(ii) Transforming Growth Factor-Beta 3 (TGFB3)

Lack of functional gene encoding transforming growth factor-beta 3 (TGFβ3) in mice exhibited cleft palate because of defective adhesion of opposing palatal shelves (Proetzel et al., 1995). Interestingly, Sun et al. (1998) showed that an exogenous application of TGFβ3 can induce palatal fusion in chicken naturally born with cleft palate. Besides, TGFβ3 signaling is also involved in sequential induction of cell cycle to medial edge epithelium of palatal shelves, cell migration and apoptosis at the advanced stages of palatal development (Ahmed et al., 2007). In humans, genetic variants in TGFβ3 was associated with non-syndromic cleft lip and palate in multiple and different populations (Lidral et al., 1998; Jugessur et al., 2003; Vieira et al., 2003; Reutter et al., 2008). To date, Kim and colleagues discovered a single-nucleotide polymorphism (SNP) of TGFβ3 increased the risk of cleft lip and palate by up to 16 times in Korean population (Kim et al., 2003).

2.5.1(a)(iii) Methylene Tetra Hydro Folate Reductase (MTHFR)

The association between folic acid deficiency and neural tube defects has well been established and the associated gene for MTHFR based on work on neural tube defects are widely reported (Trembath et al., 1999). 5, 10-MTHFR is an enzyme responsible for catalysing the conversion of 5, 10-methylenetetrahydrofolate into 5-methyl-tetrahydrofolate in the folate metabolism pathway (Wong and Hagg, 2004). The MTHFR C677T single-nucleotide polymorphism is an associated gene for MTHFR and it is thermally labile (Van der Put et al., 1995). It is considered a risk factor of neural tube defect (Van der Put et al., 1995). The risk of cleft lip and palate (non syndromic) in offspring increased by 4.6 times in the mother whose carrying MTHFR genotype (Prescott et al., 2002), and the risk of cleft lip and palate increased by 10 times in the periconceptional folic acid deficiency together with the presence of MTHFR C677T SNP in the mother's body (van Rooij et al., 2003).

2.5.1(a)(iv) Interferon Regulatory Factor-6 (IRF6)

Interferon regulatory factor-6 (IRF6) is one of the candidate genes that consider contributing to orofacial clefting. It is the only gene that has shown a consistent evidence of association across multiple studies (Zuchero et al., 2004; Ghassibe et al., 2005; Scapoli et al., 2005; Park et al., 2007; Rahimov et al., 2008).

Mutation in IRF6 was first identified as an aetiology in the autosomal dominant clefting disorder known as Van der Woude's syndrome (VDWS) and popliteal pterygium syndrome (PPS) (Kondo et al., 2002). However, the subsequent studies showed that IRF6 was also associated with non syndromic cleft lip and palate in multiple populations (Zucchero et al., 2004; Blanton et al., 2005; Ghassibe et al., 2005; Scapoli et al., 2005; Srichomthong et al., 2005; Jugessur et al., 2008; Huang et al., 2009). IRF6 is suggested as a key determinant of the keratinocyte proliferation-differentiation switch based on the animal experiments (Ingraham et al., 2006; Richardson et al., 2006). IRF6 in a mutant mice exhibit a hyper-proliferative epidermis that fails to undergo terminal differentiation, which leads to multiple epithelial adhesions that can occlude the oral cavity and result in cleft palate (Ingraham et al., 2006; Richardson et al., 2006). Another subsequent study indicated that IRF6 also has a key role in the formation of oral periderm, spatiotemporal regulation which is essential for ensuring appropriate palatal adhesion (Richardson et al., 2006).

2.5.1(a)(v) Muscle-Segment Homeobox 1 (MSX1)

Muscle-segment homeobox 1 (MSX1) is a downstream target of bone morphogenetic protein (BMP) signaling in a number of embryonic tissues and MSX1 is necessary for expression of BMP4 and/or BMP2 (Zhang et al., 2002). Ablation of MSX1 gene in mice develop a complete cleft of the secondary palate and tooth agenesis (Satokata and Maas, 1994), but in humans, MSX1 mutation was first shown to cause an autosomal dominant form of tooth agenesis (Vastardis et al., 1996). Subsequently, van den Boogaard and co-workers did a study on extended Dutch family with a common pattern of tooth agenesis together with a mixture of cleft lip with or without cleft palate and cleft palate alone (van den Boogaard et al., 2000). Direct sequencing of MSX1 revealed a disease-causing mutation suggesting an important role for MSX1 in human clefting (van den Boogaard et al., 2000). Recently, Jezewski et al performed a large scale sequence analysis of MSX1 on 917 cleft lip and palate patients and mutations identified in 16 patients with cleft lip with or without cleft palate or cleft palate alone (Jezewski et al., 2003). This could be an evidence that this gene could be involved in both forms of cleft (Jezewski et al., 2003). He also estimated that MSX1 mutations in humans contributed about 2% of all non-syndromic cleft lip and palate cases (Jezewski et al., 2003). The risk of cleft palate will increase by 9.7 times in the combination of the rare variants of TGFA and MSX1 and this shows the significance of gene-gene interaction in the aetiology of non-syndromic cleft lip and palate (Jugessur et al., 2003).

2.5.1(a)(vi) T-Box Transcription Factor-22 (TBX22)

The X-linked cleft palate (CPX) which is usually associated with ankyloglossia (tongue tie) is caused by function-impairing mutations in the T-box DNA-binding domain of the transcription factor gene T-box transcription factor-22 (TBX22) (Braybrook et al., 2001). TBX22 expression is concentrated at the palatal shelves and the base of tongue. Animal experiments revealed that the expression of TBX22 was highly restricted to the palatal shelves just before the elevation to the horizontal position, whereas at the base of the tongue corresponding to the frenum (Braybrook et al., 2002). These gene’s expression pattern closely coincide with the clinical presentation in CPX. The involvement of TBX22 in non-syndromic cleft lip and palate has been identified by a genome-wide linkage analysis whereby they identified a susceptibility locus in the vicinity of TBX22, suggesting that the linkage signal may originate from this gene (Prescott et al., 2000).

2.5.1(a)(vii) SMT3 suppressor of MIF Two 3 Homolog 1 (SUMO1)

SMT3 suppressor of Mif Two 3 Homolog 1 (SUMO1) is a 101-amino acid polypeptide involved in post translational modification of a variety of proteins (Rahimov et al., 2012). In isolated unilateral cleft lip palate patients, SUMO1 haploinsufficiency was identified as a result from a balanced reciprocal translocation of the gene (Alkuraya et al., 2006). In animal experiments, SUMO1 was expressed in the upper lip, primary palate and medial edge epithelium (MEE) of the secondary palate and mice with a SUMO1 hypomorphic allele had a cleft palate (Alkuraya et al., 2006). Other genes which is near SUMO1 also considered as gene potentially implicated in clefting however a microdeletion encompassing SUMO1 in cleft patients supports its role in human clefting (Shi et al., 2009). Genetic association between SUMO1 and nonsyndromic cleft lip and palate have been reported in two populations, China (Song et al., 2008) and Ireland (Carter et al., 2010).

2.5.1(a)(viii) Special AT-Rich Sequence Binding Protein 2 (SATB2)

Special AT-Rich sequence binding protein 2 (SATB2) is a DNA-binding proteins that specifically bind to nuclear matrix-attachment regions to regulate gene transcription in a tissue specific manner through chromatin remodeling (Britanova et al., 2005). It is located at chromosome 2q32-33. FitzPatrick et al. (2003) had discovered the role of SATB2 in orofacial clefting after they performed a fine mapping of translocation breakpoints in the 2q32 to q33 region in two unrealated patients with cleft palate. In animal experiments, SATB2 is strongly expressed in the developing palate and it is 99.6% identical to the human SATB2 at the protein level (FitzPatrick et al., 2003). Mice that have lacking of functional gene of SATB2 were reported to have severe craniofacial deformities and malformations (Britanova et al., 2006; Dobreva et al., 2006). Beaty et al in their study had found an association between SATB2 and non-syndromic cleft lip and palate in two Asian populations (Beaty et al., 2002).

2.5.2 Environmental Factors

Environmental factors, lifestyle, health conditions, and socioeconomic background have been extensively documented as having a significant role in increasing or decreasing the risk of occurrence of clefts. The involvement of environmental component in clefting was recognized when Warkany et al. (1943) found that there was a significant association CP and nutritional deficiency. However, various environmental factors contribute to the etiology of facial clefts, these include cigarette smoking, folic acid deficiency during the peri-conceptional period, maternal exposure to alcohol, teratogenic medications such as retinoids, corticosteroids, and anticonvulsants (phenytoin and valproic acid). Co-sanguineous marriages, maternal diabetes, and obesity have also been found to play a vital role and increase the risk of orofacial clefts (Mossey et al., 2009). Maternal viral infections caused by rubella and varicella have also shown evidence of causing orofacial clefts (Park et al., 2007). Potential factors imparting effect on CLP have been briefly tabulated in **Table 2.4**.

Table 2.4 A summary of lifestyle and environmental risks of CLP

Author & Year	Factors	Outcome
Safra and Oakley, 1975; Saxén and Saxén, 1975	Benzodiazepines	A possible risk has been associated in two studies.
Dravet et al., 1992; Abrishamchian et al., 1994; Shaw et al., 1995)	Anticonvulsant drugs like, Diazepam, Phenytoin, Phenobarbital	A ten-fold increased risk of OFC has been associated with the use of Phenytoin.
Park-Wyllie et al., 2000	Corticosteroids	An estimated increased risk up to three-folds has been documented.
Willhite et al., 1985; Jones, 1993	Isotretinoin	Positive teratogenic effects on pregnant females and mice were detected.
Natsume et al., 2000	Sickness	Infections during pregnancy like influenza, rubella, and common cold were significantly high among mothers of affected cases.
Tolarova, 1982; Tolarova and Harris, 1995; Shaw et al., 1999; Johnson and Little, 2008	Multivitamin	Multivitamin supplementation has shown 25% reduction in occurrence risk of clefts.
Warkany and Nelson, 1940; Johnston and Millicovsky, 1985; Lammer et al., 1985; Khoury et al., 1987; Van den Eeden et al., 1990; Rothman et al., 1995; Shaw et al., 1996; Beaty et al., 1997; Croen et al., 1998; Mitchell et al., 2003; Little et al., 2004; Tamura et al., 2005; Honein et al., 2007	Smoking	According to various studies and meta-analyses, an occurrence risk of 2-20% has been associated. Although the negative effects of public smoking, pollution, and passive smoking have not been attributed.
Gordon and Shy, 1981; Kotch and Sulik, 1992; Cartwright and Smith, 1995; Rothman et al., 1995; Munger et al., 1996; Croen et al., 1998; Shaw	Alcohol	Depending upon consumption, high quantities of routine consumption during pregnancies have been associated with a higher risk of cleft occurrence. Moreover,

and Lammer, 1999; Shaw et al., 2003		prenatal ethanol exposure has been known to cause lysis of neural crest cells, which could result in gene alteration or mutation.
Munger et al., 2004	Vitamin B6 deficiency	In Asian populations, where polished rice is staple food, increased risk of OFC has been documented.
Tolarova, 1982; Johnston and Millicovsky, 1985; Tolarova and Harris, 1995; Czeizel et al., 1996; Jacobsson and Granström, 1997; Ulrich et al., 1999; Schubert et al., 2002	Folic Acid	Folic acid supplementation during initial four months of pregnancy was found to have a protective effect against OFC and in another study, high doses of maternal folic acid supplementation have shown increased occurrence risk as compared to low doses.
Sivaloganathan, 1972; Moosey and Little, 2002; Elahi et al., 2004	Socioeconomic status	A feeble association of low-income to increased occurrence risk has been discussed in few studies.
Gordon and Shy, 1981; Garcia, 1998; Lorente et al., 2000; Shaw et al., 2003	Exposure to organic solvents	Parental exposure due to occupation or environment has been associated with an inconsistent risk.

2.5.2(a) Smoking

The relationship between maternal smoking and CLP is significant and it can increase risk for CLP. A meta-analysis strongly support an odd ratio of 1.3 among offspring for having CLP of mothers who smoke (Little et al., 2004; Shi et al., 2007; Shi et al., 2008). Smoking may raise the possibility of genes in certain metabolic pathways which may have a role in the development of CLP, namely fetal glutathione s-transferase theta 1 (GSTT1) (van Rooij et al., 2001; Shi et al., 2007; Waltrick-Zambuzzi et al. 2015). Furthermore, van Rooij and co-workers found that the combination with smoking and GSTT1 could increase the risk of CLP with odd ratio

~4.9 (van Rooij et al., 2001). Beaty et al. (2002) reported the risk of CLP increased by 7.16 times in maternal smoking and infant with MSX1 genotype.

2.5.2(b) Alcohol Use

Heavy maternal drinking will cause foetal alcohol syndrome. Apart from that, it also will increase the risk of CLP for the baby. Maternal drinking will increase risk of CLP from 1.5 to 4.7 times in a dose dependent manner (Munger et al., 1996). This result was supported by Shaw and Lammer who reported that mothers who consumed more than five drinks per occasion had a 3.4 times the risk of CLP developing in their offspring (Shaw and Lammer, 1999). However, low level of alcohol consumption did not seem to increase the risk of orofacial clefts (Natsume et al., 2000). Subsequently, Boyles et al. (2009) reported that heavy alcohol intake was associated with risk of clefts only if either the mothers or the babies carried the slow-metabolising alcohol dehydrogenase gene variant (ADH1C). Genetic susceptibility in detoxification genes increase vulnerability of the fetus to alcohol-related orofacial clefts (Wei et al., 2019; Shi et al., 2007; Shi et al., 2008).

2.5.2(c) Multivitamins Use

The risk of CLP could be tripled if the vitamin supplements were not taken during early pregnancy (Shaw et al., 2002; Brooklyin et al., 2014; Waltrick-Zambuzzi et al., 2015). In a meta-analysis, multivitamins use was associated with a 25% reduction in birth prevalence of orofacial clefts (Johnson and Little, 2008). Data suggest that a possible interaction between maternal hyperthermia during pregnancy and the use of vitamin supplements will diminish the increased risk for orofacial clefts associated with hyperthermia (Botto et al., 2002).

2.5.2(d) Folic Acid Deficiency

Folic acid deficiency in animal experiments can cause clefts (Asling et al., 1960). It is also associated with increased risk of CLP in humans (Hernandez et al., 2000; Burg et al., 2016). The true mechanisms in human cleft disorders are uncertain however Bliek et al. (2008) reported that folate deficiency disturbs normal cell development. In addition, the risk of CLP increased in folic acid deficiency with the background of TGFA Taq1 C2 genotype in humans (Jugessur et al., 2003). With the relatively frequent number and mixed evidence of observational studies publicized that high dose of supplementary intake of folic acid (10mg/d) in the first month of pregnancy could reduce about 50% the risk of cleft palate only and 65% the risk of CLP significantly (Badovinac et al., 2007; Wilcox et al., 2007).

2.5.2(e) Vitamin B6 Deficiency

Vitamin B6 deficiency, increased serum concentration of homocysteine in blood and zinc deficiency also associated with increased risk of orofacial clefts. Low level of vitamin B6 was found in Netherland populations (Wong et al., 1999) and in Philippines populations (Munger et al., 2004) and it was associated with orofacial clefts in that populations. Among Asian, vitamin B6 deficiency is common due to high intake of polished rice and they seem to have high rate of CL, CP, and CLP (Munger et al., 2004).

2.5.2(f) Zinc Deficiency

Studies have reported that high concentration of homocysteine found in mother's blood of infants with CL, CP and CLP (Wong et al., 1999; von Rooij et al., 2003; Burg et al. 2016). Besides that, zinc is also essential for foetal development. In animal experiments, zinc deficiency can cause CP and other malformations (Warkany and Petering, 1972). In Netherland population, researchers found low concentration of zinc in the mother's blood of children with CL, CP and CLP (Krapels et al., 2004) as well as the same result in the Philippines population (Tamura et al., 2005).

2.5.2(g) Teratogenic Substance

There are several teratogens that are responsible for birth defect, that upswing of risk of CLP. Medications like retinoids, anti-convulsants & steroids can cause CLP. Isotretinoin induced facial malformations in humans, include rudimentary external ears, absent or imperforate auditory canals, deformed and small skull, CP, depressed midface, and anomalies of the brain, jaw, and heart (Buser and Pohl, 2015; Lupo et al., 2010). Use of anticonvulsants is associated with an increased risk of congenital defects. Epileptic mothers managed with a multidrug anticonvulsant regime had a 10-fold increased risk of infants with CLP when compared to non-epileptic mothers. Consumption of steroids during the first 3 months of pregnancy has been associated with clefts, increasing the risk 3-5 times. Study revealed that infection of rubella, toxoplasmosis, and syphilis in the pregnant mother are somehow associated with cleft in the coming baby (Park-Wyllie et al., 2000). The name of some drugs that induced cleft has been given in **Table 2.5**.

Table 2.5. Some drugs that induced cleft (Buser and Pohl, 2015; Lupo et al., 2010; Park-Wyllie et al., 2000)

Generic Name	Trade Name	Used in
Ondansetron	Zofran	Severe nausea after cancer treatments and surgical anesthesia.
Benzodiazepines	Valium (diazepam) Xanax (alprazolam) Ativan (lorazepam) Klonopin (clonazepam)	Anxiety, depression, insomnia, nausea and vomiting, panic attacks and seizures.
Phenytoin	Dilantin, Phenytek	Epilepsy.
Phenobarbital	Luminal	Epilepsy.
Valproic Acid	Depakote, Depakene, Stavzor, Depacon	Epilepsy, Bipolar disorder.
Carbamazepine	Tegretol, Carbatrol, Equitro, Epitol	Epilepsy, Bipolar disorder, Severe neurological pain.
Trimethadione	Tridione, Trimethadione	Epilepsy.
Corticosteroids	Cortisone, Prednisone, Hydrocortisone, Fluticasone	Skin rashes, Asthma, Rheumatoid arthritis
Mycophenolate Mofetil	CellCept	After kidney, liver and heart transplants.
Retinoids		Accutane, Claravis, Sotret, Amnesteem, Myorisan, Tegison
Antineoplastics		Cancer drugs, used in chemotherapy.
Selective Serotonin Reuptake Inhibitors (SSRI)	Paxil, Zoloft, Celexa, Prozac	Major depressive and anxiety disorders.
Penicillamine	Depen	Rheumatoid arthritis, Wilson's disease.

2.6 Classification of CLP

2.6.1 Basic Classification of Cleft Lip (CL)

CL is classified based on its location and severity (Allori et al. 2017). The classsification is follows

i) Unilateral cleft lip; which affects on one side of the lip.

ii) Bilateral cleft lip; which affects on both sides of the lip.

iii) Complete cleft lip; which extends to the nose.

iv) Incomplete cleft lip; which does not extend to the nose.

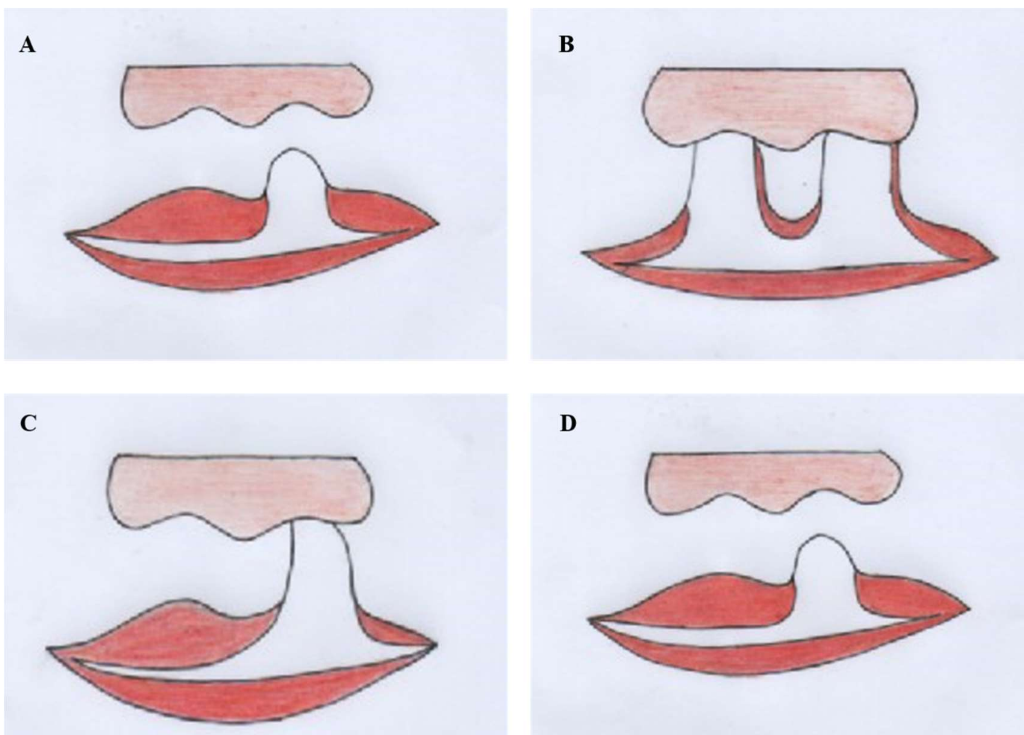


Figure 2.7 (A) Unilateral cleft lip; (B) Bilateral cleft lip; (C) Complete cleft lip; (D) Incomplete cleft lip (Redrawn from Bhalaji, 2012)

2.6.2 Basic Classification of Cleft Palate (CP)

CP is classified based on its location. If could affect the soft palate, hard palate or both (Allori et al. 2017). The classification is as follows

i) Cleft of soft palate.

ii) Cleft palate involving both hard and soft palate.

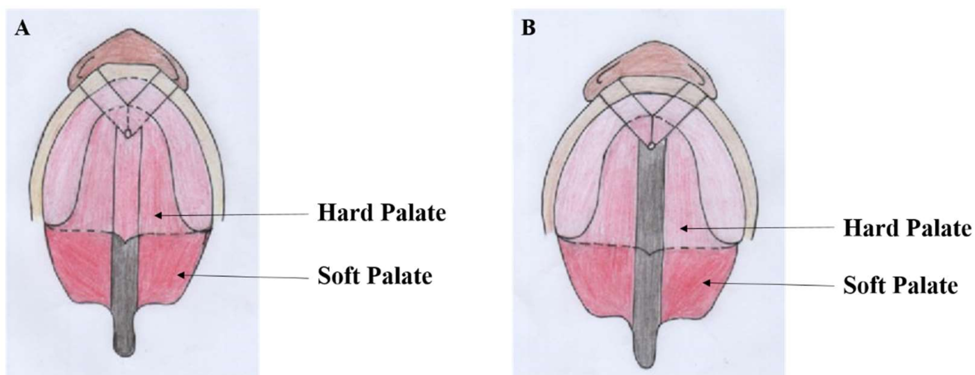


Figure 2.8 (A) Cleft of soft palate; (B) Cleft palate involving both hard and soft palate (Redrawn from Bhalaji, 2012)

From last few decades, several classifications are given by many authors (Bhalaji, 2012; Mitchel, 2007; Proffit et al., 2007; Gurkeerat, 2007). Most of those classifications were based on either morphology or embryology.

2.6.3 Overview of Classification of CLP

2.6.3(a) Davis and Ritchle Classification

The classification was established by Davis and Ritchle in 1922 (Bhalaji, 2012; Mitchel, 2007; Proffit et al., 2007; Gurkeerat, 2007). It was morphological classification; based on the position of the cleft in relation to the alveolar process. The classification was divided into three groups; group 1, group 2 and group 3 (**Figure 2.9**).

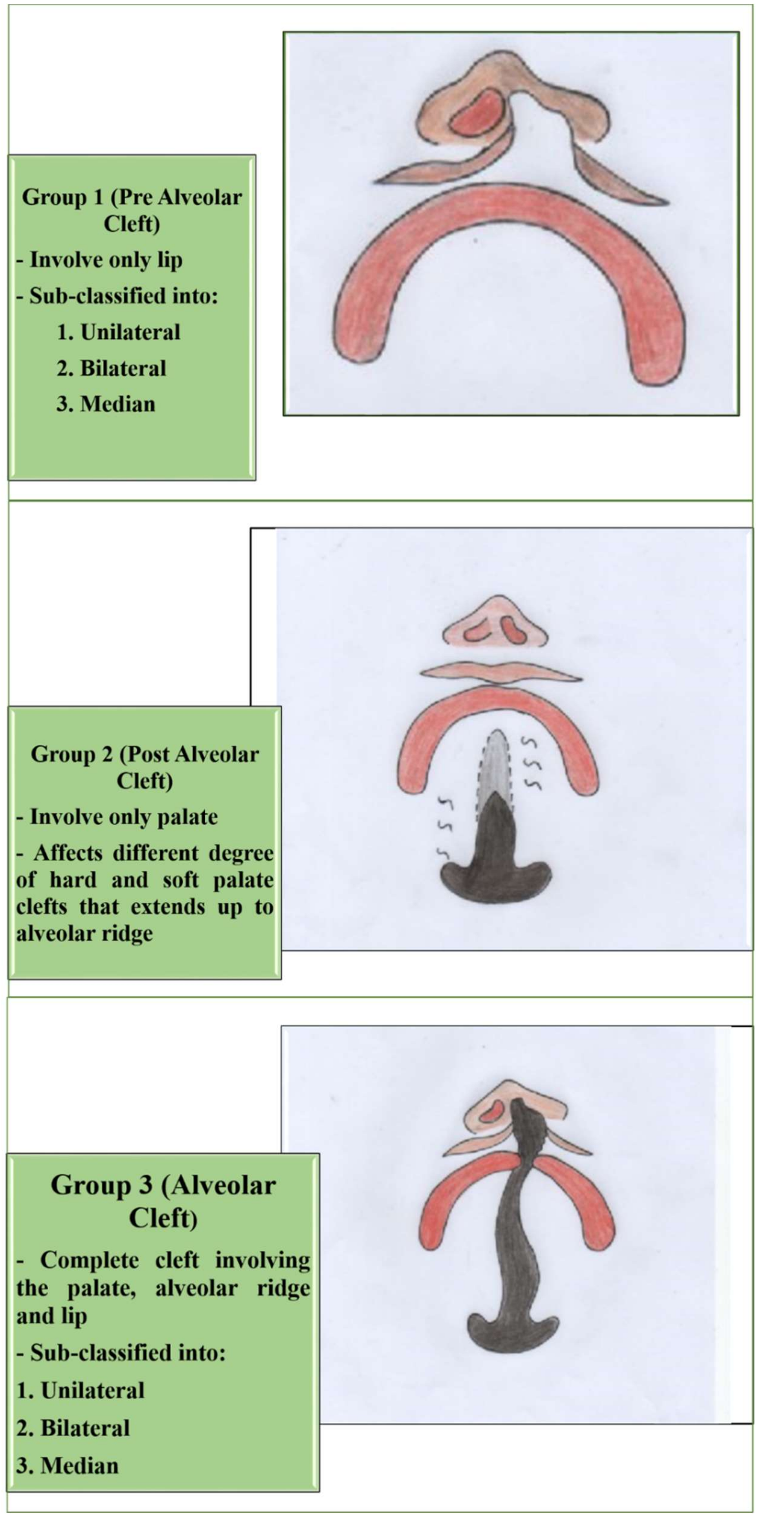


Figure 2.9 Davis and Ritchle classification (Redrawn from Bhalaji, 2012)

2.6.3(b) Veau's Classification

The classification was established by Veau in 1931 (Bhalaji, 2012; Mitchel, 2007; Proffit et al., 2007; Gurkeerat, 2007). It has classification for each CP (**Figure 2.10**) and CL (**Figure 2.11**)

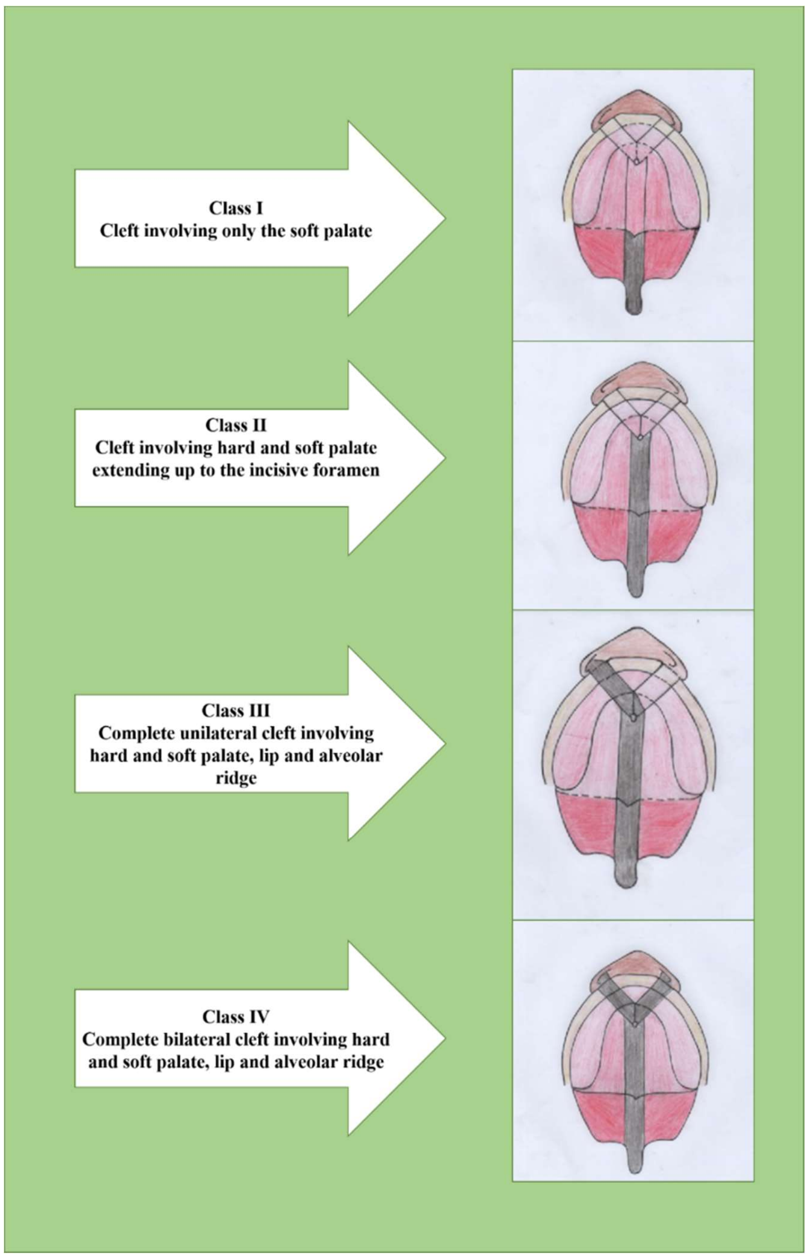


Figure 2.10 Veau's classification on cleft palate (Redrawn from Bhalaji, 2012)

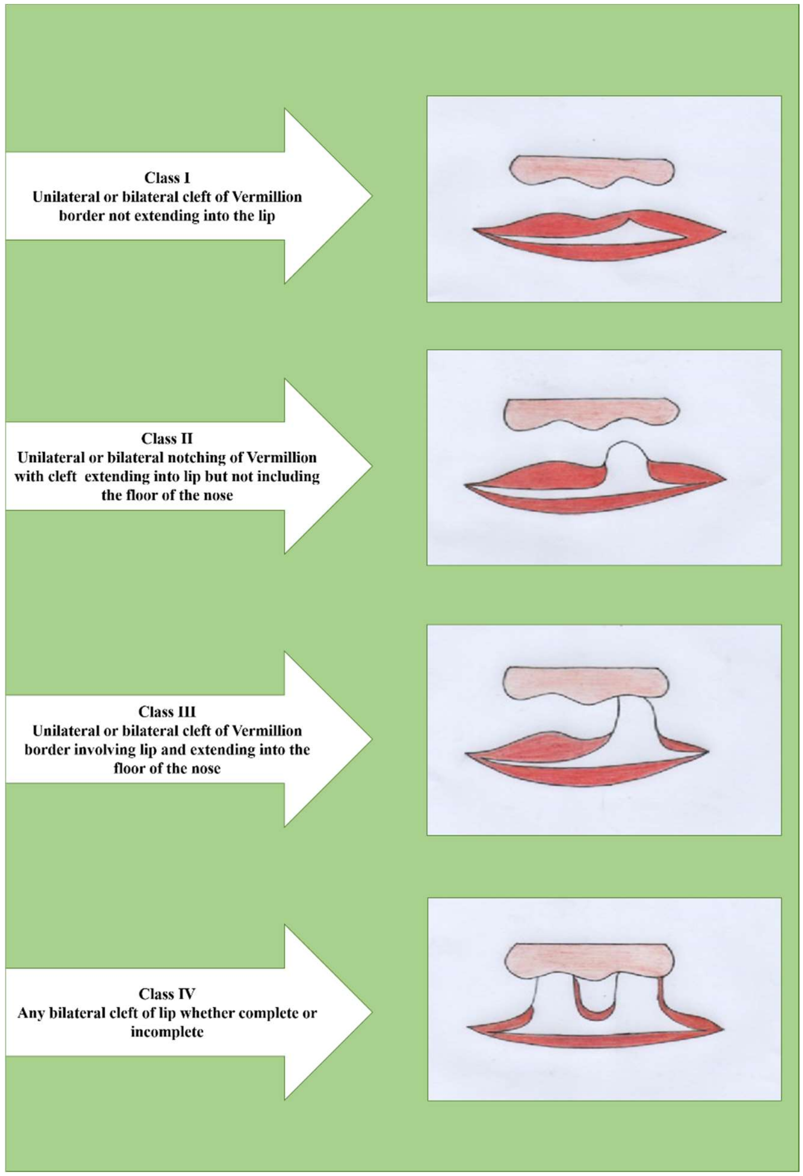


Figure 2.11 Veau's classification on cleft lip (Redrawn from Bhalaji, 2012)

2.6.3(c) Kernahan and Stark Classification

It is a symbolic classification; promoted by Kernahan and Stark. Incisive foramen is taken as reference point. The classification uses striped ‘Y’ that have number blocks. Each block represents a specific area of oral cavity. ‘Y’ logo are divided into three sections, representing the lip, the alveolus and the hard palate as far back as the incisive foramen (Proffit et al., 2007). (**Figure 2.12)**

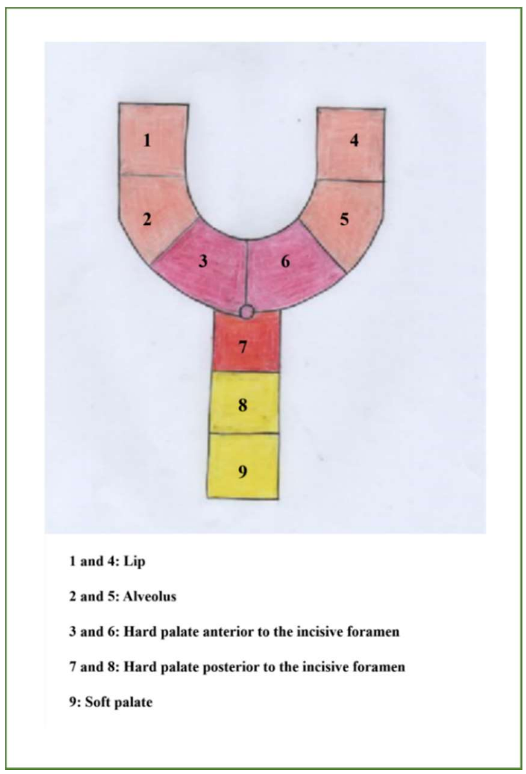


Figure 2.12 Kernahan and Stark classification (Redrawn from Proffit et al., 2007)

Example:

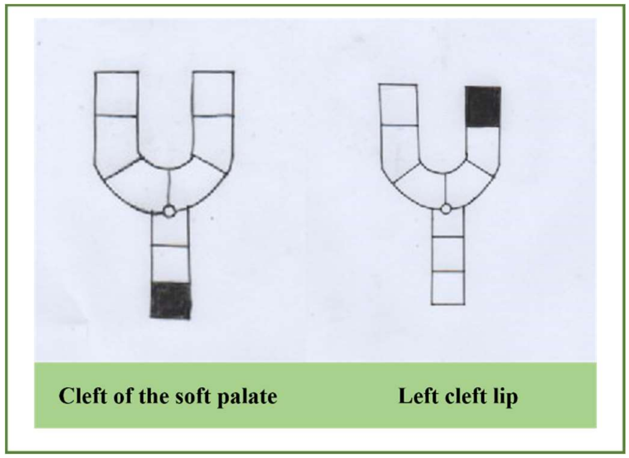


Figure 2.13 Example Kernahan and Stark classification (Redrawn Proffit et al., 2007)

2.6.3(d) Millard's Classification

The classification was described in 1977. It is a modification of Kernahan's striped 'Y' Classification. The inverted triangle represents the nasal arch and the upright triangle represents the nasal floor (Bhalaji, 2012).

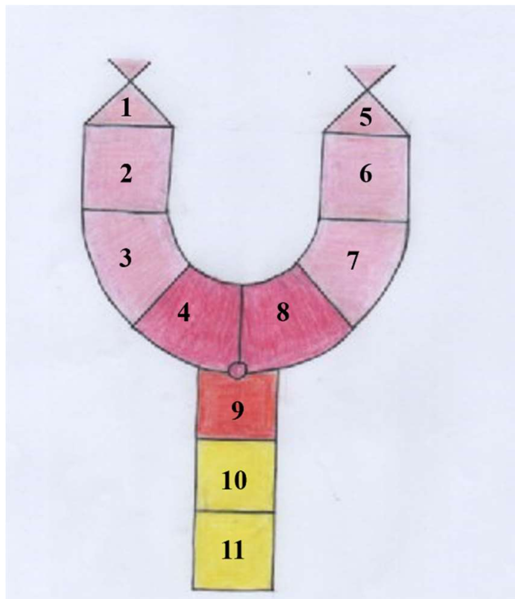


Figure 2.14 Millard's Classification (Redrawn from Bhalaji, 2012)

2.6.3(e) LAHSHAL Classification

The classification was described by O Kreins in 1987. LAHSHAL is an interpretation of the anatomic areas affected by the cleft. Capital letter indicates complete cleft (LAHSHAL). Small letter indicated incomplete cleft. (lahshal). Moreover, No cleft is presented with a dot (.).

Table 2.6 Abbreviations of LAHSHAL (Gurkeerat, 2007)

Abbreviations of LAHSHAL
L = Lip (right)
A = Alveolus (right)
H = Hard palate (right)
S = Soft palate (median)
H = Hard palate (left)
A = Alveolus (left)
L = Lip (left)

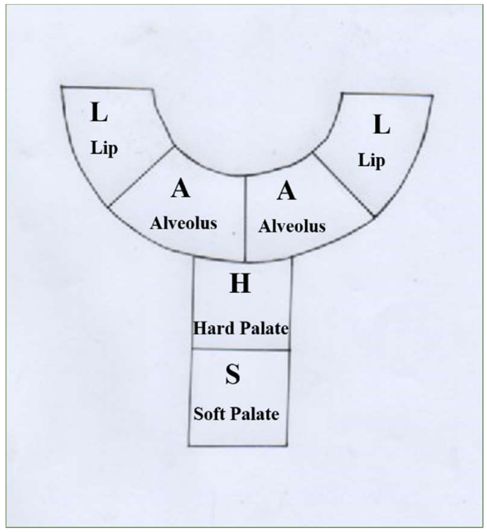


Figure 2.15 LAHSHAL classification (Redrawn from Gurkeerat, 2007)

Example

- **Bilateral complete cleft lip and palate : LAHSHAL**
- **Left complete cleft lip: . . . . . . L**
- **Right incomplete cleft lip and alveolus: la . . . . .**

Figure 2.16 Example of LAHSHAL classification

2.7 Problems Associated with CLP

Patients with CLP may demonstrate various clinical problems including dental, aesthetic, feeding, speech, hearing and also psychology (Cassolato et al., 2009).

2.7.1 Dental Problems

CLP is accompanied by a wide variety of dental anomalies, which also have a long-term impact on the patient's facial anatomy and self-esteem (Cassolato et al., 2009). Dental anomalies are considered a contributing factor in cleft formation (Stahl et al., 2006). The incidence of dental anomalies is markedly increased in children with CLP compared to the general population (Shapira et al., 1999). Generally, the specific anomaly varies according to the CLP category (Wu et al., 2011). Studies have shown that both permanent and deciduous teeth may be affected, and that dental anomaly occurs more frequently on the cleft side (Camporesi et al., 2010). The maxillary lateral incisors are the most susceptible to dental anomalies within the cleft region (Cassolato et al., 2009).

The most common dental anomalies found in CLP patients are: multiple missing teeth/hypodontia/agenesis (usually the maxillary lateral incisors); ectopic teeth; impaction; supernumerary teeth; microdontia; maxillary canines and premolars transposition; delayed development; crown and root malformation; and multiple decayed teeth (Tan and Yow, 2019; Haque and Alam, 2015a). The results of the literature survey of dental anomaly in CLP patients are summarized in **Table 2.7.**

Table 2.7 Incidence of dental anomalies in patients with CL or CP or CLP based on a literature survey

Author name and year	Cleft type *	No of subjects	Dental anomalies found
Menezes and Vieira, (2008)	UCLP	146	Agenesis Microdontia Impacted tooth Structural anomalies
Parapanisiou et al. (2009)	CLP	41 41	Supernumerary tooth (9.8% in CLP)
Al Jamal et al. (2010)	UCLP	78	Agenesis (66.7%) Supernumerary teeth (16.7%) Microdontia (37%) Taurodontism (70.5%) Transposition and/or ectopic teeth (30.8%) Dilacerations (19.2%) Hypoplasia (30.8%)
Menezes et al. (2010)	CLP	200	Agenesis (66.5% overall; MLI affected in 78.5% of lesions) Supernumerary teeth (35.5%)
Al-Kharboush, (2010)	CLP	200	Hypodontia (46.5%) Microdontia (31.6%) Ectopic eruption (10.4%) Supernumerary teeth (9%) Macrodontia (2.4%)
Wu et al. (2011)	UCLP	83	Missing MLI UCLP (56.7%)
			Supernumerary teeth UCLP (4.8%)
			Missing lower incisors a. UCLP (19.2%)
			Peg laterals UCLP (48.2%)

			Transposition a. BCLP (10.6%) b. UCLP (3.6%)
Qureshi et al. (2012)	UCLP	67	Single missing tooth a. UCLP (39%) Multiple missing tooth a. UCLP (22%) Anterior malocclusion a. UCLP (15%)
Shetty et al. (2013)	UCLP	113	Missing MLI (48.7%) Rotated maxillary right lateral incisors (22.1%) Rotated maxillary right central incisors (18.6%) Missing right lateral incisors (21.2%)
Riis et al. (2014)	CLP	30	Agenesis (significantly higher in CLP)
Al-Kharboush et al. (2014)	CLP	184	Hypodontia (66.8%) Microdontia (45.6%), Intra-oral ectopic eruption (12.5%), Supernumerary teeth (12.5%), Intra-nasal ectopiceruption (3.2), Macrodontia (3.2%)
Nicholls, (2016)	UCLP	162	94% of patients were found to have at least one dental anomaly followed by 34% patients having more than one anomaly or abnormality.

2.7.2 Aesthetic Problems

CLP interfere with the anatomy of the face causes cognitive and psychological sequelae. The orofacial structures may be malformed and congenitally missing. Deformities of the nose can also occur. The aesthetic goal of cleft repair consists of augmentation of the pyriform region and the creation of a cosmetically pleasing dental arch and dentition. Augmentation of hypoplastic pyriform region can improve alar base support and asymmetry (Kyung and Kang, 2015).

Successful surgical repair of the unilateral CL is commonly defined as one that results in normal orbicularis oris function and a near perfect symmetry of the lip and Nose (Sinko et al., 2017). Evidence from various studies shows no comparative advantage of any of the cheiloplasty techniques as far as the aesthetic outcome is concerned. However, the skill of the surgeon is considered most important (Lo et al., 2002; Lazarus et al., 1998).

2.7.3 Feeding Problem

In CLP babies, feeding is very difficult due to communication between oral cavity and nasal cavity as the underdeveloped musculature is not properly oriented to produce the necessary negative pressure in their mouth, making sucking ineffective (Goswami et al., 2016).

Spriesterbach et al. (1973) found that 91 out of 124 infants with CP had moderate to severe feeding difficulties related to their reduced sucking efficiency. The most notable problems are insufficient suction, excessive air intake, choking, nasal regurgitation, fatigue, inadequate milk intake, failure to gain weight, and excessive time required to feed. Inability to feed satisfactorily can lead to maternal stress and anxiety, and thus lead to poor mother and infant bonding (Clarren et al., 1987; Kelly, 1971). The other problems include: failure to gain weight and growth retardation especially during the first few months of life (Berkowitz, 2013; Goyal et al., 2012; Curtin, 1990); recurrent middle ear infections and acute otitis media which may lead to conductive hearing loss; poor speech due to altered intraoral anatomy (Goswami et al., 2016; Goyal et al., 2012); disturbed inter arch relationship due to altered growth of dental arches and malaligned teeth (Mizuno et al., 2002); and, increased incidence of dental caries attributable to the alternative feeding practices (Goswami et al., 2016).

2.7.4 Speech Problem

Speech defects in CLP patients are mainly due to velopharyngeal insufficiency, where the soft palate is not able to make an adequate contact with the back of the pharynx to close off the nasal airway. It can also be secondary to poor hearing (Hortis-Dzierzbicka et al., 2012).

It is generally accepted that early closure of palate leads to improved speech; however, late repair leads to improved maxillofacial growth, hence giving rise to the controversy in timing of palatoplasty. Currently, the recommendations are to close the palate by approximately 12 months of age (Hortis-Dzierzbicka et al., 2012). Satisfactory articulation development, velopharyngeal sphincter competence and good speech results may be achieved if the palate repair is done within the first year of life (Alam et al., 2018).

2.7.5 Hearing Problem

Children with a cleft of the soft palate are predisposed to middle ear infections. This is because the levator veli palatini and the tensor veli palatine are left unattached when the soft palate is cleft, making the opening of the ostium of the Eustachian tube was not patent (Gani et al., 2012). The Eustachian tube in cleft infants is also at an angle that does not promote dependent drainage. Hence, the middle ear is essentially a closed space, without a drainage mechanism where serous fluid may accumulate and result in serous otitis media that can become suppurative otitis media once it is infected (Handzic, 2018).

Conductive hearing loss caused by middle ear disease is reported to occur frequently in syndromic and non-syndromic cleft cases, with higher prevalence in the latter group (Gani et al., 2012). Surgical treatment, including closure of clefts and ventilation tube insertion, is reported to be effective in reducing conductive hearing loss but this remains controversial (Gani et al., 2012).

2.7.6 Psychological Problem

Children with CLP must deal with a visible facial disfigurement that draws the attention of other people. Because of the social significance of appearance and the attitudes of society toward the atypical, facial disfigurement with inferior self-image perception. Besides, many of these children have varying degrees of hearing loss and speech impairment, which can further impede their social interactions and contribute to social problems (Kapp-Simon, 2004). Furthermore, these children undergo multiple surgical operations, each of which may introduce emotional challenges (Demir et al. 2011). Positive support from family and friends can aid children with CLP to develop higher self-esteem than those with less family support. CLP can bring great psychological effect not only to the CLP patient but also to the effected family and the society (Sandberg et al. 2002).

2.8 Management of CLP

A multidisciplinary, complex and prolonged treatment approach including several surgeries and orthodontic treatment is required in the children with CLP. A CLP patient requires coordinated care from multiple specialties to optimize treatment outcome. To develop the capability to eat, speak and hear routinely as well as to accomplish a normal facial appearance are the main treatment goals of a CLP affected child. It is a complex lengthy treatment plan. It starts just after the birth and ends at 17-20 years of old (Bhalaji, 2012).

A standard treatment protocol of CLP patient is shown in **Figure 2.17**.

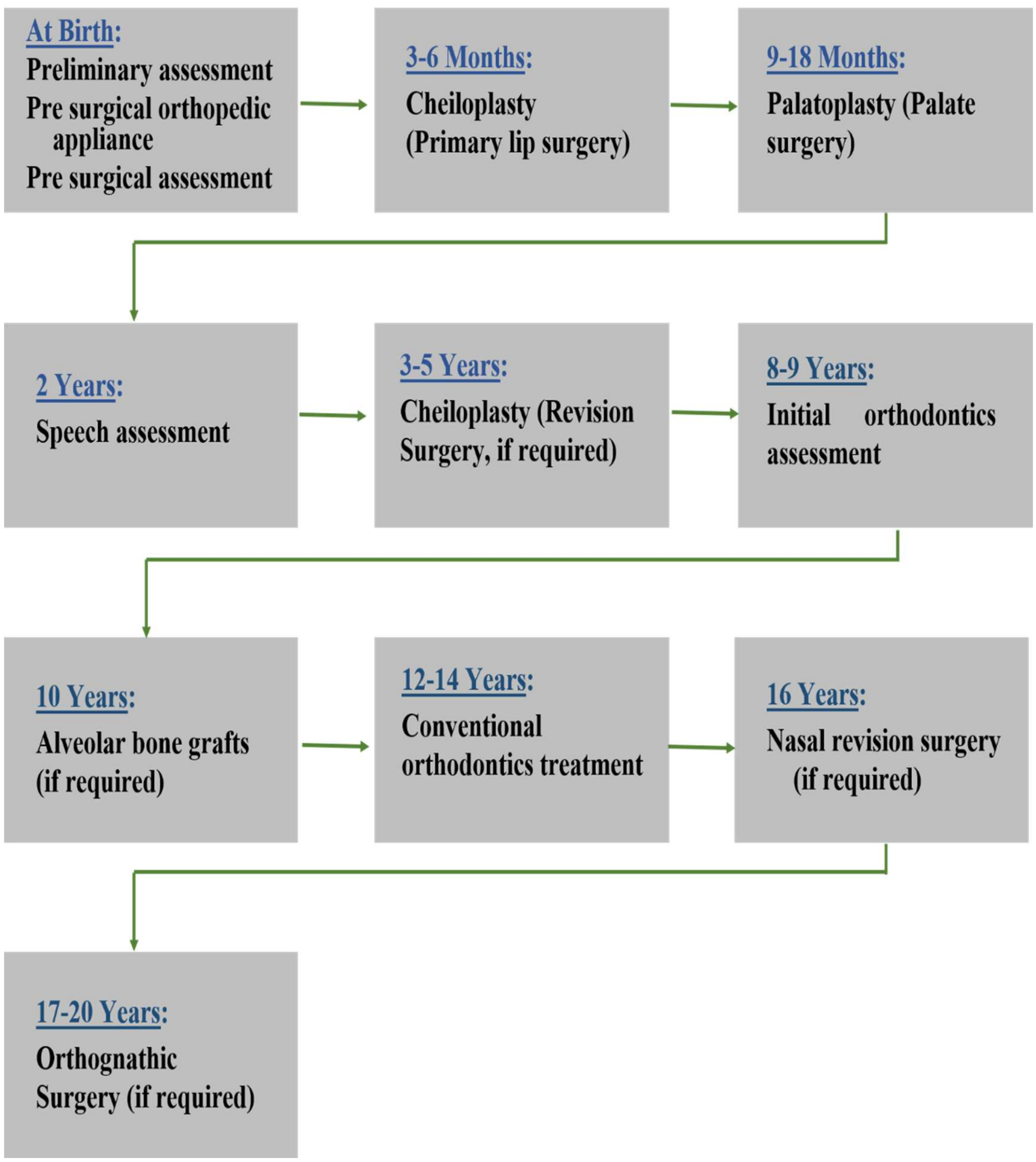


Figure 2.17 Standard treatment protocol of CLP patient (Bhalaji, 2012)

2.8.1 Pre Surgical Orthopedic Appliances Treatment (PSOT)

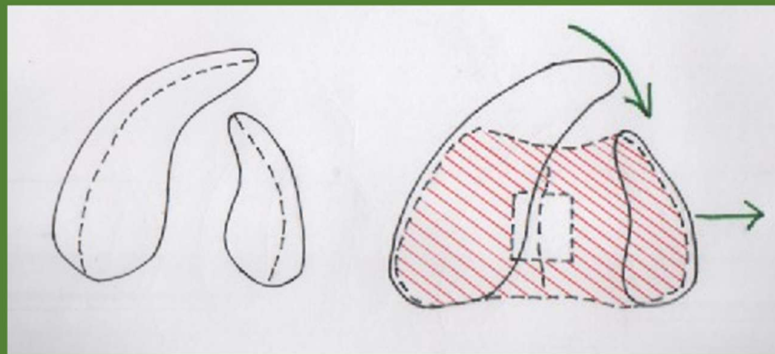
Pre surgical orthopedic appliances are mainly used to mold the maxillary alveolar and nasal tissues of CLP patients which mainly used in the first few weeks after birth and in the months prior to palatoplasty (Alzain et al., 2017; Hosseini et al., 2017; Haque and Alam, 2015b).

The main objective of PSOT is to monitor function i.e feeding and tongue posture. PSOT also guide the growth and position of maxillary segments. It also helps to narrow the alveolar cleft and reconstruct the anatomical features (Haque and Alam, 2015b).

There are two types of appliances are used; active and passive. Active appliances are preset intra-orally and are applied through elastic chains, screws and plates (**Figure 2.18**). Passive appliances maintain the distance between the 2 maxillary segments while external force is applied to reposition posteriorly (**Figure 2.19**) (Koshikawa-Matsuno et al., 2014).

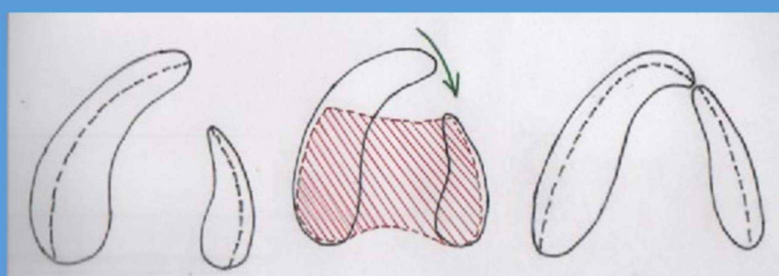
Clinical trials to assess the use of these devices suggested no significant effect of PSOT devices but naso-alveolar molding (NAM) was not studied in these trials (Grayson and Garfinkle, 2014). However, significant clinical improvements with use of PSOT have also been reported in literature (Koshikawa-Matsuno et al., 2014). In 2014, potential advantages and disadvantages of PSOT including NAM were comprehensively discussed in heated point/counterpoint articles (Grayson and Garfinkle, 2014; Hathaway and Long, 2014). Treatment outcomes of as many as 16 inter-centre studies were assessed and comparatively favourable results were found among centres where non- PSOT treatments were performed (Vig and Mercado, 2015).

Hotz plate is a passive pre surgical neonatal maxillary orthopedic appliance used in cleft lip and palate patients, made of soft and hard acrylic compound. In contemporary era, the importance of using Hotz plates is amplifying day by day since the preface of the early maxillary orthopedic intervention. Sasaguri et al. (2014) scanned maxillary dental cast between three groups and found treatment by Hotz plate had anti collapsing effect on maxillary arch after cheiloplasty and palatoplasty. Subjects who did not use pre surgical orthopedic appliance showed unfavourable condition respectively (Kajii et al. 2013; Alam et al. 2008). However, in another study the nasal form and growth was analysed using consecutively taken color photos and exemplified considerable improvement between nostril height and width ratio and height of the alar groove (Saad et al., 2019; Hoh and Sulaiman, 2019). The naris evaluation after cheiloplasty among 30 unilateral CLP patients (15 with Hotz plate and 15 without any plate) was carried out by Karube et al. (2012).



- Designed to expand and to move the lesser alveolar segment laterally.
- An acrylic appliance is placed (red shaded area) and as a result of molding the greater alveolar segment is moved towards the lesser one while the lesser segment was moved laterally by expansion to allow this. The green arrows show the direction of movement of both segments. The greater segment may then be retracted and molded into a more natural position.
- Example: McNeil Method, Latham device

Figure 2.18 Active pre surgical orthopedic appliance treatment (PSOT) (Redrawn from Alzain et al., 2017)



- No need to move the smaller alveolar segment laterally; there is enough space for larger segment to mold.
- An acrylic appliance is placed (shaded area) and as a result of molding the greater alveolar segment is moved towards the lesser one. The green arrow shows the direction of movement of the segments. Note that the lesser segment is not moved.
- Example: Hotz appliance, Naso-alveolar Molding appliance

Figure 2.19 Passive pre surgical orthopedic appliance treatment (PSOT) (Redrawn from Alzain et al., 2017)

2.8.2 Cheiloplasty

Cheiloplasty is the technical term for surgery of the lip. It is a reconstructive surgical procedure to correct a physical separation or groove-like flaw in the upper lip. The extent of separation or split varies depending on the severity of the condition. In cases where the separation extends into the base of the nostril – an opening between the oral and nasal cavities is visible (Anastassov and Joos, 2001). Fortunately, most clefts can be repaired through cosmetic plastic surgery techniques to provide significant improvement in quality of life as well as to restore normal appearance and function (Anastassov and Joos, 2001). An incomplete CL is when the split in the upper lip does not extend up to the nose (Anastassov and Joos, 2001). There are various surgical techniques which are used to repair CL (Haque and Alam, 2014). Different centres around the world have adopted different surgical techniques but it solely depends on the operating surgeon and his preference.

The aims of the surgery are to Close separation in upper lip.

- Facilitate feeding, talking.
- Evaluate ear infection and hearing problem.
- Aid in normal development of associated structure in mouth.
- Guide tooth eruption.
- Improve the aesthetics.

(Kongprasert et al. 2019; Hoffmannova et al. 2016; Seo et al. 2015)

CL closure usually performed simultaneously with nose repair. It is usually performed during the 3-6 months of life (Shkaukani et al., 2013; Farronato et al., 2014). There are several techniques of cheiloplasty.

- Tennison technique.
- Millard technique.
- Modified Millard technique.
- Olekas technique.
- Le Mesurier technique.
- Randall technique.
- Blair-Brown-Mc Dowell technique.
- Onizuka technique.
- TAN technique.
- Delaire functional cheilorhinoplasty.

(Zaleckas et al., 2011; Meyer and Seyfer, 2010; Alam et al., 2008; Apsotol et al., 2008; Tan and Atik, 2007).

Modified Millard technique and Millard rotational advancement technique are widely used all over the world (Sitzman et al., 2008; Shkaukani et al., 2013; Farronato et al., 2014; Miachon and Leme, 2014; Carrara 2018; Adetayo et al. 2019). Approximately 46% of American surgeons used the Millard technique of rotation and advancement without modification for closure of UCL and approximately 38% used the Millard technique with various modifications (Sitzman et al., 2008). In separate study, in North America has noted that 84% of responses from the practicing surgeons used Millard's rotation-advancement technique or modification of the Millard technique, 9% utilising triangular flap and 2% performed Delaire functional cheilorhinoplasty (Sitzman et al., 2008).

2.8.2(a) Literature Survey of Different Techniques of Cheiloplasty

Different studies showed different results about cheiloplasty as well as different techniques showed different results (Kongprasert; 2019). No specific techniques of cheiloplasty consistently produce ideal esthetic and functional results. Each technique can be used for the primary repair of CLP depending on the skill and training of the operating surgeon. Cheiloplasty can cause restricted growth of maxillary arch (Kongprasert; 2019; Adetayo et al. 2019; Rousseau et al., 2013).

Millard technique is one of the most popular techniques being used for cleft cheiloplasty (Millard Jr, 1961). It has been modified several times by surgeons belonging to different school of thoughts (Millard Jr, 1961). Advantages and disadvantages of Millard technique are numerous (Kirschner and LaRossa, 2000; Arosarena, 2007). Millard attempted to preserve cupid's bow, philtral dimple, and improve nose prominence (Millard Jr, 1976).

Dr. Ralph Millard initially described rotation-advancement flap technique for cheiloplasty in 1955, and his works get published in 1957. In 1958, Dr. Millard presented his technique at the first International Congress of Plastic Surgery in Stockholm, Sweden and from that moment, a new era for cleft cheiloplasty was begun. The original of cleft cheiloplasty technique consisted of simple straight line closure which resulted in notching of the lip and vertical scar contracture (Sykes and Tollefson, 2005). Besides, prior to Millard's repair, straight line repair and geometric techniques had been a norm for cleft cheiloplasty (Demke and Tatum, 2011).

A triangular flap was initially designed for cleft cheiloplasty by Tennison, which was later modified by Randall, to improve its reproducibility with ease and precision. This technique is still in use by some surgeons, and it produces predictable results (Adetayo et al. 2019; Arosarena, 2007).

Adetayo et al. (2019) compared the treatment outcomes based on cheiloplasty on UCLP subjects using the Tennison–Randall and Millard technique; did not find significant difference between two techniques. Both techniques showed significant improvements in the appearance of the scar on the lip.

Galarraga (2009) highlighted that cheiloplasty which is performed under tension can cause the collapse of the maxillary arch and deformities which later will alter the contour of the lips. Galarraga suggested that this facial development changes maybe related with the excessive removal of the soft tissues during cleft cheiloplasty and inhibition of sagittal growth of the midface. Therefore, he conducted another study to determine the important usage of the botulinum toxin in cheiloplasty in view to reduce tension on the wound which indirectly may enhance the growth of the midface region.

Li et al. (2006) also concluded in their study that cheiloplasty is the most important factor that restrains maxillary growth when they found the maxillary retrusion were identical in two groups of samples whereby one group consists of patients undergone cheiloplasty only and another group consists of patient's undergone palate and cheiloplasty. One study reported that functional closure of the lip significantly narrowed the transverse anterior cleft areas in early maxillary growth in complete UCLP (Rousseau et al., 2013).

Rullo et al. (2009), mentioned that the cleft lip closure by Delaire's cheilorhinoplasty could be responsible for maxillary retrusion and it was important to reconstruct the perilabial muscles carefully in order to have the positive maxillary growth. Meng et al. (2007), found in their animal experiments that both Millard and Tennison cheiloplastys produced a shorter, wider and caused posteriorly displacement of the maxilla, and with Tennison's surgical technique tended to create more problems to the anterior teeth and alveolus. Study done by Alam and colleagues concluded that patients who were treated by modified Millard technique seems to have fewer adverse effects and better maxillary growth in relation to the cranial base (Alam et al., 2013).

Apostol (2008) analysed the results obtained by utilising the Onizuka as the main treatment scheme of the CLP through a potential study including 63 children with CLP. He used the first version of the Onizuka technique, a scheme that resembles the Millard technique modified for extending the outer margin of the cleft, only in 3 cases, with a satisfying result, but later he used a revised method. The results had improved. As a conclusion he considered that Onizuka technique had many advantages compared to other cheiloplasty methods: clear and precise identification of all the anatomical guides that describe the pre-operatory method; post operatory scars did not cross the nostril gap like others technique. This flap did not perpendicularly cross the philtrum, like in the other techniques. One of the disadvantages of using this technique is the fact the method is precise, rigorous and as a result it must be perfectly known and the pre operator drawing must be prepared in details. Concerning the esthetical and functional results, the Onizuka technique offers bounty of satisfactions to the patients, as well as the surgeon.

Zaleckas et al. (2011), analysed 66 subjects with non syndromic complete unilateral cleft lip, alveolus and palate were examined. Among them 19 subjects (28.8%) underwent Tennison technique, 20 subjects (30.3%) underwent Millard technique and 27 subjects (40.9%) underwent Olekas technique. Outcome was assessed by score, which was given by analysing standardised photographs of naso-labial triangles. For the evaluation, the modified scale according to Mortier and Anastassoy was used. Separate anatomical elements – red lip, white lip, scars, and nose were assessed. The best appearance of the red lip and white lip was found after the Tennison technique. Height of white lip and symmetry of Cupid's bow were better restored by using the Tennison technique. The physiological configurations of the white lip and less visible scars were achieved by using the Olekas technique. All techniques were equal in red lip and nose formation.

The results of the different studies on cheiloplasty that affect maxillary growth in relation to CLP are shown in **Table 2.8**.

Table 2.8 Results of different studies on cheiloplasty that affect maxillary growth

Author	Type of Cheiloplasty	Method used	Outcome
Adetayo et al. (2019)	Tennison technique. Millard technique.	Dental cast	Both techniques showed significant improvements to improve the appearance
Alam et al. (2019)	Millard technique. Modified Millard technique.	Dental cast	Significant differences observed between two techniques.
Haque et al. (2017b)	Millard technique. Modified Millard technique.	Dental cast	Modified Millard is more favourable in relation to dental arch relationship.
Shi and Losee, (2015)	Tennison technique. Millard technique.	Animal model	Tennison's technique showed more problems to the anterior tooth and alveolus
Alam et al. (2013)	Modified Millard Modified Millard with vomer flap	Cephalograms	Modified Millard is more favourable in relation to craniofacial morphology.
Kajii et al. (2013)	Modified Millard with anterior plate closure. Modified Millard.	GY	Modified Millard is more favourable than modified Millard with anterior plate closure.
Zaleckas L et al. (2011)	Tennison technique. Millard technique. Olekas technique.	Standardised photographs.	All techniques sowed equal outcome.

Meyer and Seyfer, (2010)	Tennison- Randall technique Millard technique	Photograph	Tennison technique presented more flexibility with wide clefts while Millard technique presented outstanding results with narrow clefts
Alam et al. (2008)	Modified Millard. Modified Millard with vomerflap.	Dental casts	Modified Millard cheiloplasty is more favourable than modified Millard with vomer flap cheiloplasty.
Apostol, (2008)	Onizuka technique	Photograph	Onizuka technique offers plenty of satisfactions to the patients, as well as the surgeons regarding the esthetical and functional purpose.
Huang et al. (2002)	Millard's rotation advancement cheiloplasty	Dental casts	Cheiloplasty could mold the anterior portion of the maxillary dental arch palatally by exerting continuous pressure.

Meyer and Seyfer (2010), analysed 100 subjects with UCLP. Among them twenty-six patients received the Tennison-Randall technique and 74 received the Millard technique. After surgery they compared the results of two types of repairs, performed by a single surgeon over a period of 30 years. They found Tennison technique presented more flexibility with wide clefts, but less with narrower clefts. This associated to excellent adjustability of the volume and length of the triangular flap and Millard technique presented outstanding results with narrow clefts, but less with wide ones.

Huang et al. (2002) analysed infants with non syndromic complete UCLP to discover and examine quantitatively the development of the maxillary dental arch before and after cheiloplasty. They performed Millard's rotation advancement cheiloplasty. Maxillary dental casts were taken before and after cheiloplasty. They found that cheiloplasty could mold the anterior portion of the maxillary dental arch palatally by exerting continuous pressure.

Different techniques showed different results. No specific techniques of cheiloplasty consistently produce ideal esthetic and functional results. As a conclusion, there are evidences that cheiloplasty affects the growth of maxilla, however lack of data in the literatures mentioned about which surgical cheiloplasty technique may contribute more to the maxillary and dental arch development disturbances. It is difficult to compare the different designs of cheiloplasty due to variations in cleft severities, differences in the aims of the treatment and variations of the surgeons' expertise.

2.8.3 Palatoplasty

Palatoplasty is a surgical procedure that aims at reconstruction of the soft and/or hard palate of subjects with cleft palate. The eve of 19th century witnessed great evaluation in the technique of palatoplasty, allowing successful closure of a cleft palate and optimal outcomes.

The basic goals of the palatoplasty are to

i. close the abnormal opening between nose and mouth.
ii. help the patient to develop normal speech.
iii. aid in feeding, swallowing, breathing and normal development of associated structure in the mouth.

(Ohashi et al., 2018; Lilja et al., 2006)

Surgical repair of soft and hard palate is performed generally around 9-18 months of age (Ohashi et al., 2018; Lilja et al., 2006). Two most important factors in determining surgical outcome are timing of surgery and technique of palatoplasty used (Ohashi et al., 2018). Maxillary growth disturbances and constriction is the major drawback of the standard procedure of palatoplasty (Schilling et al., 2019; Ohashi et al., 2018). Surgery influences on the facial skeletal growth proven as an important factor in cleft surgery (Ross, 1987; Wood and Grayson, 1997; Molsted, 1999). The palatal closure inhibits the normal suture activity of the maxilla that tends to exhibit Class III facial skeletal profile (Alam et al., 2008).

2.8.3(a) Timing of Palatoplasty

The effect of surgical timing (one stage or two stage) especially for palatal closure on the dental arch relationship and maxillary growth was widely discussed in the literature and still remains controversial. Some researcher found two stage palatal surgery produced a more favourable outcome whether some other groups of research found one stage surgery had a better outcome (Schilling et al., 2019; Shaw et al., 2019). Interestingly no significant differences on the maxillary growth between one stage surgery and two-stage surgery also reported by some researchers. However, two stage palatal closure has been linked with poor speech outcomes, though it remains debatable. Many surgical techniques have been devised to repair palate using one-stage or two-stage techniques. One-stage technique involves approximating the soft and hard palate simultaneously in a single appointment. Whereas, in two-stage technique both are dealt with in separate appointments (Agrawal, 2009). The outcome of the effect of timing of palatoplasty has been illustrated in **Table 2.9**.

Table 2.9 The outcome of the effect of timing of palatoplasty

Author	Population	Outcome
Yamanishi et al. (2011)	Japan	The two stage palatal surgery produced more favourable midfacial growth.
Zemann et al. (2011)	Austria	No significant differences observed between one stage and two stage procedure.
Liao et al. (2010)	Taiwan	Two-stage palatoplasty has a smaller adverse effect than one-stage palatoplasty on the growth of the maxilla.
Pradel et al. (2009)	Germany	The one-stage palate surgery had a more positive influence on speech development and early maxillary growth than the two-stage procedure.
Stein et al. (2007)	Germany	The two stage palatal surgery produced more favourable midfacial growth.
Zemann et al. (2007)	Austria	No significant differences observed between one stage and two stage procedure.
Liao and Mars, (2006)	Sri Lanka	Palatal repair which performed after pubertal peak velocity age showed favourable maxillary growth on the anteroposterior dimension than palatal repair which performed before pubertal peak velocity age
Nollet et al. (2005)	The Netherlands	A better result of dental arch relationship reported in delayed palatal closure compared to early palatal closure.
Gaggl et al. (2003)	Austria	One stage surgery is better outcome for the maxillary growth

Prasad et al. (2000)	USA	No significant differences observed between one stage and two stage procedure.

2.8.3(b) Techniques of Palatoplasty

There are various surgical techniques which are used to repair cleft palate. There are many variations of each of these techniques. However, only a few of them are most relevant and useful.

There are various type of palatoplasty which include

i. von Langenbeck bipedicle flap technique.
ii. Veau-Wardill Kilner pushback technique.
iii. Bardach's two flap technique.
iv. Furlow Double opposing Z palatoplasty.
v. Primary pharyngeal flap.
vi. Two stage palatoplasty.
vii. Intravelar veloplasty.
viii. Vomer flap.

(Leow and Lo, 2008)

2.8.3(b)(i) von Langenbeck Technique of Palatoplasty

The amount of denuded palatal bone surface is closely related with surgical technique used for palatoplasty. The von Langenbeck palatoplasty (**Figure 2.20**) is the oldest, simple palatal closure technique introduced by von Langenbeck in 1859 and still widely used nowadays (Ohashi et al., 2018; Vig and Mercado, 2015; Arosarena, 2007). This surgical technique is ideal for incomplete cleft of secondary palate (Strong and Buckmiller, 2001).

It closes the cleft area by mobilising the bipedicled mucoperiosteal flap medially without lengthening the palate (Strong and Buckmiller, 2001). Lateral relieving incision from posterior to the maxillary tuberosity and follows the posterior region of the alveolar ridge performed to approximate the cleft margin, leaving a raw bone surface at the lateral side of the relieving incision area (Leow and Lo, 2008). Main drawback of this procedure was the poor speech outcome, and minimal increase in length of soft palate (Dreyer and Trier, 1984).

One modification of the von Langenbeck technique is the intravelar veloplasty (Strong and Buckmiller, 2001) to reproduce the normal muscle sling of velar muscle that improve velar and pharyngeal function (Huang et al., 1998). von Langenbeck technique also can be used in combination with a Furlow double opposing Z-palatoplasty to increase palatal length with minimal mucoperiosteal undermining (La Rossa, 2000).

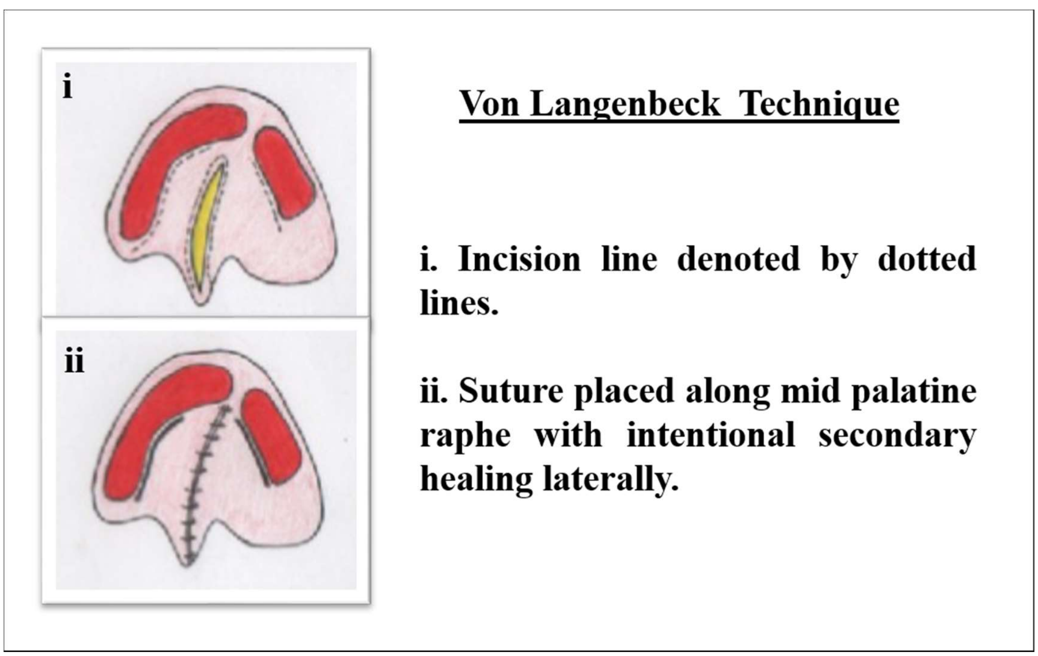


Figure 2.20 von Langenbeck technique of Palatoplasty (Redrawn from Agrawal, 2009)

2.8.3(b)(ii) Veau-Wardill-Kilner (V-Y) Pushback Technique of Palatoplasty

Recognising the drawbacks of von Langenbeck technique, efforts were made to design a technique which could address the issue of speech problems and short palatal length. To achieve sufficient palatal lengthening, one of the most commonly used technique was Veau-Wardill-Kilners' (VY) pushback palatoplasty (**Figure 2.21**) (Parikakis et al., 2019; Kirschner and LaRossa, 2000). It is ideal for incomplete cleft for hard palate (Leow and Lo, 2008).

Long term improvement of speech in UCLP especially in term of nasality and nasalance score can be achieved by this technique of surgery (von Lierde et al., 2004). The disadvantages of this technique is denudation of palatal bone at the anterior region affects the midfacial growth in cleft patients (Pigott et al., 2002; Parikakis et al., 2019).

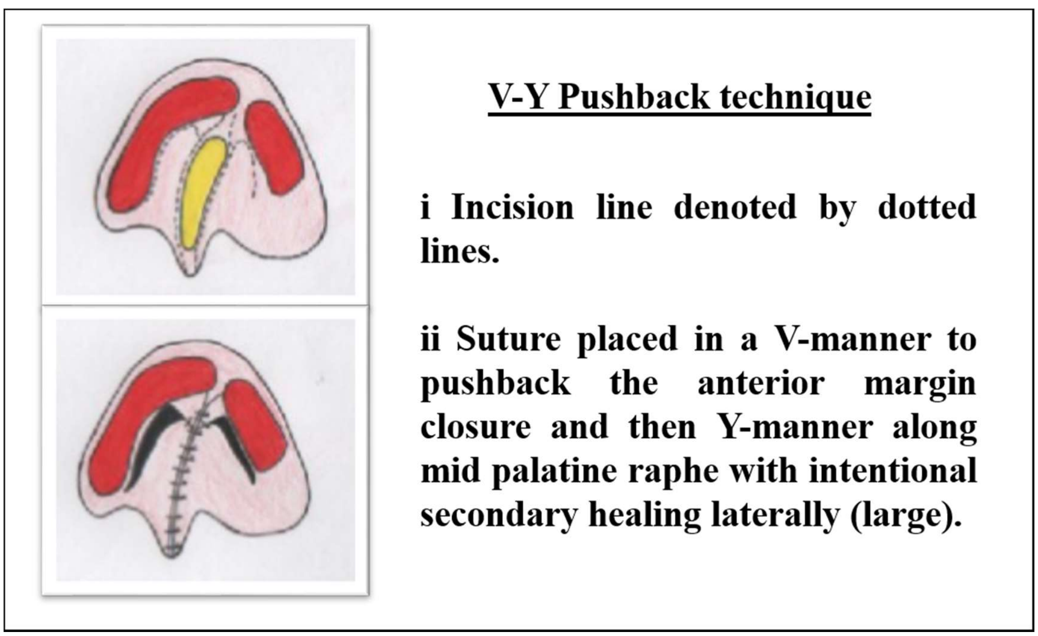


Figure 2.21 V-Y Pushback technique of Palatoplasty (Redrawn from Agrawal, 2009)

2.8.3(b)(iii) Bardach Two-Flap Technique of Palatoplasty

Bardach technique of palatoplasty (**Figure 2.22**) was first described by Janusz Bardach in Poland in 1967. The original idea of this technique is to close the narrow clefts by releasing mucoperiosteal flaps from the cleft margins. Later, some modification of this technique was done to avoid tension of the flap during palatal closure which is involved more extensive dissection and extension of the relaxing incisions along the alveolar margins to the cleft edges. This technique is commonly used for unilateral or bilateral complete clefts palate (Leow and Lo, 2008). Bardach technique is totally dependent on the greater palatine neurovascular bundle pedicle and it provides greater versatility to cover the cleft area (Bardach and Salyer, 1987).

In complete UCLP cases, cleft area closed by the mucoperiosteal flap from the medial side which can be shifted across the cleft and closed directly behind the alveolar margin. This design of flap can eliminate the fistula in the anterior hard palate area (Bardach, 1995). Bilateral nasal mucosa flap are elevated from the nasal surface of the hard palate and then reapproximated to cover the cleft followed by the oral mucosal flap closure. Two-flap palatoplasty seems to have a minimal effect on maxillofacial growth due to minimal area of bone denudation on hard palate when mucoperiosteal flaps are raised (Bardach et al., 1982; Bardach and Kelly, 1990).

However, this technique does not offer additional palatal length in repaired palate in order to allow normal speech production. Therefore, to overcome the limitation of this technique, a variation from the original flap reported using the supraperiosteal flaps instead of mucoperiosteal flaps for palatal closure (T'eblick et al., 2019; Ito et al., 2006). This new approach needs larger series of evaluation to ascertain its application for better speech improvement. Nevertheless, palatal lengthening in palatoplasty is still considered essential to reduce the posterior pharyngeal wall space to improve speech. To date, intravelar veloplasty of Furlow double opposing Z-palatoplasty are widely accepted to reduce velopharyngeal insufficiency by retropositioning and reorientation of the velar muscle (Bae et al., 2002; Salyer et al., 2006).

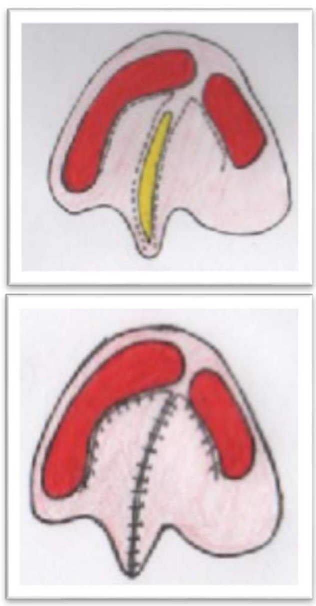


Figure 2.22 **Bardach two-flap technique of Palatoplasty (Redrawn from Agrawal, 2009)**

2.8.3(b)(iv) Furlow Double Opposing Z-Palatoplasty

This technique (**Figure 2.23**) was unofficially introduced by Leonard T. Furlow Jr. in 1978 and later published in 1986 (Furlow, 1986). It is used to repair of the soft palate (Strong and Buckmiller, 2001), submucous cleft palate and secondary correction of marginal velopharyngeal insufficiency (Friedman et al., 2010). This technique offers the lengthening of the soft palate and reconstructs the muscle sling. It is involves alternating the reversing Z-plasties oral and nasal flaps and repositioning the levator veli palatini muscle within the posteriorly mobilized flap (Furlow, 1986; Randall et al., 1986; Jackson et al., 2013; T'eblick et al., 2019; Ohashi et al., 2019).

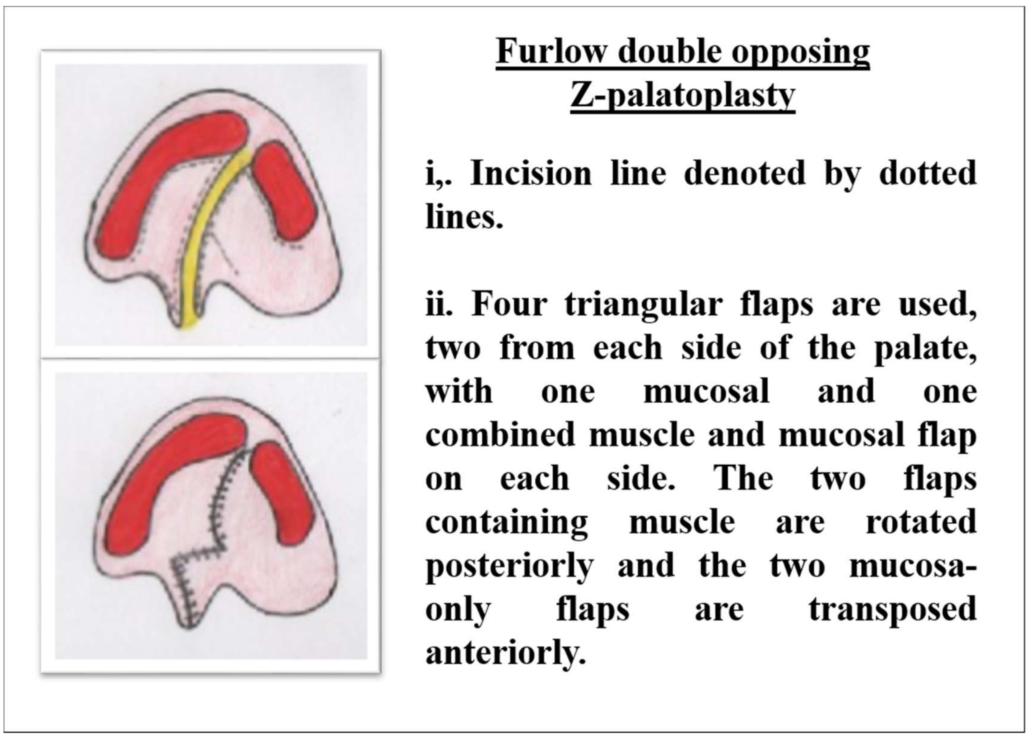


Figure 2.23 **Furlow double opposing Z-Palatoplasty (Redrawn from Agrawal, 2009)**

UCLP subjects undergo reconstructive surgeries in their first stage of life, of which palatoplasty is the commonly performed procedure. There are many surgical protocols used with UCLP patients; however, the ideal surgical technique and time for performing it are widely discussed in literatures. Throughout the years, surgical techniques have developed, presenting manifold favourable results for the subjects with cleft. The primary palate surgeries must guarantee the best functional (related to speech) and aesthetic results, with minimum harm to facial growth.

2.8.4 The Effects of Cheiloplasty and Palatoplasty on maxillary growth and facial soft tissue development

Retroposition of the maxilla, concaved mid-face and deformed dental arch are consistently reported after surgery, and no currently available surgical protocol can completely circumvent these postoperative complications (Schilling et al., 2019). Many researchers considered that palatoplasty is the only reason for midfacial retroposition, and lip repair may have an influence on the upper front teeth, and the alveolar bone but never on the development of maxilla (Adetayo et al., 2019).

Bishara et al. (1985) suggested that the tissue continuity is an important factor influencing maxillary growth. It is obvious that a maxilla with a continuous alveolar ridge and hard palate has advantages in withstanding lip pressure, and anteroposterior growth of the maxilla may not become apparent. This is in contrast to increased lip pressure forced on separate maxillary sections. The forward growth tends to be restrained or the maxilla may even be pushed back. The severity of the maxillary defect must be taken into account when analysing the effects of lip repair on maxillary growth. A retrospective study indicated that patients who had more palatal tissue at cheiloplasty showed better maxillofacial growth (Honda et al., 2002).

Coupe and Subtelny (1960) found in cephalograms that patients with CLP demonstrate apparent tissue deficiency, but this deficiency could not be found in patients with CP only. It can be concluded that the severity of the malformation is determined by the maxillary anatomy. Lip repair has a smaller effect on it with no apparent tissue deficiency and replacement, as is the case in CP.

Li et al. (2006) reported that the severity of anteroposterior growth deficiency of the maxilla was identical in repaired lip, and lip and palate. The authors also found significant reduced upper lip surface area, upper lip height and intercheilion width in patients with UCLP who had lip repair only where the reduction of upper lip height was not caused by the operation but by maxillary growth deficiency instead. Their results also indicated that the reduction of upper lip surface area was the result of a smaller upper lip height, while the reduction of intercheilion width was due to a reduced bony support.

Mucoperiosteal denudation of the palatal bone was an important inhibiting factor of maxillary growth in surgical procedure for complete UCLP cases then followed by the excessive scar tissues formation at the denuded palatal bone and the undermining of soft tissue during palatoplasty which can inhibit the forward growth of the maxilla (Carrara et al., 2018; Ohashi et al., 2018; Schilling et al., 2019; Dogan et al., 2019).

The palatal closure inhibits the normal suture activity of the maxilla that tends to exhibit Class III facial skeletal profile (Alam et al., 2008). Post-operative scar tissue close to the vomero-premaxillary suture can alter the maxillary position in the postero-anterior dimensions, meanwhile the post-surgical scar tissue which attached to the underlying palatal bone and it was continuous with the periodontal ligaments led to dental arch constriction (Zin et al., 2017). The amount of denuded palatal bone surface is closely related with surgical technique used for palatoplasty (Haque et al., 2018).

Jackson et al. (2013) examined 1500 patients treated with Furlow palatoplasty and reported no significant midfacial retrusion or crossbite; only 14% patients in this study required LeFort I advancement.

Ishikawa et al. (1998), found that the dental arch form in individual cleft palate patients is determined mostly by the location of the scar tissue. He also found the evident that severity of maxillary dental arch constriction was closely related to the scar tissue distribution on palate itself.

Gaukroger et al. (2002) done a comparison study on method of surgery of the two hospital centres which one centre used Veau-Wardill-Kilner technique while another centre used von Langenbeck palatoplasty. He reported that patients who was operated by using Veau-Wardill-Kilner technique presented with more flat facial profile and had more reduced of maxillary prominence.

One study which involved 1033 cleft palate patients is closely monitored and examined for their maxillofacial growth and researchers found that Veau-Wardill-Kilner with relieving incisions were most detrimental to maxillary growth (Koberg and Koblin., 1973).

2.9 Orthodontic Management of CLP Patients

A cleft patient come to orthodontic clinic to subside orthodontic and other problems at 8 to 9 years of age. Main orthodontic problems in CLP patients are: crowding, crossbite, abnormal shape and number of lateral incisors, orthodontic Class III tendency, supernumerary teeth, significantly smaller ANB angle, oro-nasal fistulae in some cases etc (Haque and Alam, 2015a). **Table 2.10** shows the role of orthodontist in the treatment of CLP.

Table 2.10 The role of orthodontist in the treatment of CLP. (Bhalaji, 2012; Gurkeerat, 2007)

	Time (age)	**Role**
Pre surgical orthopedics	3 to 6 weeks	Intraoral appliances to separate the collapsed lateral maxillary segments. Acrylic obturators to minimize feeding difficulties. Pre-surgical nasoalveolar molding to reduce the size of intra-alveolar cleft.
Initial Orthodontic Treatment	6 to 8 years	Management of the anteroposterior, transverse and vertical dimensions in the mixed and permanent dentition. Management of skeletal Class III malocclusions with with protraction headgear therapy.
Initial Orthodontic Treatment	9 to 10 years	Correction of anterior and posterior cross bites with palatal expanders or other types of expansion appliances.
Comprehensive Orthodontic Treatment	12 to 13 years	Orthodontic traction of impacted teeth, maintaining the coordination teeth and arch with using of pre-adjusted edgewise appliances. Chin cup headgear therapy can be used to restrain mandibular growth.
Surgical Treatment	17 to 20 years	Following the patient's growth period, pre-surgical and post-surgical orthodontics, the orthognathic surgery takes place for those patients who are indicated.

2.9.1 Orthodontic Treatment during Deciduous Dentition of CLP patient

Though the dental problems are not severe in deciduous dentition however, treatment during deciduous dentition does not give any assurance of normal occlusion in permanent teeth (Gurkeerat, 2007; Bhalaji, 2012). Noticeable posterior crossbite and maxillary arch collapse can be observed in deciduous dentition period. This crossbite can be corrected by moving (orthopedically) the maxillary segment with expander appliance following the eruption of first molar and permanent incisors. The anterior crossbite and antero-posterior dysplasia can be corrected as well (Gurkeerat, 2007; Bhalaji, 2012; Grayson and Garfinkle, 2014).

2.9.2 Orthodontic Treatment during Early Mixed Dentition of CLP patient

Usually retroclination and anterior crossbite are treated during early mixed dentition stage (Bhalaji, 2012; Grayson and Garfinkle, 2014). Anterior crossbite or edge to edge bite resulting functional shift of mandible can be relieved by choosing grinding or orthodontic treatment if the case demand. Patient with least antero-posterior inter-maxillary skeletal descripencies can be corrected with protraction headgear (Houston, 1992; Gurkeerat, 2007; Bhalaji, 2012; Grayson and Garfinkle, 2014).

2.9.3 Alveolar Bone Graft of CLP patient

Alveolar bone graft is carried out to produce a bony bridge in the CLP patient. Usually primary alveolar bone grafting and early secondary bone grafting was not carried out nowadays due to necessity of additional surgery (Mitchel, 2007). However, ‘wedge shaped’ piece of rib bone is still used for the primary bone grafting in some centres in developing country (Mitchel, 2007).

Secondary bone grafting is intended to provide the bridge in the cleft segment by grafting cancellous bone from iliac crest. The remaining alveolar cleft is filled by grafted cancellous bone which is anatomically joined with the adjacent bone (Bhalaji, 2012). It becomes indistinguishable radiographically by 3 months of grafting. The formation of the root and pattern of the eruption of maxillary lateral incisors and maxillary canine solely indicates the time of bone graft (Mitchel, 2007; Bhalaji, 2012).

Before bone grafting, orthodontics treatment is very important which aids the expansion of cleft to the standard dimension of upper arch. Usually maxillary arch expansion is done in between primary and secondary bone grafting. For the collapse upper arch, the choice of appliance is the quad helix. However, the choice of appliance for the 'V-shaped arch is the tri helix appliance (Mitchel, 2007).

2.9.4 Comprehensive Orthodontic Treatment of CLP patient

Comprehensive orthodontic treatment is started after 2/3 years of the completion of bone graft and the eruption of permanent canine as well (Grayson and Garfinkle, 2014). At the beginning of the treatment, the case of the patient is evaluated either need only orthodontic treatment or orthodontic treatment along with orthognathic surgery (Mitchel, 2007).

Table 2.11 Comprehensive orthodontic treatment of CLP patients (Grayson and Garfinkle, 2014)

Orthodontic treatment	Use
Twin-bracket edgewise or pre adjusted appliance	For the three dimensional control on teeth.
Chin cup therapy	For the correction of dental malposition and well alignment of the arch.
Space closure	For the missing tooth.
Rigid palatal retainers	For the maintenance of the arch alignment and expansion.
Prosthetic Management	In the patient in whom space closure is not possible due to aplasia or Class III malocclusion.

2.9.5 Orthognathic Surgery of CLP patient

Patients with notable maxilla-mandibular discrepancies and severe growth forms is indicated for the mutual orthodontic and orthognathic surgical treatment (Cheung et al., 2006).

2.10 Measurements of Treatment Outcome of UCLP patient

Treatment of CLP has immensely evolved over the past century. Multidisciplinary approaches and new techniques for treatment of CLP have been introduced, discussed and modified. The quality of treatment of CLP patient is demonstrated by assessing the outcome measures. With modern advancements in the field of research, surgical improvements are continuously added to the evidence based practice. Treatments should be assessed routinely in order to update outcomes of the techniques implemented (Shaw et al., 2001).

The rationale of assessing CLP outcomes is to predict and forewarn healthcare professionals, patient and the caregivers (family) in terms of burden of care (Vig and Mercado, 2015). These assessments allow discussions based on risk-benefit ratio, patient empowerment through informed consent and help improve patient's quality of life.

Both time and techniques of surgeries (cheiloplasty, palatoplasty) have been found to influence the treatment outcome (maxillary arch retardation) of UCLP patient. Not only that, UCLP type and side, family history of cleft and Class III malocclusion also thought to have an impact on treatment outcome (Alam et al., 2008). The outcome of treatment of UCLP can be assessed from multifacets of variables such as; dental arch relationship (Haque et al., 2018), cephalogram (Suzuki et al., 2007), cone-beam computed tomography (Parveen et al., 2018), maxillary arch dimension (Gopinath et al., 2017) etc.

2.10.1 Treatment Outcome Based on Dental Arch Relationships

'In the orthodontic context, an index is used to designate a rating or as a categorising system that assigns a numerical score or alphanumeric label to a person's occlusion' (Shaw et al., 1995). Indices have been developed for measuring the outcome of treatment more precisely in order to determine the degree of success in treating the cleft defects. An ideal measure of outcome should be easy to learn, quick to apply, reliable, and valid (Fudalej et al., 2019). There are different types of indices that assess treatment outcome based on dental arch relationship in patients with CLP, such as the following:

i. GOSLON Yardstick (GY) (Mars et al., 1987),
ii. 5-year-old index (Atack et al., 1997b),

iii. EUROCRAN index (EI) (Fudalej et al., 2011),

iv. Huddart Bodenham system (Huddart and Bodenham, 1972),

v. Modified Huddart Bodenham (mHB) system (Mossey et al., 2003; Gray and Mossey, 2005).

2.10.1(a) GOSLON Yardstick (GY)

The Great Ormond Street, London and Oslo, Norway (GOSLON) Yardstick was developed for categorising the degree of malocclusion (maxillary growth) with UCLP. The GY was introduced by Mars et al. (Mars et al., 1987). Contrasting other systems, the GY is treatment-linked (e.g. anterior crossbite with retroclination of the incisors can be corrected more easily than anterior crossbite with normal incisor inclination) and is therefore more useful than a specific anomaly-score alone. Not only the evaluating the effect but also the hereditary skeletal pattern is addressed by this scoring system, as it is based on the prospects for orthodontic rectification (Hathaway et al., 2011; Jack et al., 2011; Altalibi et al., 2013; Jones et al., 2014; Haque et al., 2015b; Vig and Mercado, 2015). The system was developed for categorising the degree of malocclusion in 10-year-old children with UCLP, examined in the late mixed or early permanent dentition (Mars et al., 1987). It categorisees malocclusions in patients with UCLP according to antero-posterior arch, vertical labial segment, and transverse relationships.

The functions, advantage and disadvantage of GY are as follows

Functions

i. It is useful in the assessment of dental relationships in UCLP (Altalibi et al., 2013).

ii. It has been developed for use in the late mixed and early permanent dentition (Altalibi et al., 2013).

iii. It is valuable in predicting treatment need (orthodontic treatment, surgical treatment) (Altalibi et al., 2013).

Advantages

i. The GY has proven to be able of discriminating arch relationships and interference of facial morphology outcomes between different centres (Alam et al., 2013).

ii. It considers clinically important variables in all three planes of space and permits the ranking of models in the order of difficulty to achieve a favourable outcome (Chaudhry et al., 2018; Patel, 2011).

iii. It has been shown to have good inter- and intra-examiner reliability (Mars, 1987).

iv. It has been verified as an easy and practical evaluation to differentiate between the qualities of degree of malocclusion during all stages of dental development (Alam et al., 2013).

v. It can predict surgical outcomes at an early age of 5 years (Atack et al., 1997a).

Disadvantages (Patel, 2011)

i. The GY requires the judges to be trained in the use of this index and recalibration is necessary to assure consistency.
ii. The GY can only be used to score UCLP and no other cleft types.
iii. The validity of the GY has not been investigated and it is predicted to be difficult since it requires a cluster of adults with UCLP who have been treated by primary surgery only.

2.10.1(b) EUROCRAN Index (EI)

The EI index was developed by the participants of the EUROCRAN project (2000–2004). This project was an extension of the EUROCLEFT project with the aim to recover research capabilities. This index was developed by using findings from the assessment of a mix of 118 cases from different European centres. A tally using the GY and the 5-year-old index had been maintained for these cases. The scores showed that only one of the cases was graded as 5, and two cases were graded as 1 by all the examiners involved in the study. Therefore, owing to the redundancy of the extremes in the scale of 1 to 5, it was decided that the grade options be reduced to four in the antero-posterior, vertical, and transverse dimensions, instead of the 5-grade scale. In addition, a 3-grade scale was allocated for rating the palatal form.

It is applied to study models, and the major components of this index include the degree of malocclusion in the antero-posterior and vertical dimensions, and the palatal form.

The functions, advantage and disadvantage of EI are as follows

Functions

i. It is useful in assessing surgical outcomes in patients with UCLP (Fudalej et al., 2011; Fudalej et al., 2012).

ii. It can be applied to evaluate the degree of malocclusion in both antero-posterior and vertical dimensions, as well as the palatal form (Fudalej et al., 2011; Fudalej et al., 2012).

Advantages

i. The supremacy of the EI is its validity (Fudalej et al., 2011)

ii. In order to amplify its judicious power, the index has a separate point for degree of malocclusion and palatal morphology (Fudalej et al., 2011; Fudalej et al., 2012).

iii. Compared to the GY, this index gives a more meticulous guide for cataloguing of treatment consequences (Patel, 2011).

iv. It has been shown to have moderate to very good inter- and intra-examiner reliability (Patel, 2011).

Disadvantages (Patel, 2011)

i. It requires elaborate study.

ii. It is difficult to apply and relies on conjectures. Consequently, there is more room for error.

iii. There are too many details to consider, and too many preconditions and modifications.

iv. It is more time-consuming and is more difficult to learn than the mHB scoring system.
v. Scoring the palatal vault is difficult.
vi. Scoring the palatal vault is subjective.

2.10.1(c) Modified Huddart Bodenham (mHB) Scoring System

mHB index, which is a modified version of Huddart/Bodenham index and used for measuring the maxillary arch constriction based on the over-jet, over-bite and molar occlusion. Originally, the use of the Huddart/Bodenham index was only for primary dentition which was the drawback of this index. Mossey et al. (2003) modified the index for mixed and permanent dentition. This index provide itself to be more versatile and sensitive to inter-arch discrepancies. According to World Health Organization (WHO) mHB scoring system outperformed as an ideal index (Altalabi et al., 2012).

The functions, advantage and disadvantage of mHB scoring system are as follows

Functions (Gray and Mossey, 2005)

i. It measures maxillary arch constriction in patients born with UCLP.
ii. It is applicable in any type of cleft.
iii. It measures severity of the crossbite and each maxillary tooth is scored according to its relationship with the corresponding tooth in the mandible.

Advantages

i. It is more versatile in that this index is applicable at any age after 3 years and in any type of cleft (Chaudhry et al., 2018).

ii. It is more reliable, objective, and sensitive than the GY and 5-year-old Yardstick indices (Chaudhry et al., 2018; Gray and Mossey, 2005).

iii. It is simple to use (Gray and Mossey, 2005).

Disadvantages

i. It does not score for antero-posterior skeletal and vertical discrepancies, and does not take into account incisor inclinations (Dobbyn et al., 2012).

2.10.1(d) Literature Survey of Different Indices

Different authors have studied different indices to obtain varying results. Susami et al. (2006) examined study models of 24 patients with UCLP, all prior to orthodontic treatment and alveolar bone grafting. The GY was used to rate the degree of malocclusion. Intra-and inter-examiner agreements estimated by weighted kappa statistics were high, indicating good reproducibility.

The degree of malocclusion was evaluated via the GY using intraoral dental photographs. These data suggest that intraoral dental photographs deliver a trustworthy method for rating the degree of malocclusion (Hsieh et al., 2012).

In another study, non-syndromic Caucasian children with UCLP were divided into two groups. Patients of age ranging from 5 to 10 years, who had been treated either with or without active infant orthopaedics, were selected. The study did not find any significant disparity between the two groups. While the orthopaedic group demonstrated a mean GOSLON score of 3.30, the non-orthopaedic group scored 3.21 (Chan et al., 2003).

Morris et al. (2000), assessed the maxillary growth in children born with a complete UCLP between 1983 and 1987, who had undergone primary cleft repair. The treatment outcome of this UCLP sample was then compared with the results of previously published articles. The models were assessed by using the GY. The results were of a slightly higher standard than that of previously published articles (Morris et al., 2000).

Mars et al. (1987), categorised malocclusions in patients with UCLP in a way that would symbolise the severity of malocclusion and the difficulty in correcting it. The results of the study exhibited that the GY was highly reliable and was discriminating of the quality of treatment results.

Chaudhry et al. (2018) and Altalabi et al. (2013) reviewed literature about different indices that are used to measure the treatment effectiveness in patients with UCLP, reported the GY was stated as the most frequently used index and the mHB as the best executed index, according to the WHO criteria.

Hathron et al. (1996), assessed 32 study models of patients with UCLP by using the GY. More than 50% of the sample was in the unfavourable GOSLON Groups IV and V. They planned their next surgical treatment protocol based on this assessment.

Lilja et al. (2006), found that at 19 years of age, 85% of the patients with UCLP were in GOSLON Groups I and II, whereas 12% were assigned to Group III. Only 3% of the cases were found to be in Group IV. No dental study model was found to be in Group V. This exceptional longitudinal study of patients with UCLP demonstrates the best degrees of malocclusion thus far presented using the GY.

Patel (2011) compared the reproducibility of the mHB and EI. She examined 30 study models by using these two indices and the study revealed that the mHB is more reliable than the EI.

Fudalej et al. (2011), compared the degree of malocclusion following 1-stage and 3-stage surgical protocols for UCLP. They analysed 61 dental casts using the EI and the results showed reliable outcomes. Fudalej et al. (2012), again studied the degree of malocclusion in 2 groups—exposed and unexposed—with UCLP that had been operated by the same surgeon. The degree of malocclusion and palatal morphology were rated separately by using the EI, and the treatment outcome was found to be reliable.

A study was undertaken to appraise the comparison of the effectiveness of the mHB system with that of the 5-year-old and GY in subjects with UCLP. Reiterated assessment was performed after a 1-month interval by 4 appraisers. It was found that the mHB system gave a credible valuation of the maxillary arch constriction (Gray and Mossey, 2005). A similar study was performed using study models of subjects with UCLP from England and Scotland. All the models had been previously scored by applying the 5-year-old and GY. The models were re-evaluated by applying the mHB system to compare the consequences and the mHB index proved to be a much more sensitive scoring system (Dobbyn et al., 2012).

Thus, we have reviewed different indices of diverse nature in relation to CLP. A systematic review of such complex indices may lead to better assessment and controller bias.

From this review, it can be concluded that different indices like the GY, 5-year-old Yardstick, EI, Huddert-Bodenham index, and mHB index are useful tools in clinical orthodontics for measuring treatment effectiveness in patients with CLP. The GY is the most commonly used index. The mHB index is encouraging in the assessment of malocclusions related to all types of CLP of all ages and in regulating the extent of outcomes in patients with CLP. The EI is a favorite because it can be used to evaluate the degree of malocclusion in both antero-posterior and vertical dimensions, as well as the palatal form. The 5-year-old index is the ideal index for 5-year-old patients. In orthodontics, the use of a combination of different types of indices appears to be beneficial and promising. The results of the literature survey for different indices in relation to CLP are shown in **Table 2.12.**

Table 2.12 Literature survey of different indices in relation to CLP

Author name and year	Used Index	Outcome
Susami et al. (2006)	GY.	Result showed good reproducibility.
Hsieh et al. (2012)	GY	Provided reliable treatment outcome.
Chan et al. (2003)	GY	Showed no significant group difference in the model scores of the two groups.
Kajii et al. (2013)	GY	Showed reliable results.
Morris et al. (2000)	GY	Provided useful baseline data.
Mars et al. (1987)	GY	Sufficiently reliable for general use.
Altalibi et al. (2013)	GY. 5 year old Yardstick. EUROCRAN index.	mHB was outperformed the best among the all indices.

	Huddart-Bodenham. MHB. Goal Yardstick. Bauru-Bilateral Cleft Lip and Palate Yardstick.	GY was the most commonly used index due to a longer time in use.
Hathron et al. (1996)	GY.	Showed reliable results.
Lilja et al. (2006)	GY	Produced the best GY ratings.
Alam et al. (2008)	5-year-old index. GY.	Satisfactory results by using 5-year- old index and GY.
Patel, (2011)	EI. mHB	mHB is more reliable than EI.
Johnson et al. (2000)	5-year-index.	Provided a favourable outcome.
Fudalj et al. (2011)	EI	Showed reliable outcome.
Fudalj et al. (2012)	EI	Treatment outcome was reliable.
Gray and Mossy et al. (2005)	mHB. GY. 5-year-old index.	Result showed that the mHB system provides an objective and reliable Assessment of maxillary arch constriction.
Dobbyn et al. (2011)	mHB system. GY. 5-year-old index.	mHB had been shown to be a much more sensitive scoring system.
Koshikawa- Matsuno et al. (2014)	GY. 5-year-old index.	Regarding both indices, no significant differences were found. However, the dental arch width showed some significant variations.

2.10.2 Treatment Outcome Based on Maxillary Arch Dimension

Cleft patient has a compromised maxillary arch dimension. Arch depth, interdental width, arch length were significantly smaller in UCLP patient compare to normal patients (Russel et al., 2015). The measurement of these value is essential for not only diagnosis but also for treatment in orthodontic clinic.

Four studies were evaluated maxillary arch dimension in Brazil and reported ICW was significantly smaller in UCLP subjects (Carrara et al., 2016; dos Santos et al., 2015; Garib et al., 2013; Mello et al., 2013). Only one study had been reported in Malaysia that assessed treatment outcome by measuring maxillary arch dimensions on 48 dental casts of UCLP. The study assessed only the maxillary arch dimension and compared the measurement with healthy non cleft control group. They found ICW and inter premolar width were significantly larger among control group than UCLP subjects (Gopinath et al., 2017).

Helio¨ vaara et al. (2014) conducted a study on Finnish UCLP adults in which one group needed orthognathic surgery where another group did not. However, authors' did not found any significant differences between who later needed orthognathic surgery and those who did not in terms of ICW and IMW.

A recent study was conducted on different cleft groups; UCLP and BCLP (Dogan et al., 2019). Significant diffrerences was reported between UCLP and BCLP in terms of ICW. Their UCLP groups had wider ICW than BCLP. Neamah (2011), conducted a comparison study between 30 UCLP subjects and 30 control groups; found significantly smaller ICW among UCLP subjects. ICW was the highest affected variable among all other variables followed by IMW and IPMW reported by most of the researchers.

A summary of publications of maxillary arch dimension on CLP is shown in **Table 2.13**.

Table 2.13 Literature survey of maxillary arch dimension in relation to CLP

Author	Measurement	Outcome
Dogan et al. (2019)	ICW IMW	Significant differences found in ICW between UCLP and BCLP group.
Carrara et al. (2018)	ICW ITW AL	Significant differences found in AL between pre-cheiloplasty and after palatoplasty.
Gopinath et al. (2017)	ICW IPMW IMW AD AL	ICW and IPMW was significantly larger in control group.
Cassi et al. (2017)	ICW IMW	Significant differences found in ICW between two groups.
Dos Santos et al. (2015)	ICW IMW (permanent) IMW (deciduous)	ICW showed significantly smaller in UCLP compared to the control group.
Wahaj and Ahmed, (2015)	ICW IMW	ICW showed significantly smaller in UCLP compared to the control group.
Helio¨ vaara et al. (2014)	ICW IMW (1st) IMW (2nd) AW	No significant difference found between who later needed orthognathic surgery and those who did not.
Koshikawa-Matsuno et al. (2014)	ICW IMW	Significant difference found between two different techniques of surgery in both ICW and IMW.

Kitagawa et al. (2014)	ICW IMW (deciduous) AL	Significant differences found between two groups
Mello et al. (2013)	ICW	Significant differences found.
Garib et al. (2013)	ICW IMW (permanent) IMW (deciduous)	ICW showed significantly smaller in UCLP compared to the control group.
Kozˇelj et al. (2012)	Transversal dimension Vertical dimensions Sagittal dimension	Significant difference found between the dimensions for five cleft groups and CG.
Neamah, (2011)	ICW IMW Incisor chord lengths	ICW and Incisor chord lengths were found significantly narrower in UCLP group compared to CG.
Al-Gunaid et al. (2008)	ICW IPMW IMW	Significant difference found in IPMW and IMW.
Lewis et al. (2008)	ICW IMW	ICW showed significantly smaller in UCLP compared to the control group.
Bongaarts et al. (2006)	AW AD AL Arch form Vertical dimension	No significant differences found between IO+ and IO- group
Garrahy et al. (2005)	ICW IMW AD	Significant difference found in IMW between UCL and CG. The maxillary arch dimensions were significantly greater in the CG compared to UCLP group.
Marcusson and Paulin, (2004)	ICW IMW AL	Significant differences found
Lehner et al. (2003)	Anterior arch width Posterior arch width	No significant difference found in anterior and posterior arch width between early and delayed closure of hard palate.

CG: Control Group (healthy non cleft group); AL: Arch Length; AW: Arch Width; IPMW: Inter Premolar Width;

2.11 Tooth Size Asymmetry

It is a significant challenge for the orthodontist to achieve successful treatment outcomes with constant, functional and ideal occlusion by designing a proper orthodontic treatment plan in a safe, effective and efficient way. Tooth size is one of the quantitative tools that have been developed to aid in these endeavors as dissimilarities in tooth size between the arches can hamper the appropriate tooth alignment. Therefore the orthodontist needs to record these variations properly before starting orthodontic treatment to get ideal occlusion successfully (Leung et al., 2018).

Both genetic and environmental factors are responsible for tooth size discrepancies which result in variations in number, dimensions, position, morphology, and structure. Tooth size discrepancies are also observed in different ethnic groups, races and secular trends (Akcam et al., 2008). Thus a multidisciplinary, complex and prolonged treatment approach is including orthodontic treatment that is required in the children with UCLP.

The frequency of dental anomalies is noticeably greater in UCLP children than general individuals (Shapira et al., 1999). Tooth anomalies frequently were seen on the cleft side (Camporesi et al., 2007). UCLP affected patients has quite compromised tooth size resulted from congenitally missing, pegged and malformed teeth, orthodontic anomalies like crowding, rotation, malposition of teeth, etc (Tan et al., 2018). Studies claimed that the children with UCLP often had smaller tooth size than the non-cleft patients (Foster and Lavelle, 1971; de Sabóia et al., 2013). Additionally, a remarkable asymmetry of tooth size between the cleft-side (CS) and non-cleft side (NCS) has been reported by researchers (dos Santos et al., 2015; Antonarakis et al., 2015; Lewis al at., 2008; Rawashdeh and Bakir, 2007).

Appropriate alignment of the tooth can improve the impact of tooth size discrepancies between CS and NCS of the arch. Before treatment, measuring or recording this asymmetry of the tooth may give important data to the clinician to obtain ideal occlusion, overjet, and overbite during or after treatment (Akcam et al., 2008).

In recent years, several research on MD tooth size of UCLP has been conducted worldwide and observed noticeable variations in tooth size in the published results (Sękowski et al., 2019; dos Santos et al., 2015; Antonarakis et al., 2015; Lewis al at., 2008; Akcam et al., 2008). Though, those studies were either on a particular centre or single based population and also tend to use plaster dental cast.

Recently, Sękowski et al. (2019), performed a study to measure the tooth size in 69 Polish UCLP children, reported both maxillary canines had the highest anomalies with reduced MD dimension. However, no significant association observed between the CS and NCS of maxilla in that study. In Turkish population, researchers found tooth size asymmetries between cleft group and non cleft group (Akcam et al. 2014). A study done on Jordanian UCLP subjects demonstrated that the MD dimension of permanent lateral incisor (PLI) of CS was significantly smaller than NCS of maxillae. However, that study also found a larger MD dimension of permanent canine (PC) and permanent first molar (P1M) on CS than NCS of maxillae (Rawashdeh et al., 2007).

Table 2.14 shows the literature survey of tooth size asymmetry in relation to MD dimension in cleft patients.

Table 2.14 **Literature survey of MD tooth size in relation to UCLP**

Author	Population	Outcome
Sękowski et al. (2019)	Polish	Maxillary canines had reduced MD dimension than non-cleft group.
Dindaroğlu et al. (2019)	Turkish	The maxillary central incisors had 1 mm difference between the tooth of CS and NCS maxilla in UCLP subjects.
Echtermeyer et al. (2017)	Asian European	larger MD dimension among Asian than European
dos Santos et al. (2015)	Brazilian	CS and NCS demonstrated similar maxillary tooth size except for the lateral incisor,
Akcam et al. (2014)	Turkish	Tooth size asymmetries were found in CLP subjects than control group.
Akcam et al. (2008)	Turkish	Tooth size asymmetries were found in CLP subjects than control group. The lateral incisor in the cleft region was the smallest.
Lewis al at. (2008)	South Yorkshir	Maxillary incisors are smaller on the CS than the NCS.
Rawashdeh et al. (2007)	Jordanian	Tooth size asymmetries were found in CLP subjects than control group.

2.12 3D Digital Models vs. Dental Casts

Plaster dental casts are extensively being used for clinical and research. It has advantages that the fabrication of dental cast was economical and the casts itself enable 3D assessments. However, dental casts occupied spaces in the dental office and difficult to transport from one office to the other. The dental casts have high compressive strength but brittle. Thus, there was possibilities of damage that important information may be lost. In recent years, due to inconvenience of transport, chance of destruction and expenses of dental casts as well as the advantages of digital techniques (digitation methods; such as laser, optical, stylus etc.), there has been worthy concern in alternatives to dental casts in dentistry. The replacement of dental casts with 3D digital dental cast has provided an alternative method owing to its perfect techniques of capturing images, ease of access, storage and transfer for diagnostic, clinical, and information purposes (Zilberman et al., 2003; Keating et al., 2008; Bootvong et al., 2010; Moreira et al., 2014; Lemos et al., 2015).

Dental casts in the research of UCLP children is very common in dentistry from last two decades. A very limited research has been conducted on 3D digital model in the research of UCLP children and have proven reliable and valid alternative method to dental casts (Botticelli et al., 2019; Zhu et al., 2016; Russel et al., 2015; Asquith and McIntyre, 2012; Dogan et al., 2012).

However, no research has been conducted using a combination of Next Engine Laser Scanner and Mimics software in the research of UCLP digital dental casts. In this study we used laser scanned 3D digital models (LS3DM) in assessing treatment outcome of UCLP children in three different populations.

The ability to accurately and reliably quantify the performance of LS3DM, is crucial that this would become the standard for both research and clinical use (Massoud et al., 2016). In recent years, the replacement of dental casts with 3D digital dental cast is a worthy and perfect alternative method in dentistry. There are some methods by which dental casts can be converted to digital casts, such as laser, digital photograph, stereolithography, optical, stylus etc. (Nugrahani et al., 2017; Zhu et al., 2016; Bootvong et al., 2010; Keating et al., 2008; Zilberman et al., 2003).

Some previous studies have established validity and reliability between dental casts and laser scanned digital models while measuring the treatment outcome (Nugrahani et al., 2017; Lemos et al., 2015; Moreira et al., 2014; Bootvong et al., 2010; Keating et al., 2008; Zilberman et al., 2003), but most of those studies were either on normal patient or using different devices. Our study tested Next Engine laser scanner device for converting dental casts of UCLP patient for the measurements of maxillary arch dimension and tooth size as well. Zilberman et al. (2003) evaluated a total of 40 different malocclusion patients; 20 dental casts by digital caliper and 20 LS3DM by OrthoCAD device and found highest correlation of validity and reliability of two methods. A similar study by Keating et al., (2008) on normal orthodontic patients using Minolta VIVID 900 non-contact 3D surface laser scanner to convert LS3DM and revealed the Minolta VIVID 900 digitizer is a reliable device for LS3DM which is an appropriate alternative of dental casts.

Regarding UCLP patients, few studies have published the evaluation of treatment outcome using 3D digital models and proven reliable and valid alternative method to dental casts based on dental arch relationship (Zhu et al., 2016; Russel et al., 2015; Asquith and McIntyre, 2012; Dogan et al., 2012). Our study evaluated the treatment outcome on LS3DM based on dental arch relationship, maxillary arch dimension and also tooth size asymmetry and showed that LS3DM by Next Engine laser scanner device is reliable and valid alternative tools. Based on literature, evaluation of treatment outcome by assessing dental arch relationship and maxillary arch dimension as measurements of well as tooth size of UCLP children using 3D digital models has been shown in **Table 2.15**.

Table 2.15 Evaluation of treatment outcome by assessing dental arch relationship and maxillary arch dimension using 3D digital models of UCLP children

Author	Population	Measurement	Sample size	Device Used
Chalmers et al. (2016)	Scotland	DAR	UCLP: 43	R700 Orthodontic Study Model Scanner (3Shape A/S)
Zhu et al. (2016)	Hong Kong	DAR	UCLP: 29	surface scanner (Lythos TM Digital Impression System, Ormco, Glendora, CA)
Russel et al. (2015)	US	DAR	UCLP: 29	Flatbed scanner (Microtek Scan Maker s400, Hsinchu, Taiwan)
Sabelis et al. (2015)	Netherlands	DAR	UCLP: 45	Digimodel® (Orthoproof, Doorn, The Netherlands)
Dogan et al. (2014)	Turkey	DAR	UCLP: 109	Orthomodel software program (Orthomodel VI.01, Istanbul, Turkey)
Chawla et al. (2012)	UK	DAR	UCLP: 45	R640 3Shape Desktop scanner (Copenhagen, Denmark)

Asquith and McIntyre, (2012)	UK	DAR	UCLP: 30	R250 Orthodontic Study Model Scanner (3Shape A/S, Copenhagen, Denmark)
Dogan et al. (2012)	Turkey	DAR	UCLP: 70	Digital orthodontic dental cast archiving system (Orthomodel V1.01, Istanbul, Turkey)
Kongprasert et al. (2019)	Thailand	MAD	UCLP: 16	3D scanner (R700TM Scanner; 3Shape AS, Copenhagen, Denmark)
Dogan et al. (2019)	Turkey	MAD	UCLP: 40 BCLP: 40	Orthomodel software program (Orthomodel VI.01, Istanbul, Turkey)
Falzoni et al. (2018)	Brazil	MAD	UCLP: 30	3D Scanner (3Shape's R700TM Scanner, 3Shape, Copenhagen, Denmark)
Carrara et al. (2016)	Brazil	MAD	UCLP: 114	3D Scanner (3Shape's R700™ Scanner, 3Shape, Copenhagen, Denmark)
Mello et al. (2013)	Brazil	MAD	UCLP: 50 BCLP: 25 CG: 19	3D Scanner (3Shape's R700™ Scanner, Copenhagen, Denmark)
Kitagawa et al. (2004)	Japan	MAD	UCLP:34	3D laser scanner (VIVID 910, Minolta Co., Ltd. Osaka, Japan)
Dindaroğlu et al. (2019)	Turkey	Tooth size	UCLP: 35	3D scanner (TRIOS; 3Shape, Copenhagen, Denmark)

Echtermeyer et al. (2017)	Asian European	Tooth size	UCLP: 40	Reflex microscope (Reflex Measurement Ltd, London, UK)
Present study	**Malaysia Bangladesh Pakistan**	**DAR MAD Tooth size**	**UCLP:255**	**Next Engine laser scanner (Santa Monica)**

DAR: dental arch relationship; MAD: maxillary arch dimension

2.12.1 Next Engine Laser Scanner

The Next Engine laser scanner is a desktop three-dimensional (3D) scanner that uses an array of lasers to scan objects at resolutions of 0.005 inches. The Next Engine Ultra HD professional 3D scanner was manufactured by an American company. It is able to scan different textures but also objects in colour. Its near scan surface is 130 x 97 mm and the distance is 343 x 257 mm. The Next Engine Ultra HD is based on laser triangulation and offers a maximum resolution of 0.1 mm. It can scan 50,000 points per second with a maximum accuracy of 0.13 mm (Guidi et al., 2007). The instrument is a low cost scanner, presented as a “desktop scanner” able to digitize small objects in basically two categories: “shoe box” and “soda can” size. It is very portable, being small and of light weight, and has a turning table supplied together with it, which is wired to the scanner and is controlled by the proprietary software included. Not much information is provided in literature about the used device scanning principles. However we found in a public database, a patent [Ser. No. 09/660,809 filed on Sep. 13, 2000 now U.S. Pat. NO. 6,639,684 entitled “Digitizer using intensity gradient to image features of three-dimensional objects”] issued in 2000 and granted in 2005, by the company producing the scanner, which in the embodiment describes a device very similar to the one commercialized.

The acquisition principle there described is a new one and is based on the two considerations: (i) depth data for a three-dimensional object may be calculated from an acquired intensity difference, resulting from an intensity gradient projected onto the object; (ii) existing low cost imaging devices, such as charged coupled device (CCD) or complementary metal-oxide-semiconductor (CMOS) linear array, present a very accurate and linear response to the intensity of the light received (Guidi et al., 2007).

The instruments is equipped with a twin array of 4 solid state lasers (class 1M, 10mW) with λ=650 nm and two 3 Mpixel CMOS RGB array sensors. The system acquires in two different modes corresponding to two different baselines: wide mode and macro mode respectively. For each mode, some constraints on the distance between the object and the scanner are given: the ideal position for wide mode requires the object to be 45 cm far from the front of the scanner, while macro mode requires the object to be 16 cm far away and a scanning time of 30 seconds (Guidi et al., 2007). The instrument characteristics reported in the specs is reported in **Table 2.16**.

Table 2.16 Specifications of the Next Engine laser scanner (Guidi et al., 2007)

	Macro Mode	**Wide Mode**
Field of View	130 x 96 mm	343 x 256 mm
Resolution (Geometry point density on target surface)	200 DPI	75 DPI
Texture Density (on target surface)	400 DPI	150 DPI
Accuracy	±0.127 mm	±0.381 mm
Uncertainty	Not available	Not available

CHAPTER 3

METHODOLOGY

3.1 Study Design

This research is a cross sectional study approach to determine treatment outcome among UCLP children and their associated congenital (UCLP type, UCLP side, family history of CLP, family history of Class III malocclusion) and postnatal treatment (cheiloplasty, palatoplasty) factors among Malaysian, Bangladeshi and Pakistani populations. This research was conducted over two years and ten months (June 2017 to April 2020).

3.2 Reference Population

The reference population of the study covered the UCLP children from three populations. The populations are

i) Malaysian population (Malay ethnic group)

ii) Bangladeshi population.

iii) Pakistani population

Confirmation of the ethnicity of all the subjects was obtained from patient's records.

3.3 Source of Population

The source of population of this study was patient's clinical records and plaster dental casts from the archive of School of Dental Sciences, Universiti Sains Malaysia who fulfilled the study criteria.

The data (patient's clinical records and plaster dental casts) from all populations were used in another three MSc projects of School of Dental Sciences, University Sains Malaysia. Individual ethical clearance were obtained from individual country and USM ethics committee as well (please see the appendix). After completing those projects, it was in the archive of School of Dental Sciences, Universiti Sains Malaysia.

3.3.1 Malaysian Population

Patient clinical records and plaster dental casts (taken for pre-treatment orthodontics) were obtained from the archives of Orthodontic Department School of Dental Sciences, Universiti Sains Malaysia. Plaster dental casts were made during subjects' early visits to the orthodontist at Orthodontic Department School of Dental Sciences, Universiti Sains Malaysia. Moreover, these subjects under went cheiloplasty and palatoplasty at the Department of Plastic and Reconstructive Surgery and Oral and Maxillofacial Surgery respectively in Hospital Universiti Sains Malaysia (HUSM), Kota Bharu, Kelantan between 2000 and 2012.

3.3.2 Bangladeshi Population

Patient clinical records and plaster dental models (taken for pre-treatment orthodontics) were obtained from the archives of Queens Hospital (pvt) LTD, Jessore, Bangladesh. Plaster dental casts were made during subjects' first visit to the orthodontist at the same hospital. The subjects attended their primary surgeries in the same hospital between 2010 and 2013.

3.3.3 Pakistani Population

Patient clinical records and plaster dental models (taken for pre-treatment orthodontics) were obtained from pre-existing hospital archives of a regional cleft centres located in Punjab, Pakistan. Plaster dental casts were made during subjects' first visit to the orthodontist at the same centre. The subjects attended their primary surgeries in the same centre between 2010 and 2013.

3.4 Inclusion Criteria

The inclusion criteria of this study were:

i) Non-syndromic UCLP children.

ii) Individuals aged 5-12 years (during the time of taking impression).

iii) Cheiloplasty and palatoplasty had been performed.

iv) No alveolar bone graft.

v) Orthodontic treatment had not been started.

3.5 Exclusion Criteria

The exclusion criteria of this study was subjects with bilateral CLP, CL, and alveolus and isolated CP.

3.6 Sampling Method

All subjects who fulfilled the inclusion and exclusion criteria were included in this study by simple random sampling method. Initially 111, 99 and 110 Malaysian, Bangladeshi and Pakistani UCLP subjects were selected from the record archive.

After that all UCLP subjects have been assigned a unique numbers. To avoid any selection bias, a computer software program (random number generator) randomly select numbers that have been assigned uniquely to each subject of the UCLP population for sampling.

3.7 Sample Size Calculation

1. **Specific Objectives 1-3 of Dental Arch Relationship and 1-3 of Maxillary Arch Dimension**

The sample size calculation was done based on a ratio of 1 predictor: 20 cases. In our study, there are eight predictors. Thus the minimum estimated sample size was **160**. [According to Hair et al. (2006), the minimum ratio of observation is 1:5]

2. **Specific Objectives 4 of Maxillary Arch Dimension (Between Populations)**

The sample size calculation was done based on a ratio of 1 predictor: 20 cases. In our study, there are nine predictors. Thus the minimum estimated sample size was **180**. [According to Hair et al. (2006), the minimum ratio of observation is 1:5]

3. **Specific Objectives 1-3 of Tooth Size Symmetry**

Prior data indicate that the difference in the tooth size of matched pairs is normally distributed with a standard deviation of 0.6 mm (Akcam et al., 2008). If the true difference in the mean tooth size of the side difference is 0.2 mm, we required to study **73** subjects to be able to reject the null hypothesis that this tooth size difference is zero with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05.

According to Biau et al. (2008), a larger sample size will produce more stable results for regression analysis. The sample size calculation using 1:20 between the predictor to sample was a crude estimation (Hair et al., 2006). Thus, following the strict inclusion and exclusion criteria, finally **255** (85 for each population) subjects had been selected for this study.

3.8 Research Tools

The research tools of this study were:

i) History and examination record review of Malaysian, Bangladeshi and Pakistani UCLP children.

ii) Laser scanned 3D digital models (LS3DM).

iii) Indices for assessing treatment outcome (GY, EI and mHB scoring system).

iv) Next Engine laser scanner (Santa Monica).

v) Mimics software (Belgium).

3.9 Variables

3.9.1 Dependent Variables

A. Evaluation of Dental Arch Relationship

i) GOSLON score.

ii) EUROCRAN score.

iii) mHB score.

B. Evaluation of Maxillary Arch Dimension

i) Inter-canine width.

ii) Inter-molar width.

iii) Arch depth.

C. Tooth size symmetry

i) Mesio-distal (MD) width of teeth of cleft side and non-cleft side of maxilla.

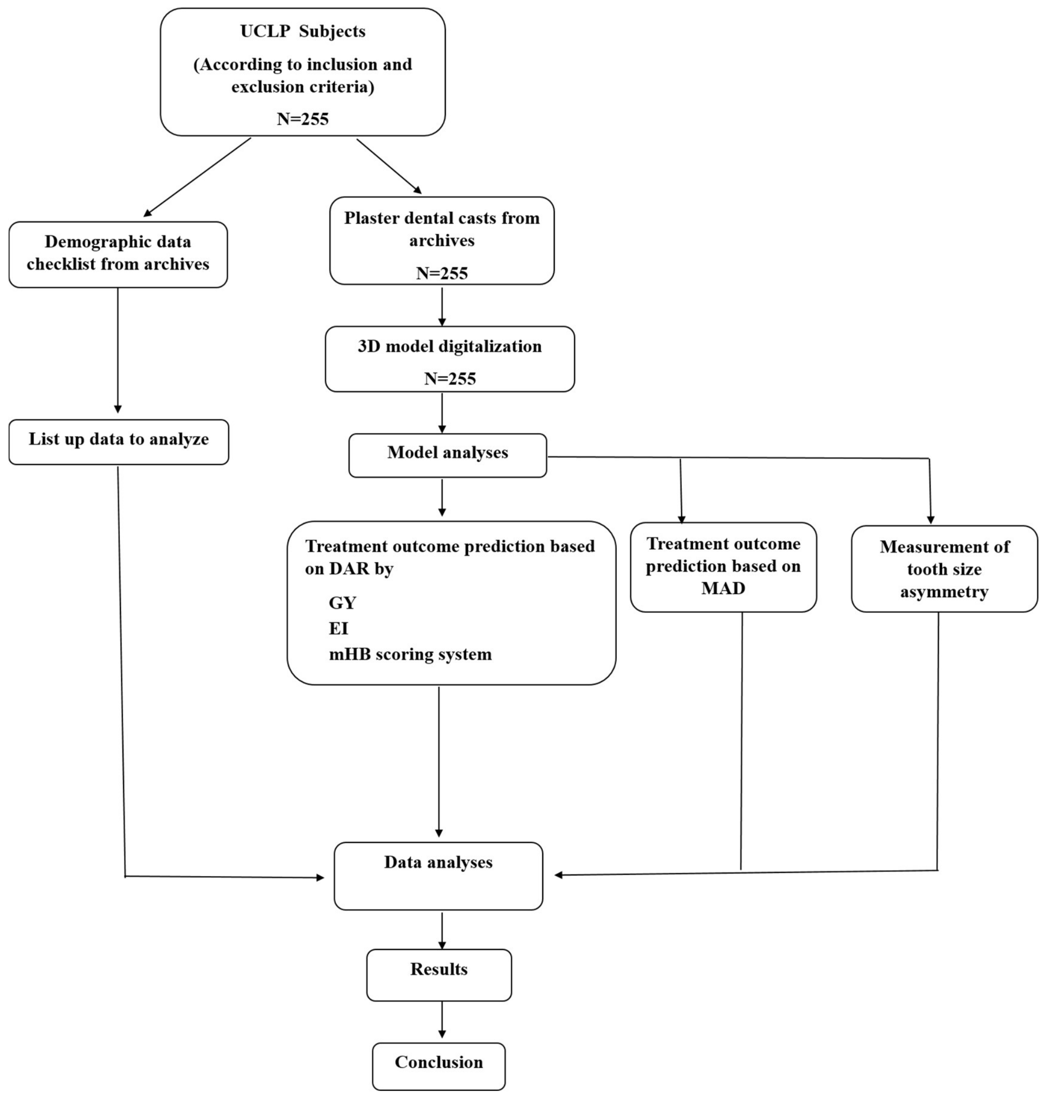
3.9.2 Independent Variables

i.	Gender	Male, Female
i.	Age	5-8 years, 9-12 years
ii.	Family history of cleft	Positive, Negative
iii.	Family history of skeletal Class III	Positive, Negative
iv.	UCLP affected side	Right, Left
v.	UCLP types	Complete, Incomplete
vi.	Techniques of Cheiloplasty	Millard technique, Modified Millard technique
vii.	Techniques of Palatoplasty	Bardach technique, von Langenbeck technique

3.10 Ethical Approval

This study was approved by the USM Ethics Committee [USM/JEPeM/17100564] which complies with the Declaration of Helsinki (1964).

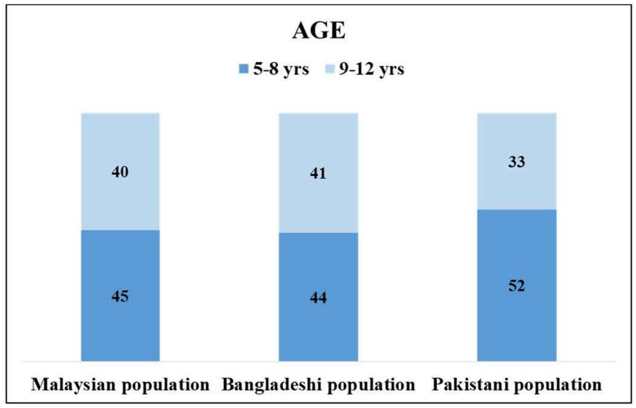
3.11 Flow chart

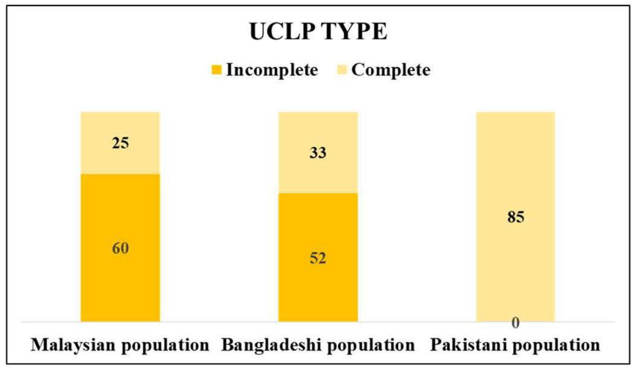


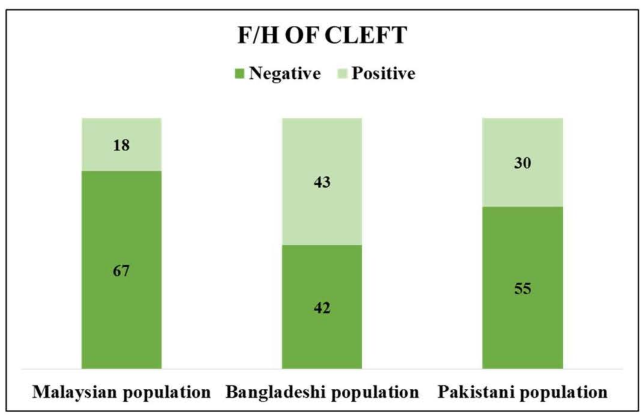
3.12 Subjects

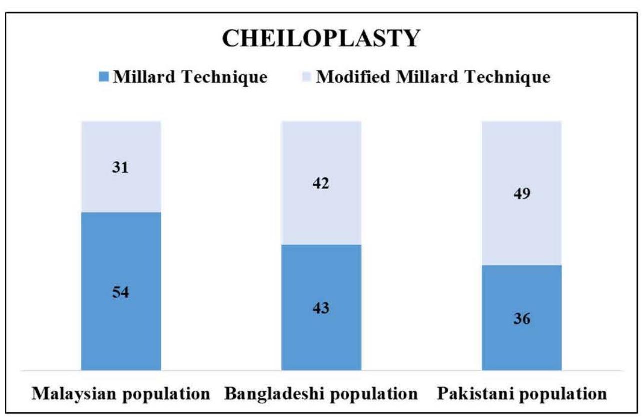
The study group was limited to a total of 255 subjects with non syndromic UCLP in which the age range of 5 to 12 (7.69± 2.46) years. All the subjects have received cheiloplasty and palatoplasty and have not received any orthodontic treatment and bone grafting. All the subjects were treated with either Millard technique or modified Millard technique of cheiloplasty at the age of 3 to 6 months and also with two different surgical protocols of palatoplasty. i.e., Bardach technique or von Langenbeck technique completed at 12-18 months of age. All the surgeries were performed by one experienced surgeon from each population.

The distribution of all subjects from three populations with multiple factors was shown in **Figure 3.1**.


AGE
5-8 yrs
9-12 yrs
40
41
33
45
44
52
Malaysian population
Bangladeshi population
Pakistani population


UCLP TYPE
Incomplete
Complete
25
33
85
60
52
0
Malaysian population
Bangladeshi population
Pakistani population


F/H OF CLEFT
Negative
Positive
18
43
30
67
42
55
Malaysian population
Bangladeshi population
Pakistani population


CHEILOPLASTY
Millard Technique
Modified Millard Technique
31
42
49
54
43
36
Malaysian population
Bangladeshi population
Pakistani population

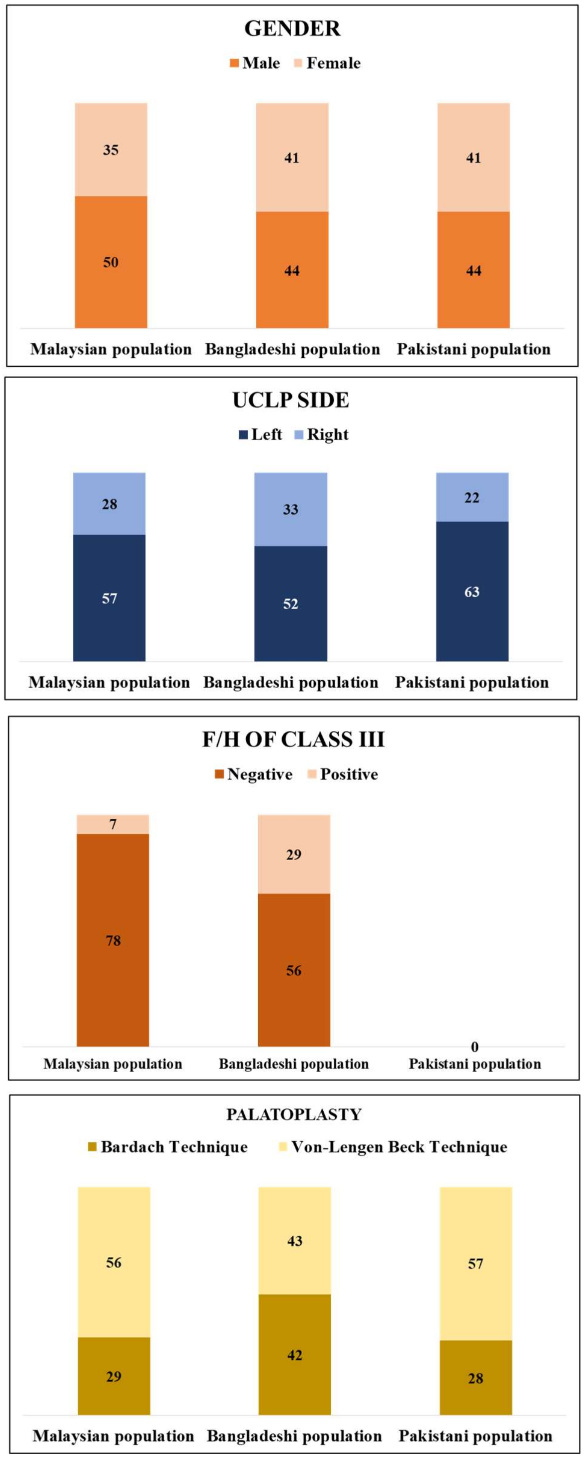


Figure 3.1 Distribution of all subjects from three populations with multiple factors. (All the Pakistani UCLP subjects were complete type of UCLP. No record was found regarding family history of Class III malocclusion in Pakistani UCLP subjects) *F/H: family history

3.13 Data collection procedure

Following the strict inclusion and exclusion criteria, all the plaster dental casts from all three populations have been collected from the record archive of the School of Dental Sciences, Universiti Sains Malaysia. Total 255 study models (85 in each group) were selected for Malaysian, Bangladeshi and Pakistani UCLP children and the data has been extracted from the patient's folder including-

No	Information	Description	
1	Age		
2	Gender	a. Male	b. Female
3	Family history of cleft	a. Positive	b. Negative
4	Family history of skeletal Class III	a. Positive	b. Negative
5	UCLP affected side	a. Right	b. Left
6	UCLP types	a. Complete	b. Incomplete
7	Cheiloplasty	a. Millard technique	b. Modified Millard technique
8	Palatoplasty	a. von LangenBeck technique	b. Bardach technique

3.13.1 Conversion of the Dental Casts into Laser Scanned 3D Dental Models (LS3DM)

Next Engine laser scanner is a device for recreating 3D digital objects which consists of computer, scanner and auto-drive (**Figure 3.2**). The Auto drive consisted of a gripper arm, platter pad, and platter shaft. The casts were carried by platter pad and fixed on gripper arm. The platter pad screw enable up, low, right and left adjustment of the dental casts. Gripper arm screw was used to move gripper arm up-down. The dental casts were scanned from every angle using 360 degree scan option from the panel. The next engine 3D laser scanner detected object's length, width and depth. The angulation of the casts was 90 degree.

First, the scanner collects surface data of the object by flashlight, and then four laser beams slowly moved across the surface of the object, capturing data points which formed the geometric structure of the object (**Figure 3.3**). The software allowed examiners to analyse the images in every aspects by manipulating the digital models on their personal computers.

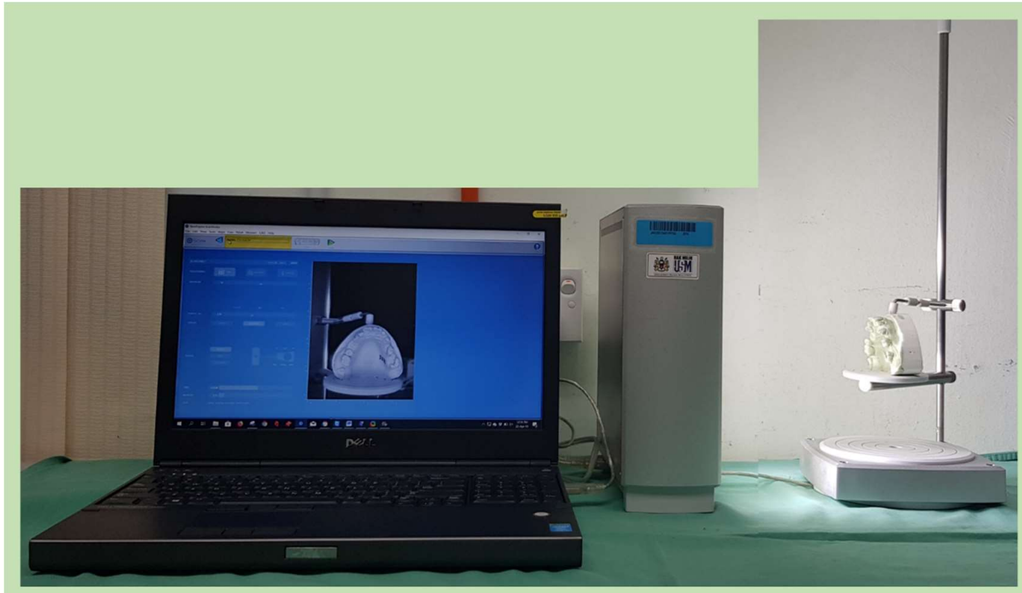


Figure 3.2 Next Engine laser scanner including computer, scanner and Auto-drive

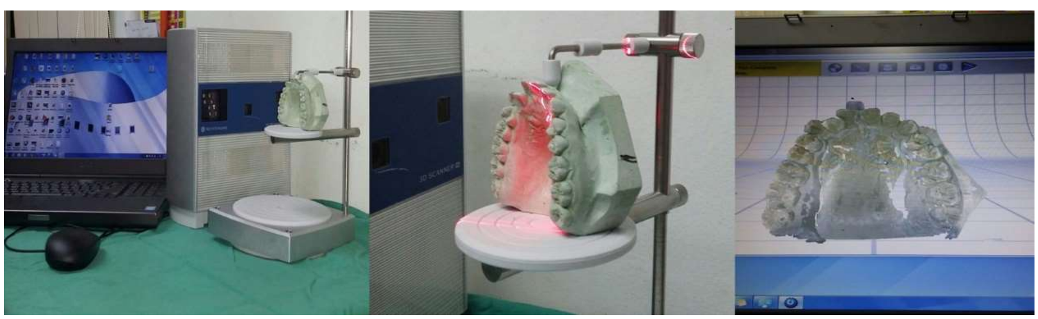


Figure 3.3 Capturing data points which formed the geometric structure of the object

3.13.2 Measurement by Mimics Software

All scanned data coordinates (in x, y, z) were transferred into Mimics software in STL format. All variables (maxillary arch dimension and tooth size assymmetry) were measured (**Figure 3.4**).

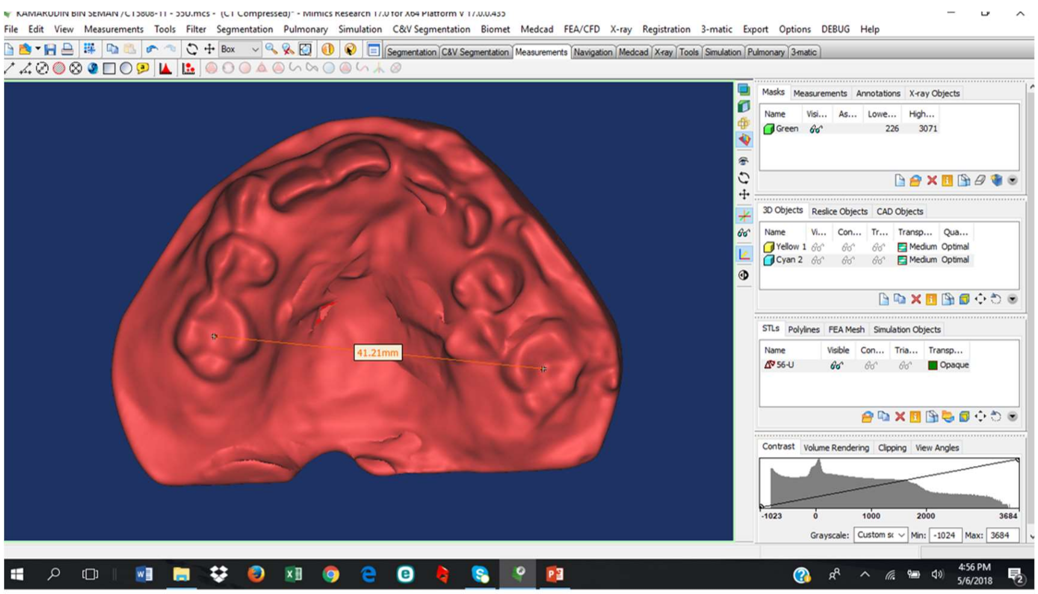


Figure 3.4 LS3DM in the STL format

3.13.3 Evaluation of Dental Arch Relationship

i) All the LS3DM were assessed using GY, EI and mHB scoring system.

ii) One examiner participated in this study for GY, EI and mHB scoring system. Each set of model given individual scores over two sessions with one-week interval. The mean score of two sessions of the examiner was chosen for the analysis.

iii) Based on scoring, all the subjects divided into two groups: favourable and unfavourable for dental arch relationship. This grouping carried out because patients in the favourable groups may not need further treatment after palatoplasty or cheiloplasty or they may need the conventional orthodontics treatment, whereas patients in the unfavourable groups sometimes required surgical correction (Chan et al., 2003).

For GY

The subjects were divided into two groups: favourable (group I-III) and unfavourable (group IV and V) groups for dental arch relationship.

For EI

The subjects divided into two groups: favourable (group I and II) and unfavourable (group III and IV) for dental arch relationship.

For mHB Scoring System

The subjects divided into two groups: favourable (group excellent, good and fair) and unfavourable (group poor and very poor) for dental arch relationship.

3.13.3(a) Evaluation of Dental Arch Relationship Using GY

It sorts out severity of malocclusions according to antero-posterior (AP) arch, vertical labial segment and transverse relationships. A score of 1 means a favourable AP relationship for orthodontic correction and a score of 5 means a very poor AP relationship with osteotomy necessary for correction. A score of 3 usually means an anterior end-to end situation.

Group I-Excellent - a favourable relationship, shows advantageous skeletal form, with a positive overjet and overbite. Patients exhibit an Angle Class II malocclusion in this group. Straightforward orthodontic treatment or no treatment need at all in this group.

Group II- Good - is also a favourable relationship with Angle Class I dental relationship and also indicates straightforward orthodontic treatment.

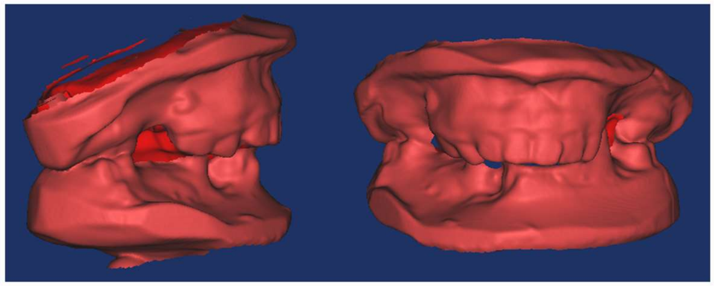
Group III- Fair - presents as an edge-to-edge dental relationship where patient need of more complex orthodontic treatment to correct the Angle Class III malocclusion and other possible arch deformities, but a good result can still be predictable.

Group IV -Poor - an unfavourable facial growth (Angle skeletal Class III relationship) with reverse overjet of 3-5 mm which indicates the limits of orthodontic treatment, may require an orthognathic procedure.

Group V- Very poor - represents a significant Angle skeletal Class III relationship with mandatory surgical correction.

The 5 categories, as given bellow with figures:-

GROUP I



<u>GROUP I (Excellent Outcome)</u>

FEATURES:

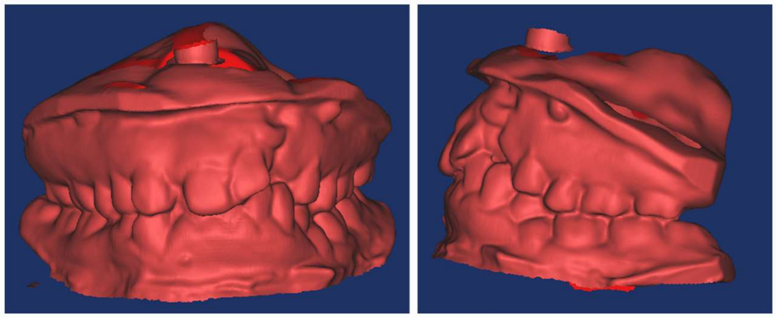
- **Favorable.**
- **Advantageous skeletal form.**
- **Positive overjet and overbite.**
- **Exhibit Angle Class II .**

TREATMENT REQUIRED:

- **Straightforward orthodontic treatment or none at all.**

Figure 3.5 Features of Group I of GOSLON Yardtick

GROUP II



GROUP II (Good Outcome)

FEATURES:

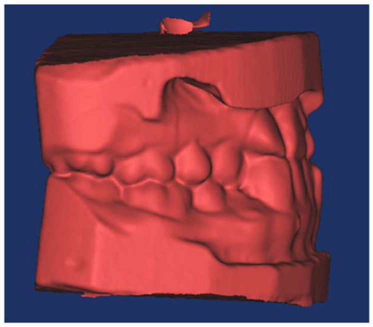
- **Favorable relationship.**
- **Angle Class I dental relationship.**

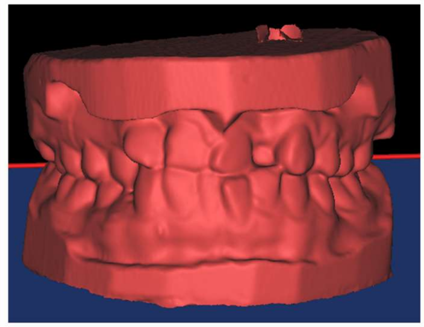
TREATMENT REQUIRED:

- **Straightforward orthodontic treatment or none at all.**

Figure 3.6 Features of Group II of GOSLON Yardtick

GROUP III





GROUP III (Fair Outcome)

FEATURES:

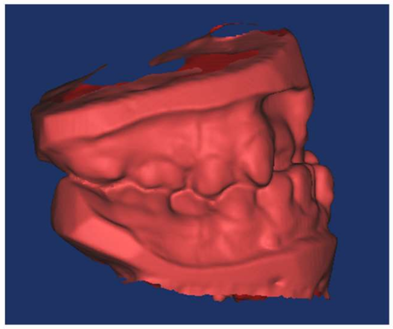
- **Edge to edge dental relationship (Angle Class III).**
- **In case of borderline case between III and IV: deep overbite, group III.**

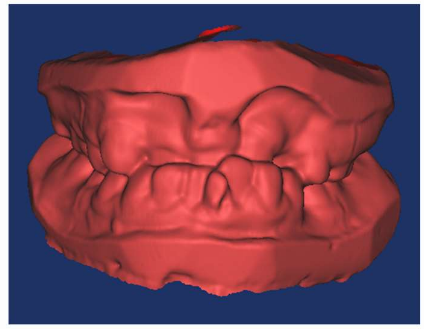
TREATMENT REQUIRED:

- **Complex orthodontic treatment.**

Figure 3.7 Features of Group III of GOSLON Yardtick

GROUP IV





GROUP IV (Poor Outcome)

FEATURES:

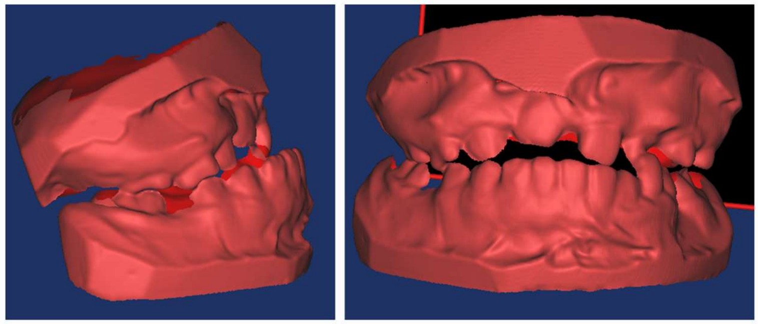
- **Unfavorable facial growth (Angle Class III)**
- **Reverse overjet of 3-5 mm case belong to group IV.**
- **In case of borderline case between III and IV: anterior open-bite, group IV.**

TREATMENT REQUIRED:

- **Borderline orthodontic treatment.**

Figure 3.8 Features of Group IV of GOSLON Yardtick

GROUP V



GROUP V (Very Poor Outcome)

FEATURES:

- **Significant Angle Class III.**
- **Reverse overjet of 3-5 mm but marked proclination of upper incisors and retroclination of lower incisor.**

TREATMENT REQUIRED:

- **Surgical treatment.**

Figure 3.9 Features of Group V of GOSLON Yardtick

3.13.3(b) Evaluation of Dental Arch Relationship Using EI

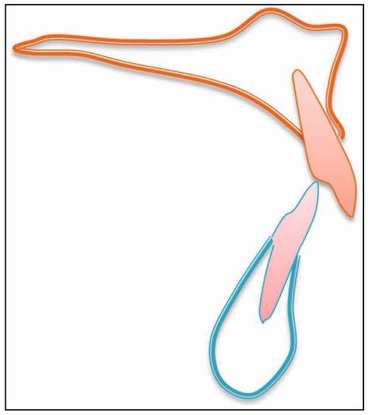
The dental arch relationship and palatal morphology will be scored by the EI, which is a scoring system for the early, late-mixed and early-permanent dentition using four categories of antero-posterior, transverse and vertical discrepancies as well as three categories of palatal morphology in patients with UCLP (Fudalej et al., 2012). The EI has two elements, an antero-posterior aspect (4 grades) and a palatal aspect (3 grades).

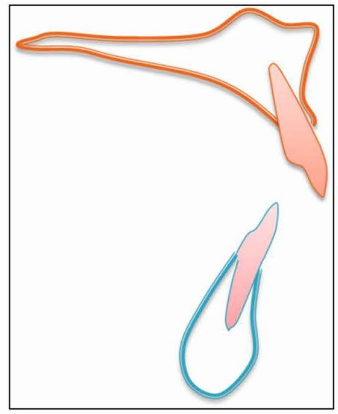
In the case of the dental arch relationship, a score of 1 or 2 implies a favourable dental relationship, a score of 3 means a less-favourable antero-posterior or end-to-end relationship, and a score of 4 indicates that the patient will possibly require orthognathic surgery to correct the antero-posterior relationship. Similarly, in the case of palatal morphology, a score of 1 indicates good morphology, whereas a score of 3 indicates poor morphology (Fudalej et al., 2011)

Following **Figure** exemplify the scoring system for the EI

Dental Arch Relationship

GROUP I





<u>Group I (Very Good Outcome)</u>

FEATURES:

a) - Apical base relationship skeletal Class I or Class II

- Both central incisors positive over-jet and overbite

Note: If both incisors have a positive over-jet and overbite but the incisor relationship was achieved by obvious dental compensation/orthodontic treatment, the case is group II

b) - Apical base relationship skeletal Class I or Class II

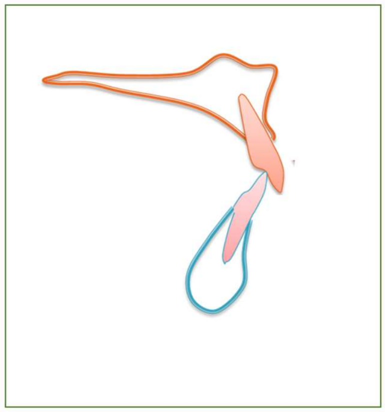
- No overbite but overjet markedly increased

Note: If there is no overbite and the overjet is not markedly increased, the case is group II

Figure 3.10 Features of Group I of EUROCRAN index (Dental arch relationship)

Dental Arch Relationship

GROUP II



<u>Group II (Good Outcome)</u>

FEATURES:

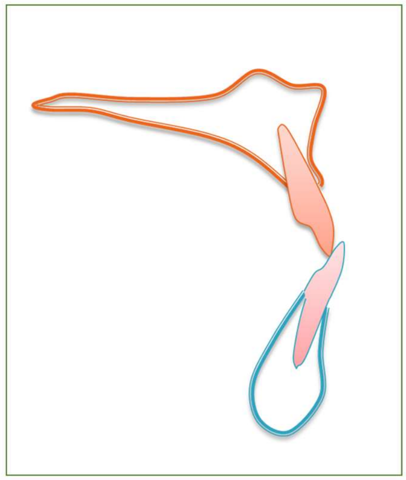
- **Apical base relationship skeletal Class I**
- **Non-cleft incisor in positive overjet and overbite**
- **Tilting or derotation would achieve stable positive over-jet and overbite of the incisor on the cleft side**

Note: the case is group III if there is a moderate open bite

Figure 3.11 Features of Group II of EUROCRAN index (Dental arch relationship)

Dental Arch Relationship

GROUP III



<u>Group III (Poor Outcome)</u>

FEATURES:

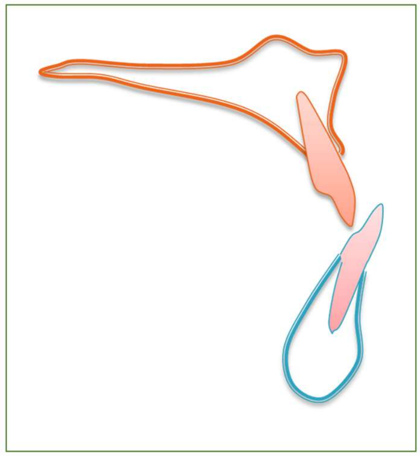
- **Apical base relationship edge-to-edge or mild Class III**
- **One or both central incisors edge-to-edge or in anterior cross-bite**
- **Tilting or derotation would not achieve a stable positive overj-et and overbite (i.e., the proclined tooth would relapse).**
- **May include moderate open bite**

Note: if both incisors have an edge-to-edge relationship but the skeletal Class is III (i.e., incisor relationship was achieved by dental compensation/orthodontic treatment), the case is group IV

Figure 3.12 Features of Group III of EUROCRAN index (Dental arch relationship)

Dental Arch Relationship

GROUP IV



<u>Group IV (Very Poor Outcome)</u>

FEATURES:

a) - Apical base relationship Class III

- Both centrals in anterior cross-bite or one in anterior cross-bite with the other edge-to-edge

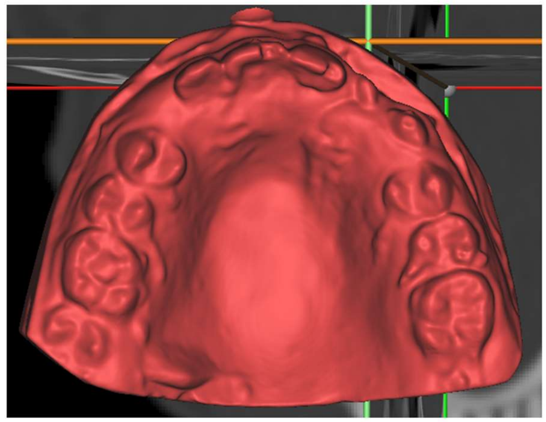
- Central incisors may or may not be in contact with the lower incisors

b) As group III but with a marked open bite

Figure 3.13 Features of Grade IV of EUROCRAN index (Dental arch relationship)

Palatal Morphology

GROUP 1



<u>GROUP I (Good Outcome)</u>

FEATURES:

- **Good anterior and posterior palatal height.**
- **Minor surface irregularities.**
- **No or minor deviation of arch form.**

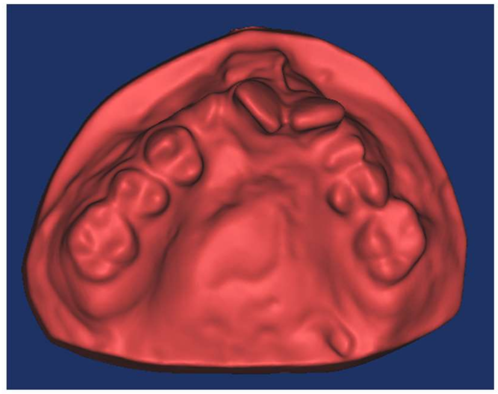
TREATMENT REQUIRED:

- **Straightforward orthodontic treatment or none at all.**

Figure 3.14 Features of Group I of EUROCRAN index (Palatal morphology)

Palatal Morphology

GROUP II



<u>GROUP II (Fair Outcome)</u>

FEATURES:

- **Moderate anterior and posterior palatal height.**
- **Moderate surface irregularities.**
- **Moderate deviation of arch form.**

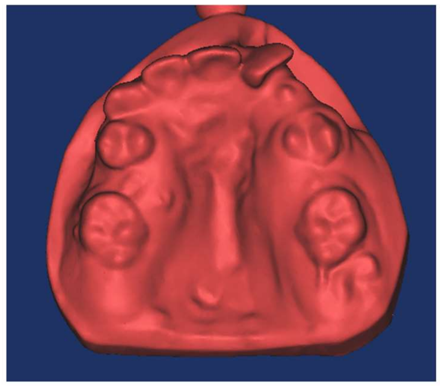
TREATMENT REQUIRED:

- **Complex/ Borderline orthodontic treatment.**

Figure 3.15 Features of Group II of EUROCRAN index (Palatal morphology)

Palatal Morphology

GROUP III



<u>GROUP III (Poor Outcome)</u>

FEATURES:

- **Severe anterior and posterior palatal height.**
- **Severe surface irregularities.**
- **Severe deviation of arch form.**

TREATMENT REQUIRED:

- **Surgical treatment (with condition).**

Figure 3.16 Features of Group III of EUROCRAN index (Palatal morphology)

3.13.3(c) Evaluation of Dental Arch Relationship Using mHB Scoring System

In mHB index, to assess the dental arch relationship, all teeth from first permanent molar forward is scored. Therefore, premolars are scored as primary molars in a same way. In case of unerupted or missing tooth, the score is given by determination of midpoint of the maxillary alveolar ridge at the position of the missing tooth.

- A cumulative score resulting from eight categorical assessments in the primary dentitions (2 deciduous central incisors, 2 deciduous canines and 4 deciduous molars) and 10 in the mixed or permanent dentitions (2 central incisors, 2 canines, 4 premolars and 2 molars) (Dobbyn et al., 2012). If the total arch constriction is towards negative scoring, it indicates that the maxillary arch constriction is more severe.

According to mHB, it measures severity of cross-bite and scored each maxillary tooth from 1st permanent molar to lateral incisor, or midpoint of the segment in relation to corresponding mandibular tooth. Total arch constriction mHB score is acquired from the entire score of each individual tooth.

- A score of 0 to +2 indicates an excellent, -1 to -5 indicates a good, -6 to -10 indicates fair, -11 to -16 indicates poor and a score of -17 to -22 indicates a very poor dental arch relationship (Manosudprasit et al., 2011).
- Other studies (Antonarakis et al., 2015; Dobbyn et al., 2012) shows a score of +2 to -10 indicates excellent to fair outcome and -10 to -30 indicates poor to very poor dental arch relationship. Based on these, in this study, a score of > 0 indicates an excellent, < -1 indicates a good, < -5 indicates fair, < -10 indicates poor and a score of < -16 indicates a very poor dental arch relationship.

- This study scored the dental arch relationshion based on Antonarakis et al. (2015) and Dobbyn et al. (2012)
- Tooth scoring: 0: Class I relationship; + 1: Class II relationship; -1: edge to edge; -2: mild Class III relationship and -3: severe Class III relationship.

Following **Figure** exemplify the scoring system for the mHB

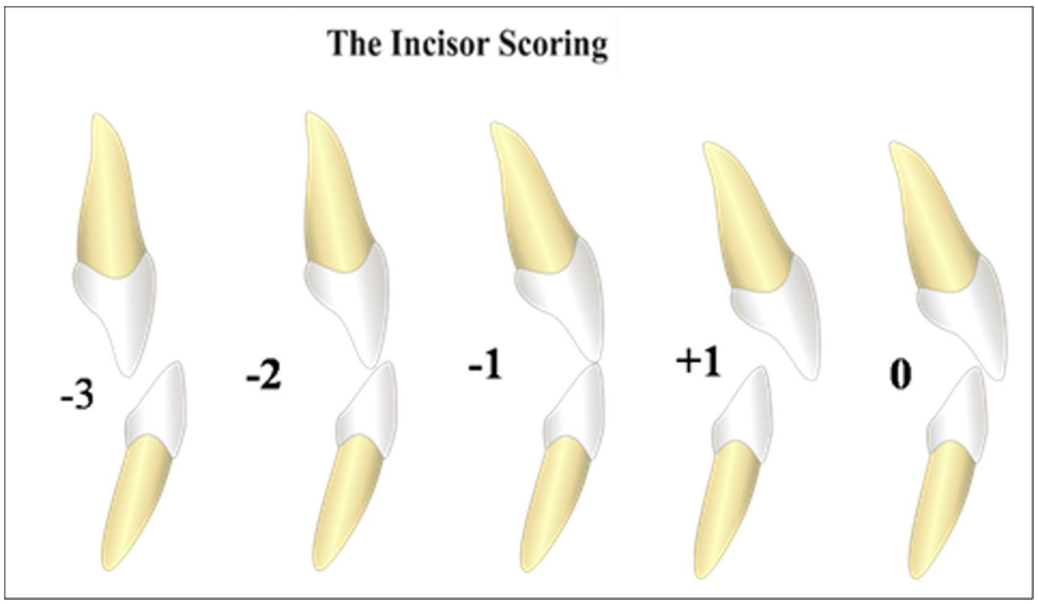


Figure 3.17 Diagram representing the scoring method for incisors when using the mHB scoring system (Redrawn from Dobbyn et al., 2012)

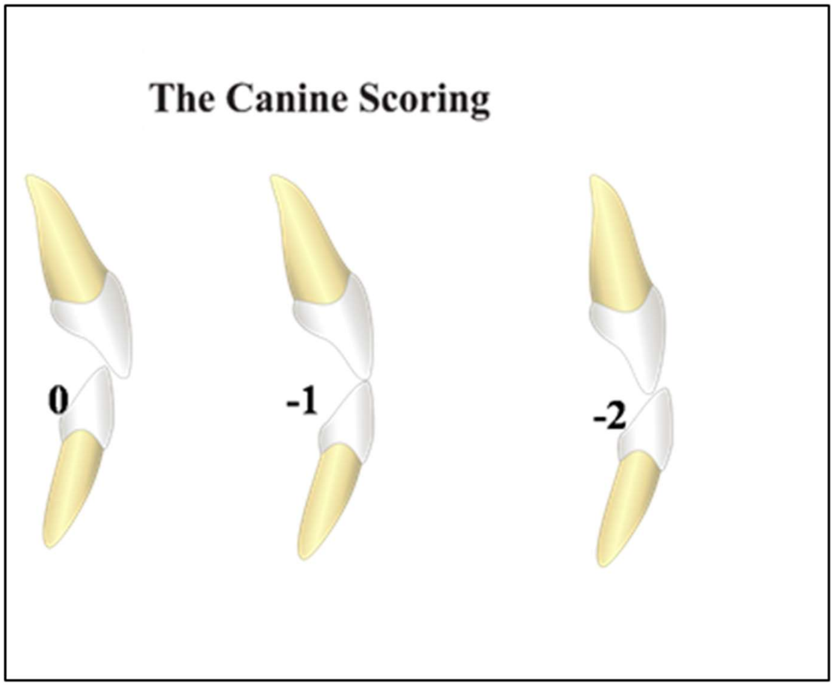


Figure 3.18 Diagram representing the scoring method for canines when using the mHB scoring system (Redrawn from Dobbyn et al., 2012)

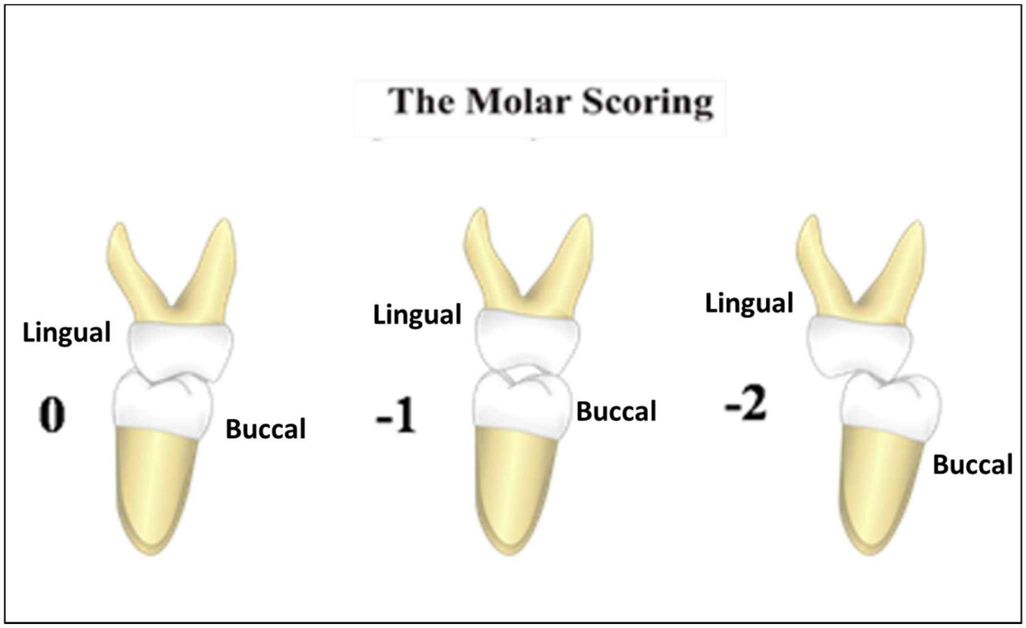


Figure 3.19 Diagram representing the scoring method for molars when using the mHB scoring system (Redrawn from Dobbyn et al., 2012)

3.13.4 Evaluation of Maxillary Arch Dimension

1. **Inter Canine Width (ICW):** The distance between cusp tips of the upper deciduous canines (**Figure 3.20**).

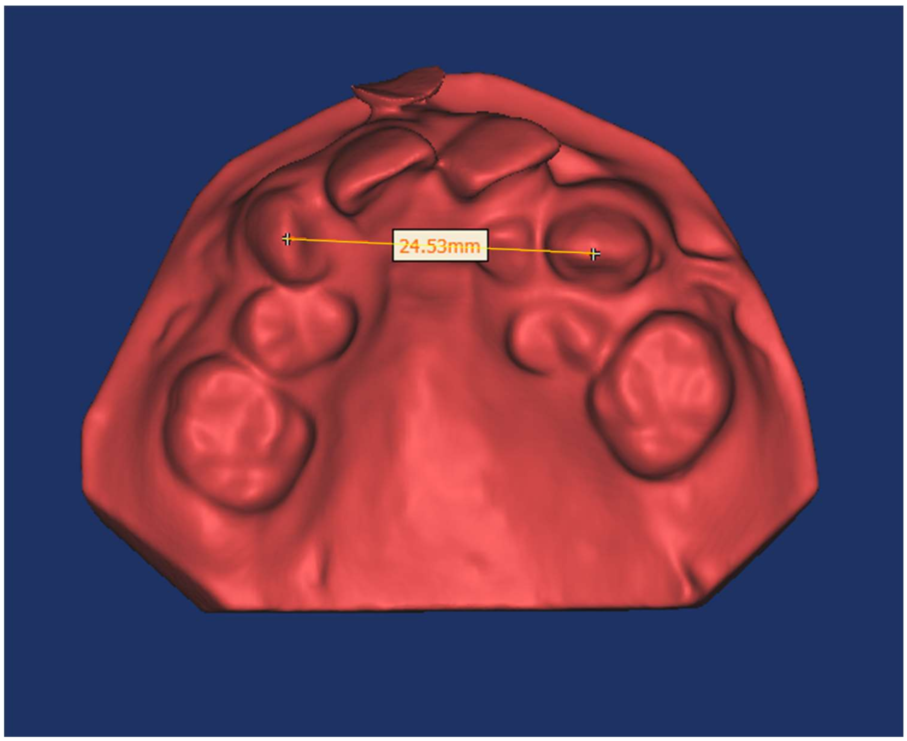


Figure 3.20 Measurements of the inter-canine width (ICW)

2. **Inter Molar Width (IMW):** The distance between the mesiolingual cusps or centres of the corresponding facets of the upper deciduous first molars (**Figure 3.21**).

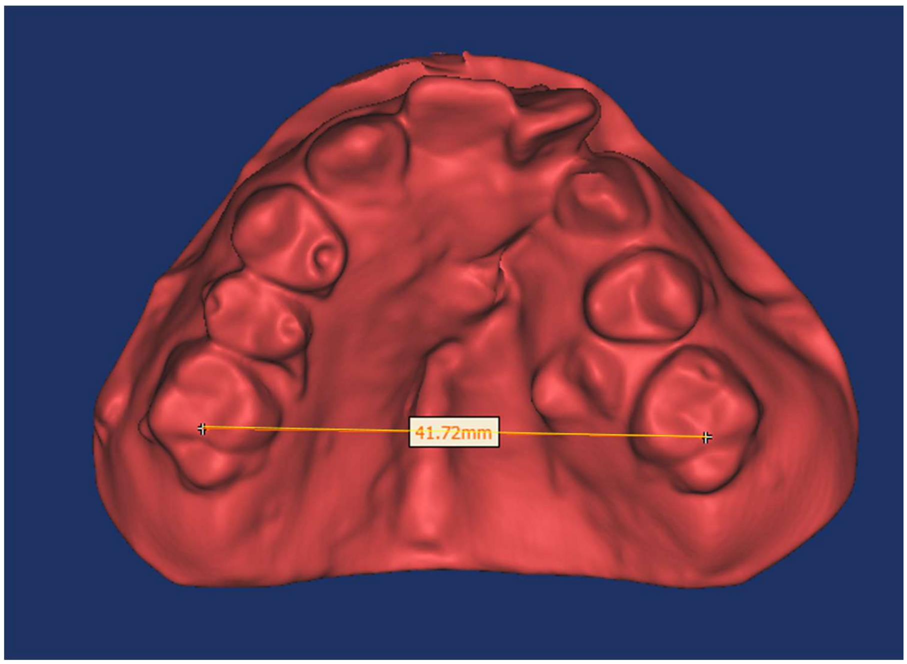


Figure 3.21 Measurements of the inter-molar width (IMW)

3. **Arch Depth (AD):** A perpendicular line from the mesial contact area of the central incisor to inter first molar width (**Figure 3.22**).

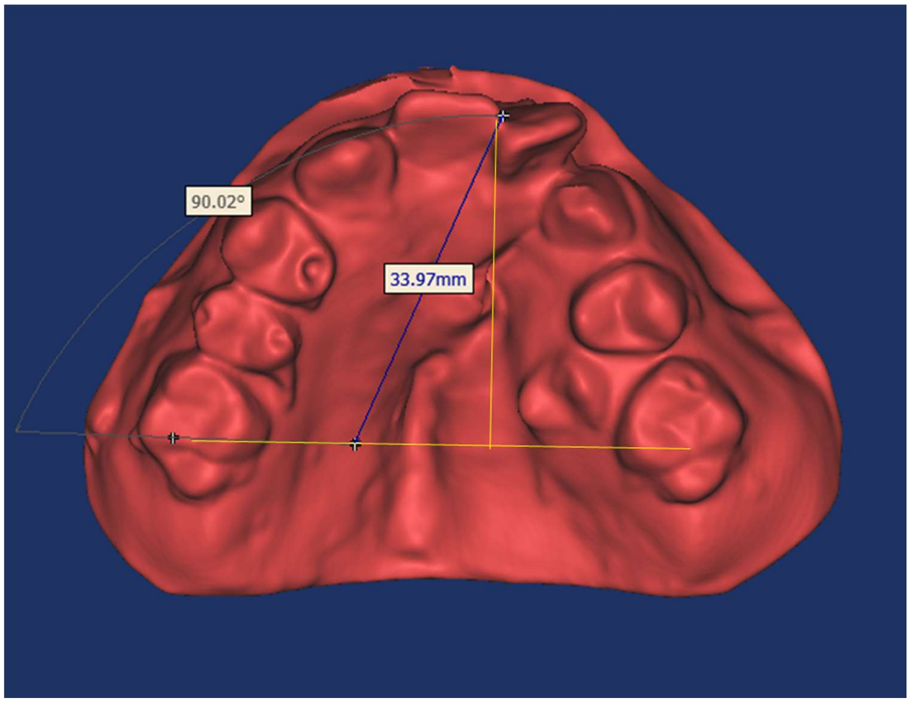


Figure 3.22 Measurements of the arch depth (AD)

3.13.5 Tooth Size Asymmetry

The MD dimensions of the teeth measured on LS3DM. The MD dimension measured as the longest distance between the anatomic mesial to the distal contact point (**Figure 3.23**) (Akcam et al., 2014).

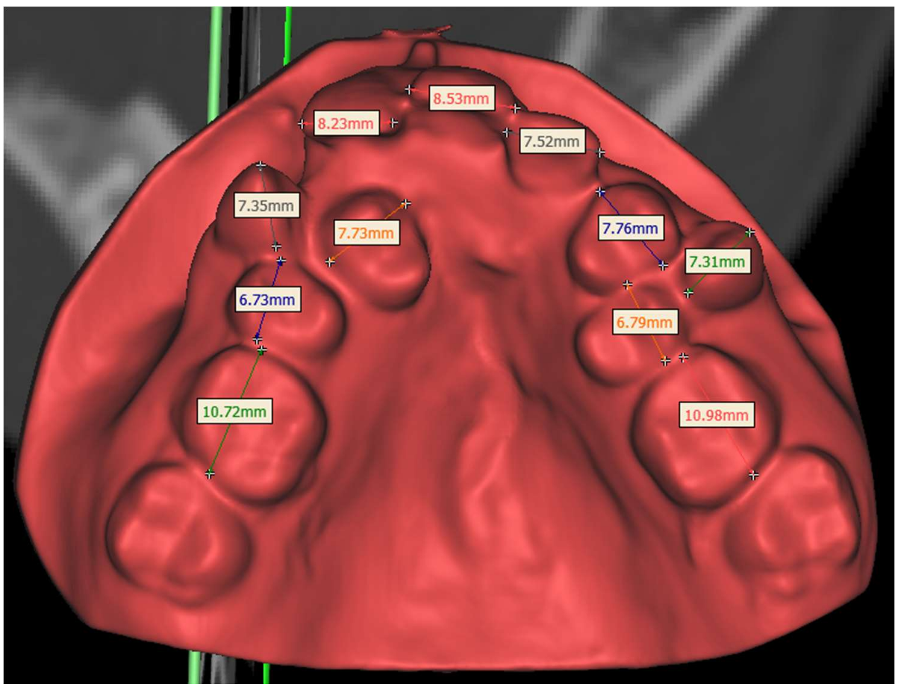


Figure 3.23 Measurements of MD dimension of tooth on LS3DM

3.14 Analysis

3.14.1 Error Study

A) For LS3DM

A total of 30 dental casts of UCLP children with 90 linear variables were measured using digital caliper while the laser scanned 3D digital model (LS3DM) were measured using Mimics software (Belgium). Intra-class correlation coefficient (ICC) was used to evaluate the intra- and inter-examiner reliabilities and also for the validity of two methods. ICC values and their 95% confidence intervals were calculated using SPSS statistical software version 24.0 (IBM, Armonk, NY, USA). Based on the 95% confident interval of the ICC estimate, value less than 0.5, between 0.5 and 0.75, between 0.75 to 0.90 and more than 0.90 are indicative of poor, moderate, good and excellent reliability, respectively.

Table 3.1 ICC value and interpretation (Koo and Li, 2016)

ICC value	Level of agreement
< 0.50	Poor
0.51 – 0.75	Moderate
0.76 – 0.90	Good
> 0.91	Excellent

Measurements by Digital Caliper

A hand held digital caliper (series 500 Digimatic ABSolute Caliper, Mitutoyo Corporation, Kawasaki, Japan), was used to manually measure the dental casts. This caliper had a measurement resolution of 0.01 mm in the 0–200 mm range.

Reliability Test

Intra examiner reliability test was conducted with interval of 2 weeks between the first and repeated measurements on all 30 dental casts and 30 LS3DM using Mimics software. Inter examiner reliability test was conducted by comparing data between two different examiners on all 30 LS3DM.

Validity Test

The data obtained from LS3DM were compared against digital caliper's data since it has been widely used. High correlation between two methods would indicate the measurement using LS3DM is valid.

B) For Dental Arch Relationship

The intra- and inter-examiner agreements were analysed with Kappa statistics for measurements. The Kappa values of intra-examiner agreements were interpreted based on Altman's Kappa benchmark range (Altman, 1991); where less than 0.20 indicated poor level of agreement; 0.21 to 0.40, a fair level of agreement; 0.41 to 0.60, a moderate level of agreement; 0.61 to 0.80, good agreement; and 0.81 to 1.00, very good agreement.

Table 3.2 Kappa value and interpretation (Altman, 1991)

Kappa value	Level of agreement
< 0.20	Poor
0.21 – 0.40	Fair
0.41 – 0.60	Moderate
0.61 – 0.80	Good
0.81 – 1.00	Very good

3.14.2 Statistical Analysis

All the analyses have been carried out using the statistical package SPSS Version 24.0 (SPSS Inc., Chicago, IL, USA). The significance level has been set at $p < 0.05$.

A. Association between treatment outcome and population differences with various factors based on dental arch relationship using GY, EI, and mHB scoring system

i) Multiple factors with favourable and unfavourable outcomes were evaluated by Chi square test.

ii) Logistic regression analysis used to explore the association between independent variable (gender, age, family history of cleft and Class III malocclusion, UCLP side, UCLP type, techniques of cheiloplasty and techniques of palatoplasty) and dependent variable (treatment outcome based on dental arch relationship).

iii) The statistical model of logistic regression analysis for Malaysian and Bangladeshi population:

$$p = \frac{Exp\begin{pmatrix} \beta_0 + \beta_1 Age + \beta_2 Gender + \beta_3 UCLP\,type + \beta_4\ UCLP\,side + \beta_5\ FH\ of\ cleft + \\ \beta_6\ FH\ of\ class\ III + \beta_7\ Cheiloplasty + \beta_8\ Palatoplasty \end{pmatrix}}{1 + Exp\begin{pmatrix} \beta_0 + \beta_1 Age + \beta_2 Gender + \beta_3 UCLP\,type + \beta_4\ UCLP\,side + \beta_5\ FH\ of\ cleft + \\ \beta_6\ FH\ of\ class\ III + \beta_7\ Cheiloplasty + \beta_8\ Palatoplasty \end{pmatrix}}$$

iv) The statistical model of logistic regression analysis for Pakistani population:

$$p = \frac{Exp\left(\beta_0 + \beta_1 Age + \beta_2 Gender + \beta_3\ UCLP side + \beta_4\ FH\ of\ cleft + \beta_5\ Cheiloplasty + \beta_6\ Palatoplasty\right)}{1 + Exp\left(\beta_0 + \beta_1 Age + \beta_2 Gender + \beta_3\ UCLP side + \beta_4\ FH\ of\ cleft + \beta_5\ Cheiloplasty + \beta_6\ Palatoplasty\right)}$$

B. Association between treatment outcome and population differences with various factors based on maxillary arch dimension

i) Multiple linear regression analyses used to evaluate the association between independent variable (gender, age, family history of cleft and Class III malocclusion, UCLP side, UCLP type, techniques of cheiloplasty and techniques of palatoplasty) and dependent variable (treatment outcome based on maxillary arch dimension).

ii) The statistical model of multiple linear regression analysis for Malaysian and Bangladeshi population:

$$y = \beta_0 + \beta_1 Age + \beta_2 Gender + \beta_3\ UCLP\ type + \beta_4\ UCLP\ side + \beta_5\ FH\ of\ cleft + \\ \beta_6\ FH\ of\ class\ III + \beta_7\ Cheiloplasty + \beta_8\ Palatoplasty$$

iii) The statistical model of multiple linear regression analysis for Pakistani population:

$$y = \beta_0 + \beta_1 Age + \beta_2 Gender + \beta_3\ UCLP side + \beta_4\ FH\ of\ cleft + \\ \beta_5\ Cheiloplasty + \beta_6\ Palatoplasty$$

C. Comparison of tooth asymmetry between cleft and non-cleft side

i) Paired t-tests performed to compare the mean of tooth size between the cleft and non-cleft side of maxilla in gender and each population.

ii) Multiple linear regression analyses used to evaluate the association between independent variable (gender and races) and dependent variable (tooth size of cleft and non-cleft side).

iii) The statistical model of multiple linear regression analysis for all populations

$y_1 = \beta_0 + \beta_1 Gender + \beta_2 Race$ (Cleft side)

$y_2 = \beta_0 + \beta_1 Gender + \beta_2 Race$ (Non-cleft side)

CHAPTER 4

RESULTS

4.1 Results of Error Study (For LS3DM)

4.1.1 Intra Examiner Reliability

Table 4.1 shows the result of intra examiner reliability of the measurements of ICW, IMW and AD in dental casts using digital caliper. ICCs for all these variables were in the range of 0.91-0.99 which indicates excellent correlation.

Table 4.1 Intra examiner reliability of ICW, IMW and AD in dental casts using digital caliper

Variables		**ICC**[b]	**95% CI**		**F Test with True Value 0**			
			LB	**UB**	**Value**	**df1**	**df2**	***p****
ICW	Single Measures	0.99[a]	0.98	0.99	417.06	18	18	**<0.001**
IMW	Single Measures	0.99[a]	0.98	0.99	269.87	29	29	<**0.001**
AD	Single Measures	0.91[a]	0.83	0.95	22.23	29	29	**<0.001**

ICC: Intraclass Correlation; CI: Confidense Interval; LB: lower bound; UB: Upper bound
***p* < 0.005 statistically significance (the correlation coefficient was not zero**)

Table 4.2 shows the result of intra examiner reliability of the measurements of ICW, IMW and AD in LS3DM using Mimics software. ICCs for all these variables were in the range of 0.91-0.99 which also indicates excellent correlation.

Table 4.2 Intra examiner reliability of ICW, IMW and AD in LS3DM using Mimics software

Variables		**ICC[b]**	**95% CI**		**F Test with True Value 0**			
			LB	**UB**	**Value**	**df1**	**df2**	***p****
ICW	Single Measures	0.98[a]	0.96	0.99	155.64	18	18	**<0.001**
IMW	Single Measures	0.99[a]	0.98	0.99	202.25	29	29	**<0.001**
AD	Single Measures	0.91[a]	0.47	0.97	45.81	29	29	**<0.001**

ICC: Intraclass Correlation; CI: Confidense Interval; LB: lower bound; UB: Upper bound
***p < 0.05 statistically significance (the correlation coefficient was not zero**)

4.1.2 Inter Examiner Reliability

Table 4.3 shows the result of inter examiner reliability of the measurements of ICW, IMW and AD in LS3DM using Mimics software. ICCs for all these variables were in the range of 0.81-0.99 which also indicates the good to excellent correlation.

Table 4.3 Inter examiner reliability of ICW, IMW and AD in LS3DM using Mimics software

Variables		**ICC[b]**	**95% CI**		**F Test with True Value 0**			
			LB	**UB**	**Value**	**df1**	**df2**	***p****
ICW	Single Measures	0.98[a]	0.95	0.99	169.97	18	18	**<0.001**
IMW	Single Measures	0.99[a]	0.98	0.99	209.83	29	29	**<0.001**
AD	Single Measures	0.81[a]	0.27	0.93	17.93	29	29	**<0.001**

ICC: Intraclass Correlation; CI: Confidense Interval; LB: lower bound; UB: Upper bound
***p* < 0.05 statistically significance (the correlation coefficient was not zero**)

4.1.3 Validity of Two Different Methods

Table 4.4 shows the results of validity of two methods of measurements using digital calipers in plaster dental casts and Mimics software in LS3DM. The ICC coefficients were statistically significant, p<0.001 and the values of coefficient were in the range of excellent (0.91-0.99) correlation.

Table 4.4 Validity of two different methods (LS3DM vs. dental cast)

Variables		**ICC[b]**	**95% CI**		**F Test with True Value 0**			
			LB	**UB**	**Value**	**df1**	**df2**	***p****
ICW	Single Measures	0.99[a]	0.99	0.99	514.68	18	18	**<0.001**
IMW	Single Measures	0.99[a]	0.97	0.99	622.34	29	29	**<0.001**
AD	Single Measures	0.91[a]	0.80	0.96	26.21	29	29	**<0.001**

ICC: Intraclass Correlation; CI: Confidense Interval; LB: lower bound; UB: Upper bound. ***p** **< 0.05 statistically significance (the correlation coefficient was not zero**)

4.2 Results of GY

4.2.1 Reliability of GY

Two examiners (Examiner A and B) participated for the scoring of models using GY. Intra-examiner agreements for examiner A was 0.70 (**Table 4.5**). The kappa score was 0.63 for the inter-examiner (**Table 4.5**). The kappa scores for the GY showed good intra- and inter-examiner agreements.

Table 4.5 Intra- and inter-examiner agreements of GY

	Kappa value	**Standard error**
	Intra-examiner aggrement	
Examiner A	0.70	0.16
	Inter-examiner aggrement	
Examiner A vs. Examiner B	0.63	0.17

4.2.2 GOSLON Score Distribution

Malaysian Population

Among the 85 subjects, scores were distributed as follows: group I= 4 subjects, II=17 subjects, III=44 subjects, IV=17 subjects and V= 3 subjects.

The mean GOSLON score was **2.97**

Bangladeshi Population

Among the 85 subjects, scores were distributed as follows: group I= 3 subjects, II=11 subjects, III=31 subjects, IV=29 subjects and V= 11 subjects.

The mean GOSLON score was **3.40**

Pakistani Population

Among the 85 subjects, scores were distributed as follows: group I = 4 subjects, II=25 subjects, III=26 subjects, IV=19 subjects and V= 11 subjects.

The mean GOSLON score was **3.09**

Figure 4.1 shows the score distribution of UCLP subjects of three populations using GY.

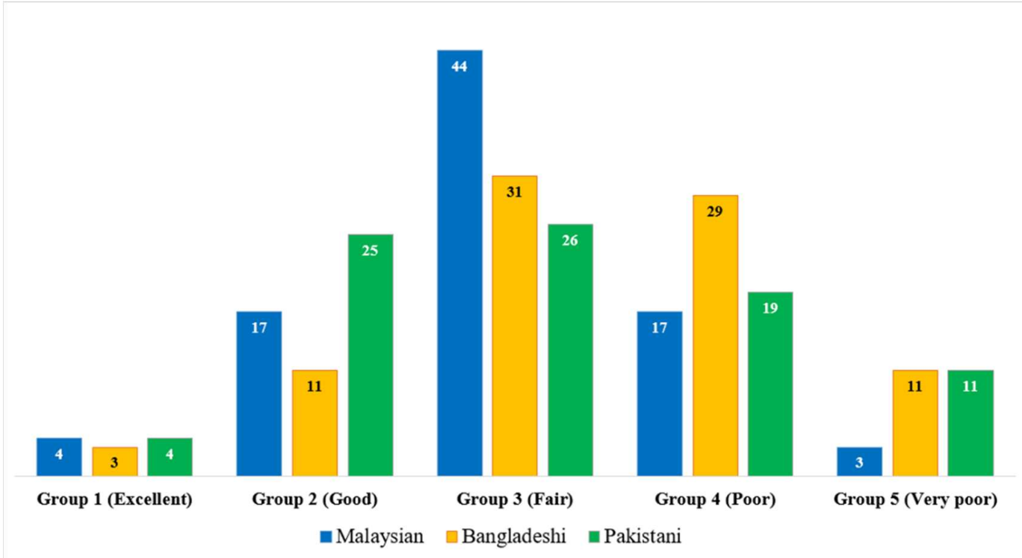


Figure 4.1 The score distribution of UCLP subjects of three populations using GY

4.2.3 Comparison of Factors between Favourable and Unfavourable Groups

Malaysian Population

Fifty-eight subjects were in favourable group and 27 subjects were in unfavourable group.

Bangladeshi Population

The number of subjects in favourable and unfavourable groups was 45 and 40, respectively.

Pakistani Population

The number of subjects in favourable and unfavourable groups was 55 and 30, respectively.

Table 4.6 shows the details distribution of all the subjects with multiple factors in favourable and unfavourable groups using GY in all the three populations.

Table 4.6 Distribution of subjects with multiple factors in favourable and unfavourable groups using GY in Malaysian, Bangladeshi and Pakistani UCLP children

Variable	Tx Outcome of Malaysian Population, n (%)		Tx Outcome of Bangladeshi Population, n (%)		Tx Outcome of *Pakistani Population, n (%)	
	Fav	Unfav	Fav	Unfav	Fav	Unfav
Age						
5-8 years	29 (34.1)	16 (18.8)	21(24.7)	23 (27.1)	36 (42.2)	16 (18.8)
9-12 years	29 (34.1)	11 (12.9)	24 (28.2)	17 (20.0)	19 (22.4)	14 (16.5)
Gender						
Male	38 (44.7)	12 (14.1)	19 (22.4)	25 (29.4)	24 (28.2)	20 (23.5)
Female	20 (23.5)	15 (17.6)	26 (30.6)	15(17.6)	31 (36.5)	10 (11.8)
UCLP Side						
Left	40 (47.1)	17 (20.0)	30 (35.3)	22 (25.9)	43 (50.6)	20 (23.5)
Right	18 (21.2)	10 (11.8)	15 (17.6)	18 (21.2)	12 (23.5)	10 (11.8)
UCLP type						
Incomplete	46 (54.1)	14 (16.5)	29 (34.1)	23 (27.1)	N/A	N/A
Complete	12 (14.1)	13 (15.3)	16 (18.8)	17 (20.0)		
F/H of Cleft						
Negative	44 (51.8)	23 (27.1)	24 (28.2)	18 (21.2)	37 (43.5)	18 (21.2)
Positive	14 (16.5)	4 (4.7)	21 (24.7)	22 (25.9)	18 (21.2)	12 (14.1)
F/H of Class III						
Negative	54 (63.5)	24 (28.2)	32 (37.6)	24 (28.2)	N/A	N/A
Positive	4 (4.7)	3 (3.5)	13 (15.3)	16 (18.8)		
Cheiloplasty						
MT	41 (48.2)	13 (15.3)	17 (20.0)	26 (30.6)	23 (27.1)	13 (15.3)
MMT	17 (20.0)	14 (16.5)	28 (32.9)	14 (16.5)	32 (37.6)	17 (20.0)
Palatoplasty						
BT	14 (16.5)	15 (17.6)	27 (31.5)	15 (17.6)	13 (15.3)	15 (17.6)
VLT	44 (51.8)	12 (14.1)	18 (21.2)	25 (29.4)	42 (49.4)	15 (17.6)

Fav: Favourable; Unfav: Unfavourable; UCLP: unilateral cleft lip and palate; F/H Cleft: Family history of cleft; F/H C-III: Family history of Class III malocclusion; MT: Millard technique; MMT: modified Millard technique; BT: Bardach Technique; VLT: von Langenbeck Technique

*all the Pakistani UCLP subjects were complete type of UCLP. No record was found regarding family history of Class III malocclusion in Pakistani UCLP subjects.

4.2.4 Association of Multiple Factors on Treatment Outcome (Favourable Vs. Unfavourable Dental Arch Relationship)

The crude logistic regression analysis was carried out to evaluate the association between each factor and dental arch relationship. The 95% confidence intervals were determined and the factors with a p-value of less than 0.05 were considered to have a significant association with dental arch relationship.

Malaysian Population

A significant association was found in techniques of palatoplasty (**$p = 0.03$**) with dental arch relationship. Subjects who underwent with von Langenbeck technique of palatoplasty had 3.42 times the odds of favourable dental arch relationship compared to those who underwent with Bardach technique. (**Table 4.7**)

Table 4.7. Logistic regression analysis of multiple factors with treatment outcome (Favourable vs. unfavourable group) using GY in Malaysian population

Independent Variable	Exp (B)	95% CI		*p* value
		Lower	Upper	
Age	1.34	0.43	4.19	0.61
Gender	0.59	0.20	1.71	0.33
UCLP Side	0.53	0.16	1.73	0.30
UCLP Type	0.39	0.12	1.25	0.11
F/H of Cleft	2.03	0.44	9.41	0.37
F/H of C-III	0.42	0.07	2.38	0.32
Cheiloplasty	0.04	0.13	1.23	0.11
Palatoplasty	3.42	1.09	10.78	**0.03***

F/H: family history; C-III: Class III malocclusion
*significant at the level of 0.05
Example of interpretation: Palatoplasty: Bardach technique coded as 0 and von Langenbeck technique coded as 1. The value 3.42 indicating that von Langenbeck technique has favourable dental arch relationship than Bardach technique.

Bangladeshi Population

Significant association was found in gender (**p = 0.03**), techniques of cheiloplasty (**p = 0.04**) techniques of palatoplasty (**p = 0.04**) with dental arch relationship. Female subjects showed 2.93 times the odds ratio to favourable dental arch relationship than male subjects. Moreover, the subjects with Millard technique of cheiloplasty and von Langenbeck technique of palatoplasty had 2.99 and 2.80 times respectively the odds to favourable dental arch relationship compared to the subject who went with modified Millard technique of cheiloplasty and Bardach technique of palatoplasty. (**Table 4.8**)

Table 4.8 Logistic regression analysis of multiple factors with treatment outcome (Favourable vs. unfavourable group) using GY in Bangladeshi population

Independent Variable	Exp (B)	95% CI		*p* value
		Lower	Upper	
Bangladeshi Population				
Age	1.29	0.47	3.52	0.62
Gender	2.93	1.09	7.85	**0.03**
UCLP Side	0.44	.015	1.32	0.15
UCLP Type	1.15	0.37	3.60	0.81
F/H of Cleft	1.05	0.37	2.96	0.93
F/H of C-III	0.60	0.21	1.76	0.36
Cheiloplasty	2.99	1.07	8.38	**0.04***
Palatoplasty	2.80	0.47	7.80	**0.04***

F/H: family history; C-III: Class III malocclusion
*significant at the level of 0.05
Example of interpretation: Palatoplasty: Bardach technique coded as 0 and von Langenbeck technique coded as 1. The value 2.80 indicating that von Langenbeck technique has favourable dental arch relationship than Bardach technique. Cheiloplasty: modified Millard technique coded as 0 and Millard technique coded as 1

Pakistani Population

A significant association was found in techniques of palatoplasty (**p = 0.04**) with dental arch relationship. Subjects who underwent with von Langenbeck technique of palatoplasty had 2.86 times the odds to favourable dental arch relationship compared to those who underwent with Bardach technique. (**Table 4.9**)

Table 4.9 Logistic regression analysis of multiple factors with treatment outcome (Favourable vs. unfavourable group) using GY in Pakistani population

Independent Variable	**Exp (B)**	**95% CI**		***p* value**
		Lower	**Upper**	
Age	0.55	0.21	1.47	0.23
Gender	2.31	0.86	6.17	0.09
UCLP Side	0.75	0.25	2.24	0.60
F/H of Cleft	0.72	0.26	1.99	0.52
Cheiloplasty	0.90	0.33	2.44	0.84
Palatoplasty	2.86	1.05	7.76	**0.04***

F/H: family history
*significant at the level of 0.05
Example of interpretation: Palatoplasty: Bardach technique coded as 0 and von Langenbeck technique coded as 1. The value 2.86 indicating that von Langenbeck technique has favourable dental arch relationship than Bardach technique

4.3 Results of EI

4.3.1 Reliability of EI

Two examiners (Examiner A and B) participated for the scoring of models using EI. Intra-examiner agreements for examiner A was 0.84 and 0.88 for dental arch relationship and palatal morphology respectively (**Table 4.10**). The kappa score 0.66 (dental arch relationship) and 0.73 (palatal morphology) were for the inter-examiner (**Table 4.10**). The kappa scores for the EI showed good to very good intra- and inter-examiner agreements.

Table 4.10 Intra- and inter-examiner agreements of EI

	Kappa value	Standard error
Intra-examiner aggrement		
Examiner A (DAR)	0.84	0.15
Examiner A (PM)	0.88	0.11
Inter-examiner aggrement		
Examiner A vs. Examiner B (DAR)	0.66	0.22
Examiner A vs. Examiner B (PM)	0.73	0.17

DAR: dental arch relationship; PM: palatal morphology

4.3.2 EI Score Distribution (Based on Dental Arch Relationship)

Malaysian Population

Among the 85 subjects, scores were distributed as follows: group I= 4 subjects, II=23 subjects, III=21 subjects and IV=37 subjects.

The mean EUROCRAN score was **3.07**

Bangladeshi Population

Among the 85 subjects, scores were distributed as follows: group I= 16 subjects, II=19 subjects, III=28 subjects and IV=22 subjects.

The mean EUROCRAN score was **2.66**

Pakistani Population

Among the 85 subjects, scores were distributed as follows: group I= 12 subjects, II=25 subjects, III=36 subjects and IV=12 subjects.

The mean EUROCRAN score was **2.56**

Figure 4.2 shows the score distribution based on dental arch relationship of UCLP subjects of three populations using EI.

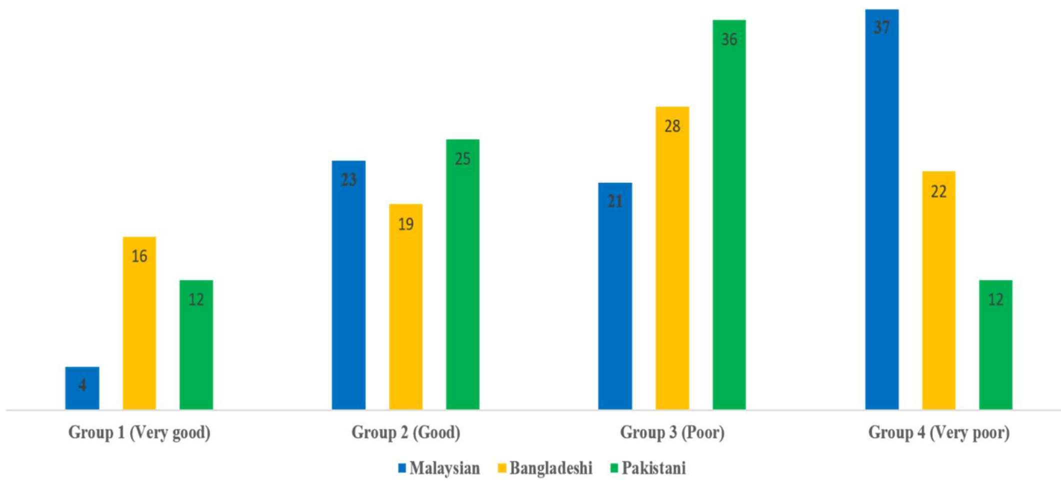


Figure 4.2 The score distribution of EI based on dental arch relationship in UCLP subjects of three populations

4.3.3 EI Score Distribution (Based on Palatal Morphology)

Malaysian Population

Among the 85 subjects, scores were distributed as follows: group I= 7 subjects (8%), II=53 subjects (62%) and III=25 subjects (30%).

The mean EUROCRAN score was **2.21**

Bangladeshi Population

Among the 85 subjects, scores were distributed as follows: group I= 16 subjects (19%), II=47 subjects (55%) and III=22 subjects (26%).

The mean EUROCRAN score was **2.07**

Pakistani Population

Among the 85 subjects, scores were distributed as follows: group I= 21 subjects (25%), II=37 subjects (43%) and III=27 subjects (32%).

The mean EUROCRAN score was **2.07**

Figure 4.3 shows the score distribution based on palatal morphology of UCLP subjects of three populations using EI.

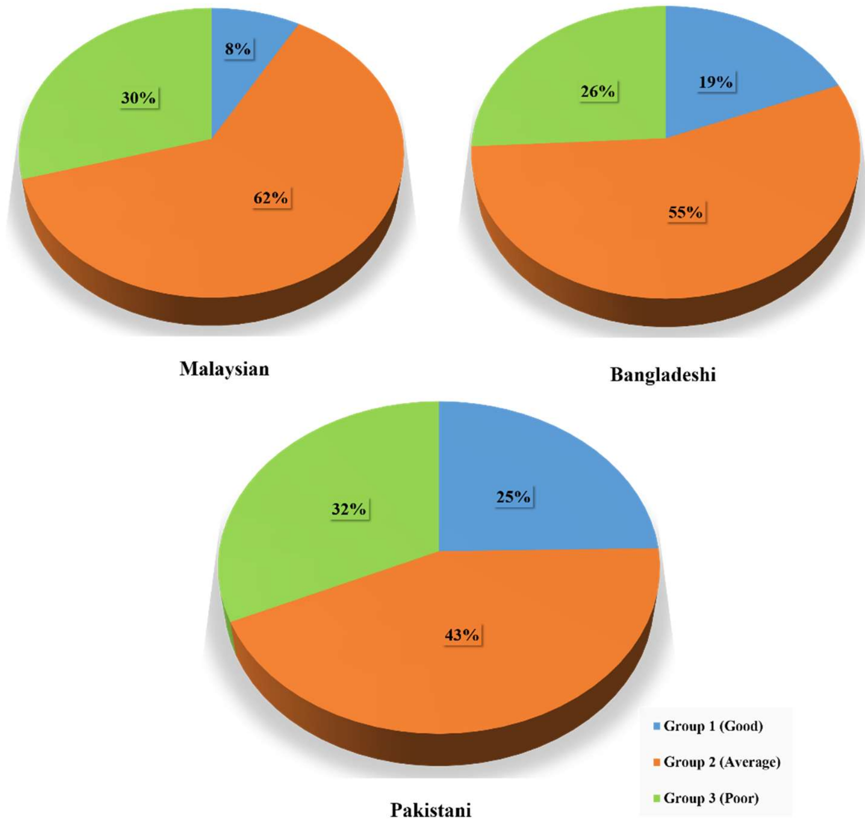


Figure 4.3 The score distribution of EI based on palatal morphology in UCLP subjects of three populations

4.3.4 Comparison of Factors between Favourable and Unfavourable Groups

Malaysian Population

Twenty-eight subjects were in favourable group and 57 subjects were in unfavourable group.

Bangladeshi Population

The number of subjects in favourable and unfavourable groups was 35 and 50, respectively.

Pakistani Population

The number of subjects in favourable and unfavourable groups was 37 and 48, respectively.

Table 4.11 shows the detailed distribution of all the subjects with multiple factors in favourable and unfavourable groups using EI of three populations.

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Table 4.11 Distribution of subjects with multiple factors in favourable and unfavourable groups using EI in Malaysian, Bangladeshi and Pakistani UCLP children

Variable	Tx Outcome of Malaysian Population, n (%)		Tx Outcome of Bangladeshi Population, n (%)		Tx Outcome of *Pakistani Population, n (%)	
	Fav	Unfav	Fav	Unfav	Fav	Unfav
Age						
5-8 years	14 (16.5)	31 (36.5)	18 (21.2)	23 (27.1)	22 (25.9)	30 (35.3)
9-12 years	14 (16.5)	26 (30.5)	17(20.0)	27 (31.8)	15 (17.6)	18 (21.2)
Gender						
Male	20 (23.5)	30 (35.3)	15 (17.6)	29 (34.1)	17 (20.0)	27 (31.8)
Female	8 (9.4)	27 (31.8)	20 (23.5)	21(24.7)	20 (23.5)	21 (24.7)
UCLP Side						
Left	21 (24.7)	36 (42.4)	24 (28.2)	28 (32.9)	24 (28.2)	39 (45.9)
Right	7 (8.2)	21 (24.7)	11 (12.9)	22 (25.9)	13 (15.3)	9 (10.6)
UCLP type						
Incomplete	21 (24.7)	39 (45.9)	23 (27.1)	29 (34.1)	N/A	N/A
Complete	7 (8.2)	18 (21.2)	12 (14.1)	21 (24.7)		
F/H of Cleft						
Negative	25 (29.4)	42 (49.4)	16 (18.8)	26 (30.6)	23 (27.1)	32 (37.6)
Positive	3 (3.5)	15 (17.6)	19 (22.4)	24 (28.2)	14 (16.5)	16 (18.8)
F/H of C-III						
Negative	24 (28.2)	54 (63.5)	23 (27.1)	33 (38.8)	N/A	N/A
Positive	4 (4.7)	3 (3.5)	12 (14.1)	17 (20.0)		
Cheiloplasty						
MT	34 (40.0)	20 (23.5)	14 (16.5)	29 (34.1)	11 (12.9)	25 (29.4)
MMT	23 (27.1)	8 (9.4)	21 (24.7)	21 (24.7)	26 (30.6)	23 (27.1)
Palatoplasty						
BT	4 (4.7)	25 (29.4)	22 (25.9)	20 (23.5)	8 (9.4)	20 (23.5)
VLT	24 (28.2)	32 (37.6)	13 (15.3)	30 (35.3)	29 (34.1)	28 (32.9)

Fav: Favourable; Unfav: Unfavourable; UCLP: unilateral cleft lip and palate; F/H Cleft: Family history of cleft; F/H C-III: Family history of Class III malocclusion; MT: Millard technique; MMT: modified Millard technique; BT: Bardach Technique; VLT: Von-Lengenbeck Technique

*all the Pakistani UCLP subjects were complete type of UCLP. No record was found regarding family history of Class III malocclusion in Pakistani UCLP subjects.

4.3.5 Association of Multiple Factors on Treatment Outcome (Favourable Vs. Unfavourable Dental Arch Relationship)

The logistic regression analysis was carried out to evaluate the association between each factor and dental arch relationship. The 95% confidence intervals were determined and *p*-value of less than 0.05 were considered to have a significant.

Malaysian Population

A significant association was found in family history of cleft (**$p = 0.03$**) and techniques of palatoplasty (**$p < 0.001$**) with dental arch relationship. Subjects who had not the history of cleft in their family showed 4.38 times the odds of favourable dental arch relationship compared to those who had the family history of cleft. Moreover, the subjects with von Langenbeck technique of palatoplasty had 1.12 times the odds of favourable dental arch relationship compared to those who underwent with Bardach technique. (**Table 4.12**)

Table 4.12 Logistic regression analysis of multiple factors with treatment outcome (Favourable vs. unfavourable group) using EI in Malaysian population

Independent Variable	Exp (B)	95% CI		*p* value
		Lower	Upper	
Age	0.97	0.33	2.87	0.96
Gender	2.54	0.85	7.56	0.09
UCLP Side	2.55	0.79	8.24	0.11
UCLP Type	1.13	0.33	3.77	0.84
F/H of Cleft	4.38	1.15	16.69	**0.03*,**
F/H of C-III	1.09	0.23	5.14	0.91
Cheiloplasty	0.14	0.03	0.58	0.84
Palatoplasty	1.12	0.35	3.54	**< 0.001*,**

F/H: family history; C-III: Class III malocclusion
*significant at the level of 0.05
Example of interpretation: Palatoplasty: Bardach technique coded as 0 and von Langenbeck technique coded as 1. The value 1.12 indicating that von Langenbeck technique has favourable dental arch relationship than Bardach technique. Family history of cleft: positive family history coded as 0 and negative e family history coded as 1

Bangladeshi Population

Significant association was found in techniques of cheiloplasty (**p = 0.01**) and techniques of palatoplasty (**p = 0.02**) with dental arch relationship. The subjects with Millard technique of cheiloplasty and von Langenbeck technique of palatoplasty had 1.40 and 3.53 times respectively the odds to favourable dental arch relationship compared to the subject who went with modified Millard technique of cheiloplasty and Bardach technique of palatoplasty. (**Table 4.13**)

Table 4.13 Logistic regression analysis of multiple factors with treatment outcome (Favourable vs. unfavourable group) using EI in Bangladeshi population

Independent Variable	Exp (B)	95% CI		*p* value
		Lower	Upper	
Age	0.89	0.32	2.48	0.83
Gender	2.06	0.76	5.57	0.15
UCLP Side	0.36	0.12	1.11	0.07
UCLP Type	0.36	0.11	1.13	0.08
F/H of Cleft	0.25	0.08	0.75	0.52
F/H of C-III	0.77	0.26	2.26	0.63
Cheiloplasty	1.40	0.49	4.02	**0.01***
Palatoplasty	3.53	1.26	9.91	**0.02***

F/H: family history; C-III: Class III malocclusion
*significant at the level of 0.05
Example of interpretation: Palatoplasty: Bardach technique coded as 0 and von Langenbeck technique coded as 1. The value 3.53 indicating that von Langenbeck technique has favourable dental arch relationship than Bardach technique. Cheiloplasty: modified Millard technique coded as 0 and Millard technique coded as 1

Pakistani Population

A significant association was found in UCLP side (**p = 0.03**), techniques of cheiloplasty (**p = 0.02**) and techniques of palatoplasty (**p = 0.04**) with dental arch relationship. Right sided UCLP subjects showed 3.51 times the odds ratio to favourable dental arch relationship than left sided UCLP subjects. Moreover, Subjects who underwent with Millard technique of cheiloplasty and von Langenbeck technique of palatoplasty had 3.21 and 2.94 times respectively the odds to favourable dental arch relationship compared to the subject who went with modified Millard technique of cheiloplasty and Bardach technique of palatoplasty. (**Table 4.14**)

Table 4.14 Logistic regression analysis of multiple factors with treatment outcome (Favourable vs. unfavourable group) using EI in Pakistani population

Independent Variable	Exp (B)	95% CI		*p* value
		Lower	Upper	
Age	1.27	0.47	3.40	0.63
Gender	1.65	0.63	4.34	0.30
UCLP Side	3.51	1.13	10.88	**0.03***
F/H of Cleft	1.84	0.66	5.16	0.24
Cheiloplasty	3.21	1.16	8.90	**0.02***
Palatoplasty	2.94	1.02	8.45	**0.04***

F/H: family history C-III: Class III malocclusion
*significant at the level of 0.05
Example of interpretation: Palatoplasty: Bardach technique coded as 0 and von Langenbeck technique coded as 1. The value 3.51 indicating that von Langenbeck technique has favourable dental arch relationship than Bardach technique. Cheiloplasty: modified Millard technique coded as 0 and Millard technique coded as 1; UCLP side: left side coded as 0 and right side coded as 1

4.4 Results of mHB Scoring System

4.4.1 Reliability of mHB Scoring System

Two examiners (Examiner A and B) participated for the scoring of models using mHB scoring system. The results of intra-examiner agreements for examiner A is summarized in **Table 4.15**. The aters showed very good intra-examiner agreements for each individual scoring and also total mHB score.

Kappa scores of inter-examiner agreements also showed very good agreements, ranged from 0.0919-0.984 (**Table 4.16**).The kappa scores for the mHB demonstrated very good intra- and inter-examiner agreements.

Table 4.15 Intra- examiner agreements of mHB scoring system

Intra-examiner agreements	Kappa value	Standard error
Examiner A		
CS Incisor	0.91	0.09
NCS Incisor	0.90	0.09
CS canine	0.81	0.12
NCS canine	0.89	0.10
CS 1st premolar	1.00	0.001
NCS 1st premolar	0.90	0.09
CS 2nd premolar	1.00	0.001
NCS 2nd premolar	0.91	0.09
CS 1st molar	0.90	0.09
CS 1st molar	0.91	0.08

CS: Cleft side; NCS: Non cleft side

Table 4.16 Inter- examiner agreements of mHB scoring system

Inter-examiner agreements	Kappa value	Standard error
Examiner A vs. B		
CS Incisor	0.65	0.15
NCS Incisor	0.71	0.12
CS canine	0.73	0.13
NCS canine	0.81	0.13
CS 1st premolar	0.90	0.09
NCS 1st premolar	0.80	0.12
CS 2nd premolar	0.90	0.08
NCS 2nd premolar	0.90	1.00
CS 1st molar	0.82	0.12
NCS 1st molar	1.00	0.001

CS: Cleft side; NCS: Non cleft side

4.4.2 mHB Score Distribution

Malaysian Population

Among 85 subjects, distribution of mean score with standard deviation of incisors: -3.60 (3.72), buccal segment of cleft side: -4.86 (3.50) and buccal segment of non cleft side: -1.53 (1.41). The total mean score of mHB was -9.98 (**Figure 4.4**)

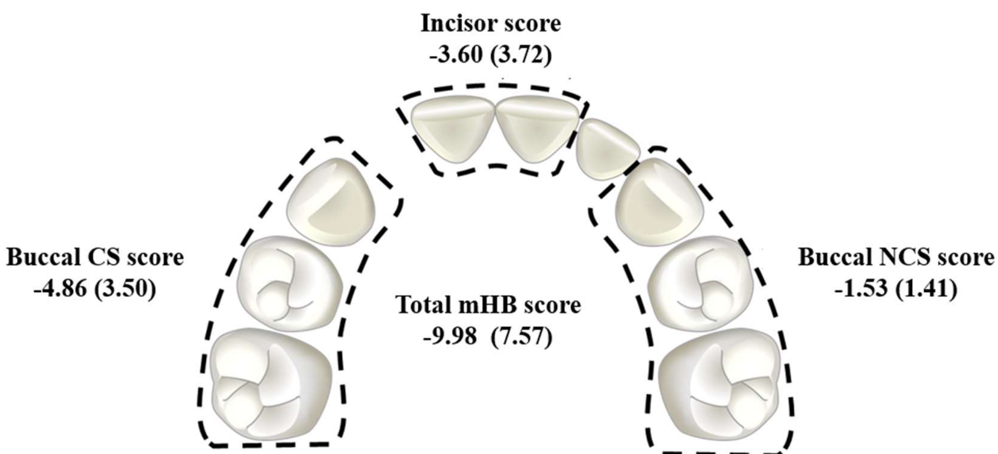

Figure 4.4 Mean score distribution (standard deviation) of mHB index of Malaysian population (CS- cleft side; NCS- non cleft side)

Bangladeshi Population

Among 85 subjects, distribution of mean score with standard deviation of incisors: -1.31 (1.40), buccal segment of cleft side: -4.42 (3.46) and buccal segment of non cleft side: -3.04 (3.77). The total mean score of mHB was -8.76 (**Figure 4.5**)

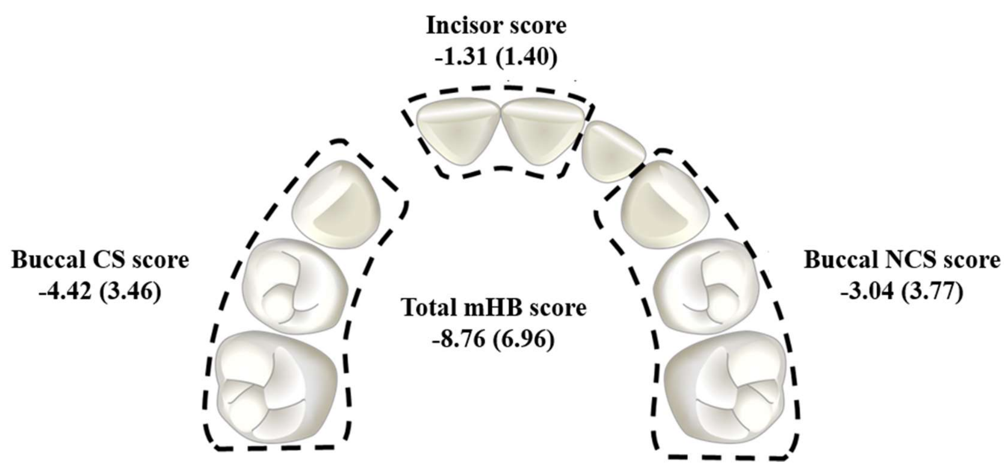

Figure 4.5 Mean score distribution (standard deviation) of mHB index of Bangladeshi population (CS- cleft side; NCS- non cleft side)

Pakistani Population

Among 85 subjects, distribution of mean score with standard deviation of incisors: - 1.15 (1.34), buccal segment of cleft side: -3.33 (4.97) and buccal segment of non cleft side: -2.09 (2.86). The total mean score of mHB was -6.57 (**Figure 4.6**)

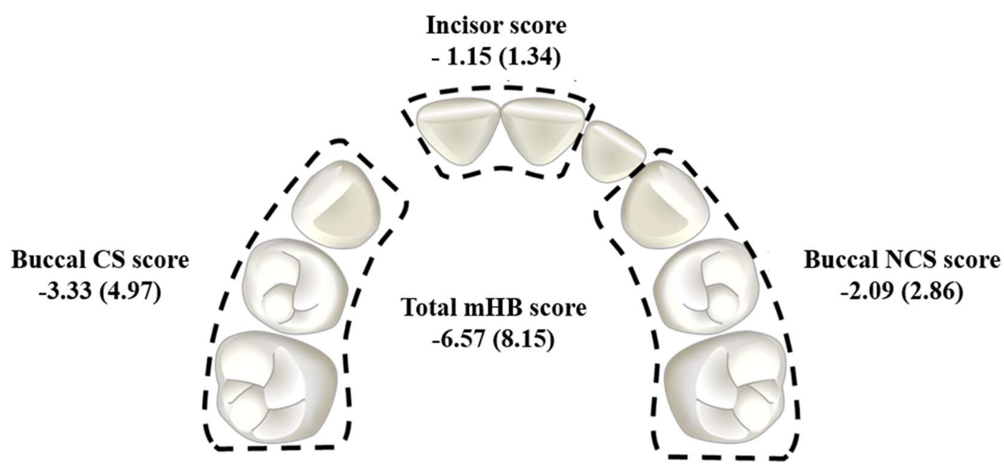

Figure 4.6 Mean score distribution (standard deviation) of mHB index of Pakistani population (CS- cleft side; NCS- non cleft side)

4.4.3 Categorisation and Grouping of Favourable and Unfavourable Dental Arch Relationship

Malaysian Population

Distribution of the subjects based on the five categories: Excellent = 11 (13%) subjects, Good = 13 (15%) subjects, Fair = 19 (22%) subjects, Poor = 22 (26%) subjects and Very poor = 20 (24%) subjects. (**Figure 4.7)**

The results of the distribution of favourable and unfavourable dental arch relationship were 43 (51%) and 42 (49%) respectively (dental arch relationship score of <-10 = Favourable group and ≥-10 = Unfavourable group).

Bangladeshi Population

Distribution of the subjects based on the five categories: Excellent = 9 (10%) subjects, Good = 22 (26%) subjects, Fair = 21 (25%) subjects, Poor = 18 (21%) subjects and Very poor = 15 (18%) subjects. (**Figure 4.7)**

The results of the distribution of favourable and unfavourable dental arch relationship were 52 (61%) and 33 (39%) respectively (dental arch relationship score of <-10 = Favourable group and ≥-10 = Unfavourable group).

Pakistani Population

Distribution of the subjects based on the five categories: Excellent = 23 (27%) subjects, Good = 23 (27%) subjects, Fair = 10 (11%) subjects, Poor = 12 (14%) subjects and Very poor = 17 (20%) subjects. (**Figure 4.7)**

The results of the distribution of favourable and unfavourable dental arch relationship were 56 (65%) and 29 (35%) respectively (dental arch relationship score of <-10 = Favourable group and ≥-10 = Unfavourable group).

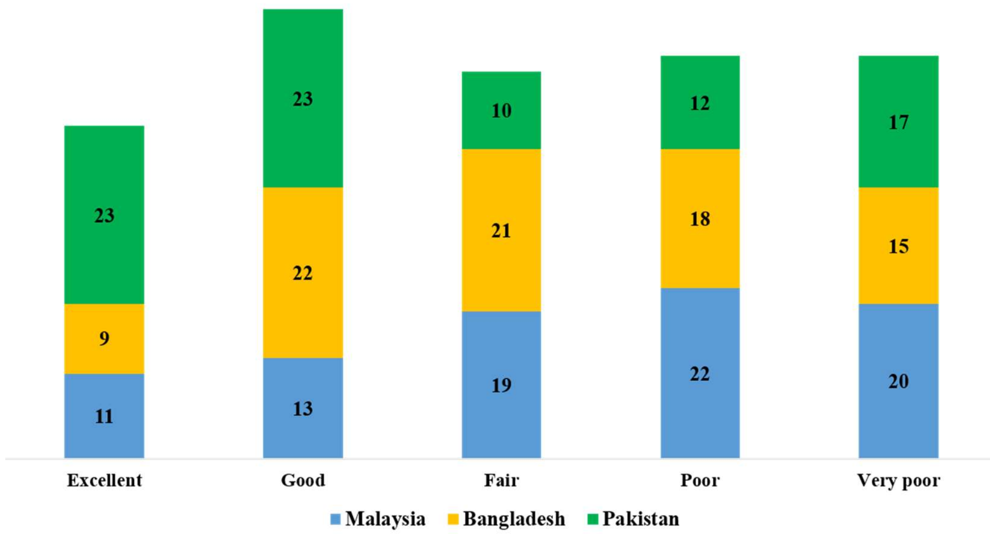

Figure 4.7 The individual score distribution of mHB scoring system in UCLP subjects of three populations

4.4.4 Comparison of Factors between Favourable and Unfavourable Groups

Malaysian Population

Thirty-three subjects were in favourable group and 52 subjects were in unfavourable group.

Bangladeshi Population

The number of subjects in favourable and unfavourable groups was 36 and 49, respectively.

Pakistani Population

The number of subjects in favourable and unfavourable groups was 53 and 32, respectively.

The **table 4.17** shows the detailed distribution of all the subjects with multiple factors in favourable and unfavourable groups using mHB scoring system.

Table 4.17 Distribution of subjects with multiple factors in favourable and unfavourable groups using mHB in Malaysian, Bangladeshi and Pakistani UCLP children

Variable	Tx Outcome of Malaysian Population, n (%)		Tx Outcome of Bangladeshi Population, n (%)		Tx Outcome of *Pakistani Population, n (%)	
	Fav	**Unfav**	**Fav**	**Unfav**	**Fav**	**Unfav**
Age						
5-8 years	17 (20.0)	28 (32.9)	17(20.0)	27 (31.8)	35 (41.2)	17 (20.0)
9-12 years	16 (18.8)	24 (28.2)	19 (22.4)	22 (25.9)	18 (21.2)	15 (17.6)
Gender						
Male	20 (23.5)	30 (35.3)	14 (16.5)	29 (34.1)	25 (29.4)	19 (22.4)
Female	13 (15.3)	22 (25.9)	22 (25.9)	20(24.7)	28 (32.9)	13 (15.3)
UCLP Side						
Left	24 (28.2)	33 (38.8)	22 (25.9)	30 (35.3)	38 (44.7)	25 (29.4)
Right	19 (22.4)	9 (10.6)	14 (16.5)	19 (22.4)	15 (17.6)	7 (8.2)
UCLP type						
Incomplete	10 (11.8)	15 (17.6)	23 (27.1)	29 (34.1)	N/A	N/A
Complete	23 (27.1)	37 (43.5)	13 (14.1)	20 (24.7)		
F/H of Cleft						
Negative	23 (27.1)	44 (51.8)	13 (15.3)	29 (34.1)	37 (43.5)	18 (21.2)
Positive	10 (11.8)	8 (9.4)	23 (27.1)	20 (23.5)	16 (18.8)	14 (16.5)
F/H of Class III						
Negative	32 (37.6)	46 (54.1)	25 (29.4)	31 (36.5)	N/A	N/A
Positive	1 (3.0)	6 (7.1)	11 (12.9)	18 (21.2)		
Cheiloplasty						
MT	23 (27.1)	31 (36.5)	23 (27.1)	20 (23.5)	21 (24.7)	15 (17.6)
MMT	10 (11.8)	21 (24.7)	13 (15.3)	29 (34.1)	32 (37.6)	17 (20.0)
Palatoplasty						
BT	7 (8.2)	22 (25.9)	11 (12.9)	31 (36.5)	10 (11.8)	18 (21.2)
VLT	26 (30.6)	30 (35.3)	25 (29.4)	18 (21.2)	43 (50.6)	14 (16.5)

Fav: Favourable; Unfav: Unfavourable; UCLP: unilateral cleft lip and palate; F/H Cleft: Family history of cleft; F/H C-III: Family history of Class III malocclusion; MT: Millard technique; MMT: modified Millard technique; BT: Bardach Technique; VLT: von Lengenbeck Technique

*all the Pakistani UCLP subjects were complete type of UCLP. No record was found regarding family history of Class III malocclusion in Pakistani UCLP subjects.

4.4.5 Association of Multiple Factors on Treatment Outcome (Favourable Vs. Unfavourable Dental Arch Relationship)

In this study, a crude logistic regression analysis was performed to investigate the association between each factor and the dental arch relationship. The 95% confidence intervals were determined, and the factors with a p-value of less than 0.05 were considered to have a significant association with the dental arch relationship.

Malaysian Population

A significant association was found in family history of cleft (**p = 0.02**) and techniques of palatoplasty (**p = 0.03**) with dental arch relationship. Subjects who had not the history of cleft in their family showed 3.70 times the odds of favourable dental arch relationship compared to those who had the family history of cleft. Moreover, the subjects with von Langenbeck technique of palatoplasty had 3.51 times the odds of favourable dental arch relationship compared to those who underwent with Bardach technique. (**Table 4.18**)

Table 4.18 Logistic regression analysis of multiple factors with treatment outcome (Favourable vs. unfavourable group) using mHB in Malaysian population

Independent Variable	Exp (B)	95% CI		*p* value
		Lower	Upper	
Age	1.54	0.56	4.24	0.39
Gender	0.70	0.25	1.92	0.49
UCLP Side	0.41	0.13	1.25	0.11
UCLP Type	1.12	0.36	3.43	0.84
F/H of Cleft	3.70	1.19	11.43	**0.02***
F/H of C-III	0.10	0.01	1.19	0.06
Cheiloplasty	1.12	0.38	3.32	0.82
Palatoplasty	3.51	1.07	11.51	**0.03*,b**

F/H: family history; C-III: Class III malocclusion
*significant at the level of 0.05
Example of interpretation: Palatoplasty: Bardach technique coded as 0 and von Langenbeck technique coded as 1. The value 3.51 indicating that von Langenbeck technique has favourable dental arch relationship than Bardach technique. Family history of cleft: positive family history coded as 0 and negative e family history coded as 1

Bangladeshi Population

A significant association was found in family history of cleft (**p = 0.04**) and techniques of palatoplasty (**p = 0.01**) with dental arch relationship. Subjects who had not the history of cleft in their family showed 2.96 times the odds of favourable dental arch relationship compared to those who had the family history of cleft. Moreover, the subjects with von Langenbeck technique of palatoplasty had 3.48 times the odds of favourable dental arch relationship compared to those who underwent with Bardach technique. (**Table 4.19**)

Table 4.19 Logistic regression analysis of multiple factors with treatment outcome (Favourable vs. unfavourable group) using mHB in Bangladeshi population

Independent Variable	Exp (B)	95% CI		*p* value
		Lower	Upper	
Age	1.34	0.47	3.83	0.57
Gender	1.94	0.72	5.20	0.18
UCLP Side	0.90	0.29	2.78	0.85
UCLP Type	1.11	0.34	3.63	0.85
F/H of Cleft	2.96	1.01	8.62	**0.04***
F/H of C-III	0.61	0.19	1.91	0.39
Cheiloplasty	2.23	0.80	6.21	0.12
Palatoplasty	3.48	1.28	9.43	**0.01***

F/H: family history; C-III: Class III malocclusion
*significant at the level of 0.05
Example of interpretation: Palatoplasty: Bardach technique coded as 0 and von Langenbeck technique coded as 1. The value 3.48 indicating that von Langenbeck technique has favourable dental arch relationship than Bardach technique. Family history of cleft: positive family history coded as 0 and negative e family history coded as 1

Pakistani Population

A significant association was found in techniques of palatoplasty (**p < 0.001**) with dental arch relationship. von Langenbeck technique of palatoplasty had 6.57 times the odds to favourable dental arch relationship compared to the subject who went with Bardach technique of palatoplasty. (**Table 4.20**)

Table 4.20 Logistic regression analysis of multiple factors with treatment outcome (Favourable vs. unfavourable group) using mHB in Pakistani population

Independent Variable	Exp (B)	95% CI		*p* value
		Lower	Upper	
Age	0.43	0.15	1.24	0.12
Gender	1.67	0.59	4.68	0.32
UCLP Side	1.60	0.49	5.23	0.43
F/H of Cleft	0.57	0.20	1.63	0.29
Cheiloplasty	1.17	0.42	3.28	0.75
Palatoplasty	6.57	2.25	19.15	**< 0.001***

F/H: family history
*significant at the level of 0.05
Example of interpretation: Palatoplasty: Bardach technique coded as 0 and von Langenbeck technique coded as 1.The value 6.57 indicating that von Langenbeck technique has favourable dental arch relationship than Bardach technique

4.5 Results of Maxillary Arch Dimension

4.5.1 Reliability of Maxillary Arch Dimension

The intra-class correlation for all measurements (ICW, IMW, and AD) ranged from 0.916-0.990 for intra-examiner reliability. Meanwhile, the intra-class correlation for inter-examiner reliability of all measurements (ICW, IMW, and AD) ranged from 0.816-0.990. This indicated good to excellent reliability of all the measurements (**Table 4.2 and Table 4.3**).

4.5.2 Result of Malaysian population

4.5.2(a) Inter-Canine Width (ICW)

The mean (SD) dimension of ICW was 26.88 mm (5.04 mm).

Multiple linear regression was carried out to quantify the effects contributed from each factor on ICW of maxillae. A p-value of less than 0.05 was considered to have a significant association with ICW. Techniques of cheiloplasty (**$p < 0.001$**) and palatoplasty (**$p = 0.04$**) showed significant association with ICW. In addition, regarding cheiloplasty, subjects who underwent Millard technique of cheiloplasty had larger ICW compared to those who underwent modified Millard technique of cheiloplasty. Furthermore, subjects who underwent von Langenbeck technique of palatoplasty had larger ICW compared to those who underwent Bardach technique of palatoplasty. Results for the effects of various factors on ICW are illustrated in **Table 4.21**.

Table 4.21 The effects of multiple factors on inter canine width (ICW)

Variable	Unstandardised Coefficients		Standardised Coefficients	t	*p* Value
	B	**Std. Error**	**Beta**		
Age	-1.46	1.40	-0.13	-1.04	0.30
Gender	-0.37	1.31	-0.03	-0.28	0.77
UCLP Type	-0.91	1.28	-0.08	-0.71	0.48
UCLP Side	-0.29	1.31	-0.02	-0.22	0.82
F/H Cleft	1.04	1.43	0.09	0.72	0.47
F/H C-III	-0.34	2.25	-0.01	-0.15	0.87
Cheiloplasty	-4.69	1.27	-0.45	-3.69	**< 0.001**[*,a]
Palatoplasty	2.65	1.29	0.25	2.04	**0.04**[*,b]

UCLP: unilateral cleft lip and palate; F/H Cleft: Family history of cleft; F/H C-III: Family history of Class III malocclusion.
*significant at the level of 0.05
Example of interpretation: cheiloplasty. i.e Millard technique coded as 0 and modified Millard technique coded as 1. The value -4.69 indicating that Millard technique has larger ICW than modified Millard technique. Palatoplasty: Bardach technique coded as 0 and von Langenbeck technique coded as 1

4.5.2(b) Inter-Molar Width (IMW)

The mean (SD) dimension of IMW was 45.24 mm (4.76 mm).

Table 4.22 displays the effects of multiple factors on IMW. However, there was no significant association observed on IMW statistically.

Table 4.22 The effects of multiple factors on inter molar width (IMW)

Variable	Unstandardised Coefficients		Standardised Coefficients	t	*p* Value
	B	Std. Error	Beta		
Age	-0.40	1.23	-0.03	-0.32	0.74
Gender	-1.27	1.12	-0.13	-1.14	0.25
UCLP Type	1.50	1.18	0.14	1.27	0.20
UCLP Side	-0.18	1.14	-0.01	-0.16	0.86
F/H Cleft	-1.96	1.17	-0.19	-1.66	0.10
F/H C-III	0.73	1.94	0.04	0.37	0.70
Cheiloplasty	-1.83	1.14	-0.18	-1.61	0.11
Palatoplasty	1.25	1.15	0.12	1.09	0.27

UCLP: unilateral cleft lip and palate; F/H Cleft: Family history of cleft; F/H C-III: Family history of Class III malocclusion.

4.5.2(c) Arch Depth (AD)

The mean (SD) dimension of AD was 29.81mm (5.75 mm).

Association between multiple factors and AD are detailed in **Table 4.23**. However, there was no significant association observed on AD statistically.

Table 4.23 The effects of multiple factors on arch depth (AD)

Variable	Unstandardised Coefficients		Standardised Coefficients	t	*p* Value
	B	Std. Error	Beta		
Age	-0.05	1.49	-0.01	-0.04	0.96
Gender	-2.24	1.35	-0.19	-1.66	0.10
UCLP Type	2.21	1.42	0.17	1.54	0.12
UCLP Side	-0.32	1.37	-0.02	-0.23	0.81
F/H Cleft	-1.03	1.41	-0.08	-0.73	0.46
F/H C-III	-0.72	2.34	-0.03	-0.30	0.75
Cheiloplasty	-2.51	1.37	-0.21	-1.82	0.07
Palatoplasty	1.35	1.39	0.11	0.97	0.33

UCLP: unilateral cleft lip and palate; F/H Cleft: Family history of cleft; F/H C-III: Family history of Class III malocclusion.

4.5.3 Result of Bangladeshi Population

4.5.3(a) Inter-Canine Width (ICW)

The mean (SD) dimension of ICW was 26.61 mm (4.33 mm).

Techniques of palatoplasty (**p = 0.02**) showed significant association with ICW. In addition, subjects who underwent with von Langenbeck of palatoplasty had larger ICW compared to those who underwent with Bardach technique of palatoplasty. Results for the effects of various factors on ICW are illustrated in **Table 4.24**.

Table 4.24 The effects of various factors on inter-canine width (ICW)

Variable	Unstandardised Coefficients		Standardised Coefficients	t	*p* Value
	B	Std. Error	Beta		
Age	1.16	1.27	0.13	0.91	0.36
Gender	-1.85	1.23	-0.21	-1.50	0.14
UCLP Type	0.10	1.53	0.01	0.06	0.94
UCLP Side	-0.43	1.38	-0.05	-0.31	0.75
F/H Cleft	0.88	1.42	0.10	0.62	0.53
F/H C-III	0.72	1.40	0.08	0.51	0.60
Cheiloplasty	-1.00	1.49	-0.11	-0.67	0.50
Palatoplasty	3.87	1.72	0.45	2.25	**0.02**[*,b]

UCLP: unilateral cleft lip and palate; F/H Cleft: Family history of cleft; F/H C-III: Family history of Class III malocclusion.
*significant at the level of 0.05
Example of interpretation: Palatoplasty: Bardach technique coded as 0 and von Langenbeck technique coded as 1. The value 3.87 indicating that von Langenbeck technique has larger ICW than Bardach technique.

4.5.3(b) Inter-Molar Width (IMW)

The mean (SD) dimension of IMW was 42.89 mm (5.48 mm).

Table 4.25 displays the effects of various factors on IMW. However, there was no significant association observed on IMW statistically.

Table 4.25 The effects of various factors on inter-molar width (IMW)

Variable	Unstandardised Coefficients		Standardised Coefficients	t	*p* Value
	B	Std. Error	Beta		
Age	1.85	1.28	0.17	1.44	0.15
Gender	-0.56	1.22	-0.05	-0.45	0.64
UCLP Type	-1.00	1.55	-0.09	-0.64	0.52
UCLP Side	0.53	1.37	0.04	0.38	0.70
F/H Cleft	-0.53	1.33	-0.04	-0.40	0.68
F/H C-III	-1.45	1.34	-0.12	-1.07	0.28
Cheiloplasty	0.43	1.39	0.04	0.31	0.75
Palatoplasty	-0.39	1.57	-0.03	-0.24	0.80

UCLP: unilateral cleft lip and palate; F/H Cleft: Family history of cleft; F/H C-III: Family history of Class III malocclusion.

4.5.3(c) Arch Depth (AD)

The mean (SD) dimension of AD was 29.06 mm (5.72 mm).

Association between various factors and AD are detailed in **Table 4.26.** The type of UCLP (**p = 0.01**) showed significant association with AD. The subjects who had complete type of UCLP showed shorter AD compared to those who had incomplete type of UCLP.

Table 4.26 The effects of various factors on arch depth (AD)

Variable	Unstandardised Coefficients		Standardised Coefficients	t	P Value
	B	Std. Error	Beta		
Age	1.54	1.30	0.13	1.18	0.24
Gender	0.42	1.24	0.03	0.33	0.73
UCLP Type	-3.89	1.57	-0.33	-2.46	**0.01**[*,b]
UCLP Side	-1.85	1.39	-0.15	-1.33	0.18
F/H Cleft	0.12	1.35	0.01	0.09	0.92
F/H C-III	2.52	1.36	0.21	1.85	0.06
Cheiloplasty	1.43	1.40	0.12	1.01	0.31
Palatoplasty	-2.28	1.59	-0.20	-1.43	0.15

UCLP: unilateral cleft lip and palate; F/H Cleft: Family history of cleft; F/H C-III: Family history of Class III malocclusion.
*significant at the level of 0.05
Example of interpretation: UCLP type. i.e incomplete UCLP coded as 0 and complete UCLP coded as 1. The value -3.89 indicating that complete UCLP has shorter AD than incomplete UCLP.

4.5.4 Result of Pakistani Population

4.5.4(a) Inter-Canine Width (ICW)

The mean (SD) dimension of ICW was 26.69 mm (5.70 mm).

Multiple linear regression was carried out to quantify the effects of each factors on ICW of maxillae. A p-value of less than 0.05 were considered to have a significant association with ICW. Results for the effects of various factors on ICW are illustrated in **Table 4.27.** However, there was no significant association observed on ICW statistically.

Table 4.27 The effects of various factors on inter canine width (ICW)

Variable	Unstandardised Coefficients		Standardised Coefficients	t	*p* Value
	B	Std. Error	Beta		
Age	-0.78	1.53	-0.06	-0.51	0.61
Gender	-0.85	1.47	-0.07	-0.58	0.56
UCLP Side	-0.70	1.61	-0.05	-0.43	0.66
F/H Cleft	0.60	1.58	0.05	0.37	0.70
Cheiloplasty	1.68	1.48	0.14	1.13	0.26
Palatoplasty	-0.35	1.64	-0.02	-0.21	0.83

UCLP: unilateral cleft lip and palate; F/H Cleft: Family history of cleft

4.5.4(b) Inter-Molar Width (IMW)

The mean (SD) dimension of IMW was 43.33 mm (4.66 mm).

Table 4.28 displays the effects of various factors on IMW. However, there was no significant association observed on IMW statistically.

Table 4.28 The effects of various factors on inter molar width (IMW)

Variable	Unstandardised Coefficients		Standardised Coefficients	t	*p* Value
	B	Std. Error	Beta		
Age	-0.16	1.06	-0.01	-0.15	0.87
Gender	0.36	1.20	0.03	0.30	0.76
UCLP Side	0.85	1.11	0.08	0.76	0.44
F/H Cleft	0.14	1.13	0.01	0.12	0.89
Cheiloplasty	1.48	1.08	0.15	1.37	0.17
Palatoplasty	-0.04	1.09	-0.01	-0.03	0.97

UCLP: unilateral cleft lip and palate; F/H Cleft: Family history of cleft

4.5.5(c) Arch Depth (AD)

The mean (SD) dimension of AD was 27.06mm (5.26 mm).

Association between various factors and AD are detailed in **Table 4.29**. However, there was no significant association observed on AD statistically.

Table 4.29 The effects of various factors on arch depth (AD)

Variable	Unstandardised Coefficients		Standardised Coefficients	t	*p* Value
	B	Std. Error	Beta		
Age	-0.42	1.19	-0.04	-0.35	0.72
Gender	-1.52	1.35	-0.12	-1.12	0.26
UCLP Side	-0.08	1.25	-.001	-0.07	0.94
F/H Cleft	-0.40	1.27	-0.03	-0.31	0.75
Cheiloplasty	1.17	1.21	0.11	0.96	0.33
Palatoplasty	-0.93	1.23	-.008	-0.75	0.45

UCLP: unilateral cleft lip and palate; F/H Cleft: Family history of cleft

4.5.5 Comparison of the Maxillary Arch Dimension between Three Populations

Comparison of treatment outcome based on congenital and postnatal treatment factors in non-syndromic UCLP children in LS3DM using maxillary arch dimension (ICW, IMW, AD) among the three different populations.

Inter-Canine Width (ICW)

Multiple linear regression was carried out to quantify the effects of each factors on ICW of maxillae. A p-value of less than 0.05 were considered to have a significant association with ICW. Results for the effects of races on ICW are illustrated in **Table 4.30.** However, there was no significant association observed on ICW statistically.

Table 4.30 The effects of races on ICW

Variable	Unstandardised Coefficients		Standardised Coefficients	t	*p* Value
	B	Std. Error	Beta		
ICW	-0.05	0.47	-0.01	-0.10	0.91

Inter-Molar Width (IMW)

Table 4.31 displays the effects of races on IMW. Signicicant association observeved between three population in terms of IMW (**p = 0.03**). Comparison between individual races based on IMW was also carried out. Malaysian vs. Bangladesh (**p < 0.001**) and Malaysian vs. Pakistan (**p < 0.001**) showed significant association with each other in terms of IMW. However, Bangladesh vs. Pakistan did not showed any significant association with each other (**Table 4.32**). Malaysian UCLP subjects had the largest IMW of maxilla followed by Pakistani and Bangladeshi UCLP subjects.

Table 4.31 The effects of races on IMW

Variable	**Unstandardised Coefficients**		**Standardised Coefficients**	**t**	***p* Value**
	B	**Std. Error**	**Beta**		
IMW	-0.86	0.40	-0.14	-2.12	**0.03**

Table 4.32 Comparison between individual races based on IMW

Variables	**Unstandardised Coefficients**		**Standardised Coefficients**	**t**	***p* value**
	B	**Std. Error**	**Beta**		
Malay vs. Paki	-1.90	0.72	-0.19	-2.63	**< 0.001**
Ban vs. Malay	2.34	0.79	0.22	2.96	**< 0.001**
Ban vs. Paki	0.43	0.78	0.04	0.55	0.57

Malay: Malaysia; Ban: Bangladesh; Paki: Pakistan

Arch Depth (AD)

Signicicant association observed between three populations in terms of AD (**p < 0.001**).Association between races and AD are detailed in **Table 4.33.** Comparison between individual races Bangladesh vs. Pakistan (**p = 0.02**) and Malaysian vs. Pakistan (**p < 0.001**) showed significant association with each other in terms of AD. However, Malaysian vs. Bangladesh did not show any significant association with each other (**Table 4.34**). Pakistani UCLP subjects had the smallest AD of maxilla followed by Bangladeshi and Malaysian UCLP subjects.

Table 4.33 The effects of races on AD

Variable	Unstandardised Coefficients		Standardised Coefficients	t	*p* Value
	B	Std. Error	Beta		
AD	-1.33	0.45	-0.19	-2.91	**< 0.001**

Table 4.34 Comparison of individual races based on AD

Variables	Unstandardised Coefficients		Standardised Coefficients	t	p value
	B	Std. Error	Beta		
Malay vs. Paki	-2.75	0.84	-0.24	-3.25	**< 0.001**
Ban vs. Malay	0.71	0.87	0.06	0.81	0.41
Ban vs. Paki	-1.99	0.84	-0.18	-2.37	**0.02**

Malay: Malaysia; Ban: Bangladesh; Paki: Pakistan

4.6 Results of Tooth Size Asymmetry

4.6.1 Reliability of Tooth Size Asymmetry

The intra-class correlation for all measurements ranged from 0.91-0.99 for intra-examiner reliability. (**Table 4.35**).

Meanwhile, the intra-class correlation for inter-examiner reliability of all measurements ranged from 0.79-0.96 (**Table 4.36)**.

This indicated good to excellent reliability of all the measurements.

Table 4.35 **Intra examiner reliability of all teeth from CS and NCS of maxilla**

Variables		**ICC**[b]	**95% CI**		**F Test with True Value 0**			
			LB	**UB**	**Value**	**df1**	**df2**	***p* value**
				CLEFT SIDE				
P CI	Single Measures	0.95[a]	0.89	0.98	44.12	20	20	**<0.001**
P LI	Single Measures	0.98[a]	0.86	0.99	159.31	5	5	**<0.001**
D C	Single Measures	0.97[a]	0.92	0.98	66.85	17	17	**<0.001**
D 1M	Single Measures	0.96[a]	0.88	0.99	53.20	10	10	**<0.001**
D 2M	Single Measures	0.98[a]	0.97	0.99	159.74	21	21	**<0.001**
P 1M	Single Measures	0.91[a]	0.82	0.96	23.36	24	24	**<0.001**
				NON-CLEFT SIDE				
P CI	Single Measures	0.98[a]	0.97	0.99	170.34	20	20	**<0.001**
P LI	Single Measures	0.98[a]	0.91	0.99	131.06	5	5	**<0.001**
D C	Single Measures	0.93[a]	0.82	0.97	33.16	17	17	**<0.001**
D 1M	Single Measures	0.99[a]	0.97	0.99	224.74	10	10	**<0.001**
D 2M	Single Measures	0.92[a]	0.81	0.96	28.99	21	21	**<0.001**
P 1M	Single Measures	0.94[a]	0.88	0.97	35.05	24	24	**<0.001**

ICC: Intraclass Correlation; CI: Confidence Interval; LB: Lower Bound; UB: Upper Bound; PCI: Permanent Central Incisor; PLI: Permanent Lateral Incisor; DC: Deciduous Canine; PC: Permanent Canine; D1M: Deciduous 1st Molar; D2M: Deciduous 2nd Molar; P1M: Permanent 1st Molar

Table 4.36 Inter examiner reliability of all teeth from CS and NCS of maxilla

Variables		ICC[b]	95% CI		F Test with True Value 0			
			LB	UB	Value	df1	df2	*p* value
			CLEFT SIDE					
P CI	Single Measures	0.94[a]	0.86	0.97	34.81	20	20	**<0.001**
P LI	Single Measures	0.91[a]	0.59	0.98	24.08	5	5	**<0.001**
D C	Single Measures	0.85[a]	0.64	0.94	11.89	17	17	**<0.001**
D 1M	Single Measures	0.96[a]	0.86	0.99	48.47	10	10	**<0.001**
D 2M	Single Measures	0.84[a]	0.67	0.93	12.04	21	21	**<0.001**
P 1M	Single Measures	0.81[a]	0.62	0.91	10.28	24	24	**<0.001**
			NON-CLEFT SIDE					
P CI	Single Measures	0.96[a]	0.90	0.98	48.52	20	20	**<0.001**
P LI	Single Measures	0.95[a]	0.75	0.99	43.68	5	5	**<0.001**
D C	Single Measures	0.79[a]	0.53	0.91	8.52	17	17	**<0.001**
D 1M	Single Measures	0.85[a]	0.55	0.95	11.99	10	10	**<0.001**
D 2M	Single Measures	0.81[a]	0.60	0.91	10.54	21	21	**<0.001**
P 1M	Single Measures	0.81[a]	0.62	0.91	9.66	24	24	**<0.001**

ICC: Intraclass Correlation; CI: Confidence Interval; LB: Lower Bound; UB: Upper Bound; PCI: Permanent Central Incisor; PLI: Permanent Lateral Incisor; DC: Deciduous Canine; PC: Permanent Canine; D1M: Deciduous 1st Molar; D2M: Deciduous 2nd Molar; P1M: Permanent 1st Molar

4.6.2 Comparison of MD Tooth Size between CS and NCS

Malaysian Population

A paired-samples t-test was conducted to compare MD tooth size in CS and NCS of maxillae for male and female individually. There was a significant difference observed in the scores for permanent central incisor (PCI), permanent lateral incisor (PLI), deciduous canine (DC), deciduous first molar (D1M), deciduous second molar (D2M) and permanent first molar (P1M) of CS and NCS of maxillae in male Malaysian UCLP subjects. Significant difference also observed in the scores for permanent lateral incisor (PLI), deciduous canine (DC), deciduous first molar (D1M), deciduous second molar (D2M) and permanent first molar (P1M) of CS and NCS of maxillae in female Malaysian UCLP subjects. **Table 4.37** displays the differences of MD tooth size in CS and NCS of maxillae in the Malaysian population briefly.

Table 4.37 Tooth size asymmetry between cleft side and non-cleft side in Malaysian population

Variable	N	Mean (SD) (mm)		95.0% CI		t statistics (df)	*p* value
		CS	NCS	Lower	Upper		
Male							
Pair 1 (PCI)	45	6.97(1.47)	7.58(1.30)	-0.84	-0.35	-4.95	**<0.001**
Pair 2 (PLI)	10	4.81(0.47)	6.04(1.23)	-1.93	-0.51	-3.89	**0.004**
Pair 3 (DC)	34	4.59(1.29)	5.83(1.05)	-1.70	-0.75	-5.26	**<0.001**
Pair 4 (PC)	11	6.52(1.12)	7.20(1.06)	-1.60	0.23	-1.67	0.17
Pair 5 (D1M)	32	6.07(1.10)	6.61(0.82)	-0.78	-0.30	-4.54	**<0.001**
Pair 6 (D2M)	44	6.36(1.11)	6.84(1.09)	-0.79	-0.17	-3.10	**0.003**
Pair 7 (P1M)	50	9.09(0.85)	9.45(0.82)	-0.52	-0.19	-4.40	**<0.001**
Female							
Pair 1 (PCI)	29	7.63(1.40)	7.81 (0.97)	-0.58	0.20	-0.97	0.34
Pair 2 (PLI)	8	4.28 (0.86)	5.59 (0.62)	-2.01	-0.60	-4.40	**0.003**
Pair 3 (DC)	19	5.05 (1.32)	6.25 (0.82)	-1.69	-0.71	-5.18	**<0.001**
Pair 4 (PC)	-	-	-	-	-	-	**-**
Pair 5 (D1M)	24	5.97 (1.18)	6.59 (0.80)	-1.02	0-.22	-3.17	**0.004**
Pair 6 (D2M)	29	6.52 (1.15)	7.47 (1.10)	-1.29	-0.60	-5.69	**<0.001**
Pair 7 (P1M)	34	8.94 (1.07)	9.65 (0.77)	-1.04	-0.37	-4.27	**<0.001**

CS: cleft side; NCS: non cleft side; PCI: Permanent Central Incisor; PLI: Permanent Lateral Incisor; DC: Deciduous Canine; PC: Permanent Canine; D1M: Deciduous 1st Molar; D2M: Deciduous 2nd Molar; P1M: Permanent 1st Molar

Bangladeshi Population

All the variables between CS and NCS of maxilla in both male and female revealed significant difference statistically. Differences between CS and NCS of all variables are detailed in **Table 4.38**

Table 4.38 Tooth size asymmetry between cleft side and non-cleft side in Bangladeshi population

Variable	N	Mean (SD) (mm)		95.0% CI		t statistics (df)	*p* value
		CS	NCS	Lower	Upper		
Male							
Pair 1 (PCI)	41	6.86 (1.31)	7.68 (1.04)	-1.04	-0.59	-7.40	**<0.001**
Pair 2 (PLI)	13	4.67 (1.16)	6.39 (1.16)	-2.23	-1.19	-7.18	**<0.001**
Pair 3 (DC)	20	5.21 (0.95)	6.35 (0.75)	-1.56	-0.70	-5.52	**<0.001**
Pair 4 (PC)	13	6.77 (1.13)	7.27 (0.80)	-0.87	-0.13	-2.99	**0.01**
Pair 5 (D1M)	27	6.04 (1.03)	6.64 (0.81)	-0.84	-0.35	-5.00	**<0.001**
Pair 6 (D2M)	38	5.96 (1.16)	6.73 (1.00)	-1.04	-0.48	-5.49	**<0.001**
Pair 7 (P1M)	43	8.55 (1.11)	9.37 (1.01)	-1.01	-0.62	-8.56	**<0.001**
Female							
Pair 1 (PCI)	38	7.07 (1.34)	7.83 (1.21)	-1.04	-0.46	-5.32	**<0.001**
Pair 2 (PLI)	14	5.09 (1.24)	5.85 (0.76)	-1.21	-0.31	-3.66	**0.003**
Pair 3 (DC)	20	4.93 (0.89)	6.05 (0.79)	-1.62	-0.60	-4.55	**<0.001**
Pair 4 (PC)	9	7.02 (0.76)	7.79 (0.68)	-1.29	-0.24	-3.39	**0.009**
Pair 5 (D1M)	22	5.76 (1.02)	6.47 (1.01)	-0.99	-0.41	-5.07	**<0.001**
Pair 6 (D2M)	32	6.87 (1.22)	7.36 (1.10)	-0.77	-0.22	-3.68	**0.001**
Pair 7 (P1M)	41	8.69 (0.93)	9.44 (0.78)	-0.97	-0.51	-6.47	**<0.001**

CS: cleft side; NCS: non cleft side; PCI: Permanent Central Incisor; PLI: Permanent Lateral Incisor; DC: Deciduous Canine; PC: Permanent Canine; D1M: Deciduous 1st Molar; D2M: Deciduous 2nd Molar; P1M: Permanent 1st Molar

Pakistani population

All the variables between CS and NCS in maxillae revealed significant difference statistically. **Table 4.39** displays the difference for all the variables between CS and NCS in maxillae of the Pakistani population.

Table 4.39 Tooth size asymmetry between cleft side and non-cleft side in Pakistani population

Variable	N	Mean (SD) (mm)		95.0% CI		t statistics (df)	*p* value*
		CS	NCS	Lower	Upper		
Male							
Pair 1 (PCI)	37	7.03 (1.39)	7.65 (1.15)	-0.84	-0.40	-5.66	**<0.001**
Pair 2 (PLI)	18	5.26 (1.12)	6.31 (0.93)	-1.56	-0.52	-4.26	**0.001**
Pair 3 (DC)	26	5.44 (0.67)	6.31 (0.39)	-1.12	-0.61	-7.04	**<0.001**
Pair 4 (PC)	11	7.18 (0.64)	7.54 (0.48)	-0.57	-0.15	-3.79	**0.004**
Pair 5 (D1M)	28	5.79 (0.94)	6.49 (0.78)	-0.94	-0.46	-6.09	**<0.001**
Pair 6 (D2M)	36	5.69 (1.18)	6.31 (1.01)	-0.88	-0.34	-4.63	**<0.001**
Pair 7 (P1M)	43	8.57 (0.96)	9.36 (0.98)	-1.00	-0.57	-7.32	**<0.001**
Female							
Pair 1 (PCI)	34	7.23 (1.23)	7.98 (1.18)	-1.04	-0.45	-5.21	**<0.001**
Pair 2 (PLI)	19	5.29 (0.89)	6.13 (0.68)	-1.22	-0.44	-4.46	**<0.001**
Pair 3 (DC)	23	5.40 (0.75)	6.07 (0.73)	-1.00	-0.33	-4.10	**<0.001**
Pair 4 (PC)	15	7.05 (0.58)	7.58 (0.49)	-0.84	-0.20	-3.51	**0.003**
Pair 5 (D1M)	26	5.78 (0.85)	6.41 (0.69)	-0.86	-0.38	-5.45	**<0.001**
Pair 6 (D2M)	31	6.08 (1.12)	6.82 (1.07)	-1.12	-0.35	-3.95	**<0.001**
Pair 7 (P1M)	40	8.60 (1.19)	9.17 (1.14)	-0.77	-0.35	-5.54	**<0.001**

CS: cleft side; NCS: non cleft side; PCI: Permanent Central Incisor; PLI: Permanent Lateral Incisor; DC: Deciduous Canine; PC: Permanent Canine; D1M: Deciduous 1st Molar; D2M: Deciduous 2nd Molar; P1M: Permanent 1st Molar

4.6.3 Associations of Various Factors on Tooth Size among Three Populations

Gender (Male/Female)

This study also evaluated the effects of gender on the MD tooth size of both CS and NCS among three populations. The results showed significant associations between gender and D1M of both CS (**$p < 0.001$**) and NCS (**$p = <0.001$**). **Table 4.40** shows the effects of gender on the MD tooth of both CS and NCS among three populations.

Table 4.40 Associations of gender with tooth size among three populations

Dependent Variable	USC		SC	95% CI			
	B	SE	Beta	LB	UB	t	p Value
CLEFT SIDE							
P CI	0.32	0.19	0.12	-0.05	0.69	1.73	0.09
P LI	0.05	0.23	0.02	-0.41	0.50	0.20	0.84
D C	0.04	0.18	0.02	-0.31	0.39	0.24	0.81
P C	-0.15	0.27	-0.08	-0.69	0.39	-0.57	0.57
D 1M	-0.16	0.16	-0.08	-0.48	0.16	-0.99	0.32
D 2M	0.48	0.17	0.20	0.16	0.81	2.94	**< 0.001**
P 1M	-0.02	0.13	-0.10	-0.28	0.24	-0.14	0.89
NON-CLEFT SIDE							
P CI	0.21	0.15	0.09	-0.09	0.52	1.35	0.17
P LI	-0.33	0.20	-0.18	-0.73	0.07	-1.63	0.10
D C	-0.00	0.13	-0.01	-0.27	0.26	-0.03	0.97
P C	0.16	0.23	0.10	-0.29	0.63	0.73	0.46
D 1M	-0.11	0.13	-0.07	-0.37	0.13	-0.91	0.36
D 2M	0.61	0.14	0.27	0.32	0.90	4.12	**<0.001**
P 1M	0.02	0.11	0.01	-0.21	0.25	0.17	0.86

USC: Unstandardised Coefficients; SC: Standardised Coefficients; SE: Std. Error; LB: Lower Bound; UB: Upper Bound; P: permanent; D: deciduous; CI: central incisor; LI: lateral incisor; C: canine; 1M: 1st molar; 2M: 2nd molar

Races (Malaysian, Bangladeshi, and Pakistani)

This study evaluated the association of MD tooth size of both CS and NCS among three different populations. We found significant associations in CS PLI (**$p = 0.01$**), CS DC (**$p < 0.001$**), CS PC (**$p = 0.02$**), CS D2M (**$p < 0.001$**), CS P1M (**$p < 0.001$**) and NCS D2M (**$p < 0.001$**) with three different populations. Details can be showed in **Table 4.41.**

Table 4.41 Associations of races with tooth size among three populations

Dependent Variable	USC		SC	95% CI			
	B	SE	Beta	LB	UB	t	*p* Value
CLEFT SIDE							
P CI	-0.07	0.11	-0.04	-0.30	0.14	-0.67	0.49
P LI	0.36	0.14	0.27	0.07	0.65	2.49	**0.01**
D C	0.32	0.10	0.26	0.12	0.53	3.18	**<0.001**
P C	0.41	0.17	0.32	0.05	0.77	2.32	**0.02**
D 1M	-0.11	0.09	-0.09	-0.31	0.07	-1.20	0.22
D 2M	-0.29	0.10	-0.20	-0.49	-0.09	-2.95	**<0.001**
P 1M	-0.22	0.08	-0.18	-0.38	-0.07	-2.88	**<0.001**
NON-CLEFT SIDE							
P CI	0.06	0.09	0.04	-0.12	0.25	0.63	0.52
P LI	0.20	0.12	0.17	-0.05	0.45	1.56	0.12
D C	0.10	0.08	0.11	-0.05	0.26	1.34	0.18
P C	0.19	0.15	0.17	-0.11	0.50	1.25	0.21
D 1M	-0.06	0.07	-0.06	-0.22	0.08	-0.85	0.39
D 2M	-0.29	0.09	-0.21	-0.46	-0.11	-3.20	**<0.001**
P 1M	-0.12	0.07	-0.11	-0.27	0.01	-1.76	0.07

USC: Unstandardised Coefficients; SC: Standardised Coefficients; SE: Std. Error; LB: Lower Bound; UB: Upper Bound; P: permanent; D: deciduous; CI: central incisor; LI: lateral incisor; C: canine; 1M: 1st molar; 2M: 2nd molar

CHAPTER 5

DISCUSSION

The present study was attempted to evaluate treatment outcome based on dental arch relationship and maxillary arch dimension and also to evaluate tooth size asymmetry of CS and NCS of maxilla. Furthermore this study also explored the association of multiple congenital and post natal factors on treatment outcome of Malaysian, Bangladeshi and Pakistani UCLP subjects using 3D digital models.

5.1 Profile of the subjects

In this study, we analysed 255 UCLP subjects from three different populations which was relatively much higher sample size than the number of subjects in the previous studies (Fudalej et al., 2019; Hassan et al., 2018; Gopinath et al., 2017; dos Santos et al., 2015; Southall et al., 2012). All the subjects of this study were between 5 to 12 years of age. This range of age was chosen as most UCLP patients first received orthodontic treatment at the age of 5-6 years old (Rocha et al., 2012). Most of these UCLP subjects exhibited Class III malocclusions and other dental anomalies, and have yet to undergo alveolar bone grafting by the age of 12 (Rocha et al., 2012). So the selection of this age range may represent the actual knowledge of treatment outcome to the orthodontist as well as to the surgeon. Like ours, some other researchers also conducted their researches with the same age range (Alam et al., 2008; Kajii et al., 2013; Yew et al., 2016).

Bone grafting and orthodontic treatment are part of treatment of cleft patient. Bone grafting helps the arch to develop normally and orthodontic treatment is for correction of underdeveloped maxillary arch. This study did not include bone grafting and orthodontic treated subjects. This eliminate alveolar bone grafting and any pre-operative orthodontic expansion influencing factor on the dental arch relationship (treatment outcome).

The distributions of the subjects in our study showed that males were slightly more affected by CLP than females in all populations. It has been reported that risk of CLP is higher in males compared to females (Niswander et al., 1972; Owens et al., 1985; Mossey and Little, 2002; Kim and Baek, 2006; Dixon et al., 2011; Sokal et al., 2014), which is explained by Rittler et al. (2004) that the male embryos have a higher interaction between gene and environment. The contributions of environmental factors with known associations with CLP and possible links to sex differentiation such as maternal age, smoking, diabetes, and epilepsy have been reported in the literatures (Mossey and Little, 2002; Sokal et al., 2014; Dixon et al., 2011).

Left sided cleft were seen more among the all subjects and the distribution of the occurrences of left sided cleft is 67.1%, 61.2% and 74.1% in Malaysian, Bangladeshi and Pakistani population respetively. Many studies have also reported that the prevalence of left sided UCLP is higher than the right side (Jamilian et al., 2016; Zreaqat et al., 2009). However the etiology of this phenomenon is still irresolute.

Majority (70.6% and 61.2%) of subjects consist of incomplete type of UCLP in Malaysian and Bangladeshi populations respectively. However, in this study all the subjects from Pakistani population had the complete type of UCLP due to availability of data in the archive. Anatomically, the defect completely involve the soft palate, hard palate, alveolus and lip in complete CLP cases. Surgical intervention is required to repair the defect. In this study, both Millard and modified Millard technique was found almost equally in Bangladeshi population; yet modified Millard technique was found to be popular in lip surgery in Pakistani population and 42 (49.41%), 49 (57.64%) of cases respectively were treated with modified Millard technique for cheiloplasty. On the other hand, 63.52% of subjects from Malaysian population were treated with Millard technique of cheiloplasty. We found that most of the surgeons preferred to use von Langenbeck technique for palatoplasty and 56 (65.88%), 43 (50.58%) and 57 (67.05%) of cases repectively were treated using this technique in Malaysian, Bangladeshi and Pakistani population. The choice of different techniques of cheiloplasty and palatoplasty was subjected on the surgeon's preferences and different cases as well.

5.2 Error Study

3D digital model has superseded plaster dental casts due to its reliability and effectiveness (Zilberman et al., 2003; Keating et al., 2008; Bootvong et al., 2010; Moreira et al., 2014; Lemos et al., 2015). Current trend in high impact research and publication also emphasise on the incorporation of digital technology in research (Bootvong et al., 2010). Laser scanned models is the most relevant and desired method amongst all having three dimensions of object as well as time consuming method. The ability to accurately and reliably quantify the performance of LS3DM is crucial because this would become the standard for both research and clinical use. Our study evaluated the treatment outcome on LS3DM based on dental arch relationship, maxillary arch dimension and also tooth size asymmetry and showed that LS3DM by Next Engine laser scanner device is reliable and valid alternative tools.

In this study, the dental casts were converted into LS3DM from Next Engine laser scanner and evaluated the reliability and validity of the LS3DM using Mimics software by benchmarking its measurements with the digital caliper's measurements. It was an excellent correlation (ICC 0.916-0.995) of intra-examiner reliability for

LS3DM using Mimics software and digital caliper and good to excellent correlation (ICC 0.816-0.990) in terms of inter-examiner reliability for LS3DM. Regarding validity of LS3DM method, our study also showed high correlation (ICC 0.913-0.996) between the measurements of LS3DM using Mimics software and digital caliper.

To the best of our knowledge, present study is the first that use a combination of Next Engine Laser Scanner and Mimics software in the research of UCLP on 3D digital dental casts. Some previous studies have used this device but most of those studies were either on normal orthodontic patient or the patients from different fields (Beebe, 2014; Massoud et al., 2016). Likewise, both of those previous studies reported that Next Engine laser scanner device is a sound, reliable and valid alternative tools.

5.3 Evaluation of Treatment Outcome Based On Dental Arch Relationship

Mid-facial growth is probably a reasonable indicator of surgical outcome, especially in UCLP patients, and this may be reflected in the dental arch relationships. An assessment of the dental arch relationship is considered being the most valuable benchmark of treatment outcome which can give clear concept for facial growth as well as revealing an important indicator for worth of cleft treatment outcome.

Numerous studies have been conducted to assess the CLP treatment outcomes based on dental arch relationship (Schilling et al. 2019; Kongprasert et al. 2019; Hay et al. 2018; Haque et al. 2018; Zin et al. 2017; Arshad et al. 2017; Sasaguri et al., 2014; Kajii et al. 2013; Fudalej et al., 2012; Fudalej et al., 2011; Zaleckas et al., 2011; Apostol, 2008; Alam et al, 2008). There are several indices have been established to evaluate treatment outcome based on the dental arch relationship in UCLP subjects. Yet, no single index has been identified to have the qualities to describe the treatment outcomes fairly in all aspects. This field of research remains unexhausted and ever growing towards improvement of patient care and quality of life. In this study we used three indices; GY, EI and mHB scoring system to evaluate treatment outcome based on dental arch relationship.

5.3.1 Reasons of selecting these three indices

GOSLON Yardstick (GY)

To date GY remains the most widely accepted and used technique to assess the treatment outcome based on dental arch relationship and found to be a more sensitive tool in discriminating differences in outcomes of dentofacial growth in the participating centre (Hassan et al., 2018; dos Santos et al., 2015; Ganesh et al., 2015; Ness et al., 2015; Vig and Mercado, 2015; Long et al., 2011; Lilja et al., 2006; Molsted et al., 2005; Kitagawa et al., 2004; Mars et al., 1992; Shaw et al., 1992). We have used GOSLON to formulate a database for further comparison. This index has been attributed to be simple, precise, reliable and quick and universally accepted. We optimise that it could play a key role in pioneering evidence based practice in the target population (Chaudhry et al., 2018; Buj-Acosta et al., 2017). According to the GOSLON scale, groups 1 and 2 have occlusions that require simple orthodontic treatment, and group 3 needs complex orthodontic treatment. Patients in group 4 are at the limits of orthodontic treatment, and orthognathic surgery will generally be necessary, whereas subjects in group 5 require combined orthodontic-surgical therapy (Mars et al., 1987; Mars et al., 1992; Mars et al., 2006). This categoriseation was sufficiently sensitive to distinguish treatment results at different population and centre as well. Similarly, in this study, the GY was used to evaluate dental arch relationships in Malaysian, Bangladeshi and Pakistani UCLP children.

EUROCRAN Index (EI)

EI is the latest addition to the various indices that have been used to assess primary surgical treatment outcomes. The EI is a relatively new, novel and moderately innovative tool for assessing the UCLP patient and has been shown to have moderate to very good inter- and intra-examiner reliability (Fudalej et al., 2011). It has two components of rating dental models; dental arch relationship and palatal morphology. It basically includes the desirable components of the two indices. Unlike many studies, the EI can evaluate not only surgical outcomes but also the degree of malocclusion in both antero-posterior and vertical aspect, as well as the palatal outward appearance. It should be noted, however, that other indices, such as the GY (Mars et al., 1987) and the mHB for crossbite (Mossey et al., 2003, Gray and Mossey, 2005) can evaluate only the dental arch relationship. By using EI, we will contribute new evidence to the literature which can then be compared with other populations to establish global protocols for cleft care.

Modified Huddart Bodenham (mHB) scoring system

The advantages of mHB scoring system are its objectivity, versatility, sensitivity, no requirement for any special training, and its ability to be applied to any cleft subgroup at any age. It is a continuous scale of severity of arch constriction rather than a categorical scale and therefore provides a greater degree of sensitivity and the ability to differentiate the severity within the categories. mHB is a less prevalent scoring system which arrives at a result by quantitatively assessing the data. Its objective nature of scoring is appealing to statisticians as it behaves well when analysed. Maxillary arch constriction has been considered as an important facet in determining the growth outcome as a result of primary surgeries (Joos, 1995; Kramer et al., 1996; Adcock and Markus, 1997; Markus and Precious, 1997). We used mHB as it weighs the transverse discrepancies heavily and provide a clear picture of maxillary arch constriction based on the total occlusion score.

5.3.2 Evaluation of treatment outcome using GOSLON Yardstick (GY)

We assessed 255 LS3DM of non syndromic UCLP subjects from three populations for the evaluation of dental arch relationship using GY. The index was found to have good inter- and intra-examiner reliability in present study which also correspond with the findings of the earlier studies (Chaudhry et al., 2018; Buj-Acosta et al., 2017; Lilja et al., 2006).

The mean GOSLON score of Malaysian subjects was 2.97. In the present study, the treatment outcome of Malaysian subjects was good to fair (between groups 2 and 3), representing 71.8% of all cases. Of the leftover, 4.70 % was excellent, 20 % was poor and 3.5 % was a very poor outcome. Two studies were conducted in Malaysia previously (Zreaqat et al., 2009; Asif et al., 2016). Zreaqat et al. (2009) evaluated the treatment outcome among 82 UCLP subjects who attended to the orthodontic clinic of HUSM between 2004 and 2010; reported total mean GOSLON score of 3.15 with 62% of all cases. On the other hand, 107 UCLP subjects were evaluated by Asif et al. (2016) who came to the same hospital in between 2000 and 2012. Interestingly this study also found the same mean GOSLON score of 3.15 represented with 68% of all cases. The same GOSLON score of previous studies indicated towards the similar treatment outcome which could be due to the use of same surgical technique/protocol and same institution as well even though the samples were different. Both of the studies used plaster dental casts in their researches.

The mean GOSLON score of Bangladeshi UCLP was 3.40. The treatment outcome of Bangladeshi subjects had fair to the poor outcome representing 70.59% of all subjects. Only a study found that evaluated dental arch relationship on the Bangladeshi UCLP subjects using plaster dental casts reported a mean GOSLON score of 3.238 with 68% of all subjects (Haque et al., 2017a).

The mean GOSLON score of Pakistani UCLP was 3.01. The treatment outcome of most Pakistani subjects of our study was fair; representing 30.59% of all cases. Of the leftover, 4.70 % was excellent, 29.41 % was good, 22.35% was poor and 12.94 % was a very poor outcome. The current findings are consistent with the results of Arshad et al. (2017a), which is the only study found in literature on the Pakistani population.

All these previous studies in Malaysia, Bangladesh and Pakistan were done using plaster dental casts separately. Consistent with literature, 3D digital model is more accurate, precise, robust and reliable compared to plaster dental casts (Zilberman et al., 2003). To our knowledge, for the first time, our study evaluated dental arch relationship (treatment outcome) in multi-population UCLP subjects using LS3DM which is the most important property of the present study.

There have been many studies done on UCLP with GOSLON Yardstick in other populations. Different populations showed different results. For example, in a recent multicentre study, found the mean GOSLON score ranged from 2.58 to 3.07 among three centres and also reported one stage palatoplasty showed the low GOSLON score (better outcome) than two stage palatoplasty (Fudalej et al., 2019).

Another multicentre study between 1985 and 2000 on Turkish populations reported GOSLON score of 3.16 to 3.70 among different cleft centres (Dogan et al., 2014). Their findings is comparable to our Bangladeshi and Pakistani outcome, keeping in mind that the surgeons involved in the treatment of UCLP patients still practice the same old protocols of surgery in such populations. A study of Japanese population by Alam et al. (2008) found fair to poor outcome (GOSLON 3 and 4) in 80% of the UCLP patients. In Western Australia, a mean GOSLON score of 3.17 was demonstrated in a study which included 66 cases of UCLP (Southall et al., 2012).

These differences may be due to use of different technique of cheiloplasty and palatoplasty and/or the experience of the surgeons.

The techniques of cheiloplasty and palatoplasty were the only disparity of treatment protocols among the subjects all the three populations of this study and one well trained, highly skilled, experienced surgeon performed all of the surgeries, utilising the standardised surgical protocol in all populations separately. Finding the fair to poor outcome provide the evidence of using same surgical method among all the populations.

However, enhancements in surgical methods have headed to better outcomes in different populations. Recent advancements in techniques and centralization of cleft care has reduced the GOSLON score (Nollet et al., 2005; Harila et al. 2014; Ganesh et al., 2015). This favourable decrease in GOSLON score signifies the importance of newly established techniques; such as Tennison technique of cheiloplasty, two stage palatoplasty, alveolar extension palatoplasty etc. Whereas, in Malaysia, Bangladesh and Pakistan, traditional techniques are still widely used, which could explain the fair to poor outcomes.

The current findings of the study demonstrated that the treatment outcome in the three populations was comparable. The Malaysian subjects presented comparatively favourable outcomes than the other two populations and Bangladeshi subjects were tend more towards unfavourable outcomes. It should be noted that presenting different outcomes in different populations and races of treatment outcomes based on the dental arch relationship seemed to be attributable to surgical procedures, but racial difference in the craniofacial morphology also deserves consideration.

5.3.3 Evaluation of treatment outcome using EUROCRAN Index (EI)

In our study, we evaluated treatment outcomes based on the dental arch relationship and palatal morphology using EI in Malaysian, Bangladeshi and Pakistani UCLP children. The intra- and inter-examiner agreements of both dental arch relationship and palatal morphology showed good to very good agreements. Nevertheless, the EI conversely shown to have unsatisfactory reliability score in some studies (Patel, 2011; Altalibi et al., 2013; Jones et al., 2014). However, it had conversely shown good reliability in our study. The similar satisfactory reliability of EI for the scoring of dental arch relationship and palatal morphology was reported by Fudalej et al., 2011; Fudalej et al., 2012; Sabelis et al., 2016; Yew et al., 2016; and Arshad et al., 2017b.

In this study, the treatment outcome based on the dental arch relationship was poor to very poor in Malaysian UCLP subjects, representing 68% of the cases; good to poor in Bangladeshi and Pakistani UCLP subjects, representing 55% and 72% of the cases respectively.

Regarding palatal morphology, 62%, 55% and 43% of subjects demonstrated moderate outcomes, whereas 8%, 19% and 25% had good and 30%, 26% and 32% had poor outcomes of palatal morphology in Malaysian, Bangladeshi and Pakistani UCLP subjects respectively.

Only a study found in Malaysia using EI where dental arch relationship and palatal morphology score of 3.32 and 1.99 was documented respectively (Yew et al., 2016). However, their findings was not consistent with our study which showed comparatively more reduced (good) dental arch relationship and higher (worse) palatal morphology in Malaysian subjects. This differences may be due to the selection of different techniques of cheiloplasty and palatoplasty and use of two different type of tools as well.

Based on literature, only one study was found in Bangladeshi population. A mean dental arch relationship score of 2.44 and 1.93 was scored for palatal morphology (Haque et al., 2017b). The good to poor treatment outcome was noticed in their study which was similar to our findings though the difference of EI score was 0.22 and 0.14 for dental arch relationship and palatal morphology respectively.

Correspondingly, Arshad et al. (2017b) reported a score of 2.72 and 2.20 for dental arch relationship and palatal morphology using EI; the only previous study in Pakistani. Interestingly, the present study reported comparatively reduced (good) EI score in both dental arch relationship and palatal morphology. This differences also could be due to the use of different techniques of palatoplasty and also to use of different types of research tools; i.e. 3D digital models.

All the previous studies in Malaysia, Bangladesh and Pakistan have evaluated treatment outcome on plaster dental casts. The present study evaluated treatment outcome using EI on virtual model for the first time which is robust, more accurate, reproducible, efficacious, and effective than conventional dental casts (Elbashti et al., 2017; Nugrahani et al., 2017; Quimby et al., 2004; Zilberman et al., 2003; Santoro et al., 2003).

There have been very few studies was carried out on UCLP with EI in other populations. For example, based on dental arch relationship, the mean score was ranged from 2.5 to 3.04 in studies conducted in Netherland and Switzerland (Mueller et al., 2012; Fudalej et al., 2012; Fudalej et al., 2011). The range is similar to our findings in regard to Malaysia, Bangladesh and Pakistan. Based on palatal morphology, the mean score was higher (worse) than Swiss populations (1.81 to 1.88) reported by Fudalaj et al. (2012). However, palatal morphology was not revealed for the Dutch population (Mueller et al. 2012).

In our study, the mean score for both dental arch relationship and palatal morphology in Malaysian subjects is relatively higher (worse) than Bangladeshi and Pakistani subjects. This findings indicates that the treatment outcome of Malaysia subjects were more towards to the unfavourable outcome. It should take into consideration that racial variation of the craniofacial morphology may also influence the treatment outcome of UCLP subjects. All the Malaysian samples in this study consist of Malay ethnic children and most of them appear to have unfavourable dental arch relationship and palatal morphology. Craniofacial morphology varies among races. A study done among three races (Malay, Chinese and Indian) of Malaysia reported 50% of Malays had a high prevalence of Class III malocclusion with a norm of an edge to edge incisor relationship (Woon et al., 1989). In addition, 68 % of Class III malocclusion patients underwent surgical intervention reported in a multi-ethnic Asian population study which reflected the severity of dento facial deformities including or facial cleft patients in Asian population and in Malays particularly (Chew, 2006). Therefore, further study is needed to explore the effect of racial differences in craniofacial morphology on dental arch relationship particularly in Malay UCLP subjects.

5.3.4 Evaluation of treatment outcome using mHB Scoring System

This study measured the upper dental arch constriction of children with UCLP by means of the frequency and severity of crossbites in the labial and lateral segments. Therefore, we assessed the LS3DM using mHB index; according to this index total arch score will represent the degree or severity of maxillary arch constriction. The more negative the score, the more severe the arch constriction. According to this numerical scoring system, the score ranging from a score of >0 indicates an excellent, < -1 indicates a good, < -5 indicates fair, < -10 indicates poor and a score of < -16 indicates a very poor dental arch relationship.

Based from this outline, we found the mean score of incisors, CS buccal segment and NCS buccal segment were -3.60, -4.86 and -1.53 respectively; hence the total mHB score was -9.98 in Malaysian subjects indicating near to poor arch constriction; 42 (49.4%) of cases were having unfavourable maxillary arch constriction (category ratings poor and very poor) and 43 (50.6%) presented with favourable maxillary arch constriction (category ratings excellent, good and fair).

The mean score of incisors, CS buccal segment and NCS buccal segment were -1.31, -4.42 and -3.04 respectively in Bangladeshi. The total mHB score of Bangladeshi subjects were -8.76 indicating fair arch constriction where 33 (38.8%) of cases were having unfavourable maxillary arch constriction (category ratings poor and very poor) and 52 (61.2%) of cases were having favourable maxillary arch constriction (category ratings excellent, good and fair). Similar outcome was also reported by

Antonarakis et al. (2015) in a Canadian UCLP study and Haque et al. (2018) in another Bangladeshi study.

The mean score of incisors, CS buccal segment and NCS buccal segment were -1.15, -3.33 and -2.09 in Pakistani subjects. The total mHB score of Pakistani subjects were -6.57 indicating fair arch constriction where 29 (34.1%) of cases were having unfavourable maxillary arch constriction (category ratings poor and very poor) and 56 (65.9%) of cases were having favourable maxillary arch constriction (category ratings excellent, good and fair). Mikoya et al. (2015), reported -6.43 as total mHB score among 68 Japanese UCLP subjects which is consistent with the score of Pakistani subjects of this study. However, the outcome of earlier Pakistani study reported more negative score (-8.92) compared to ours (Arshad et al., 2018). Their findings indicate more near to poor arch constriction. These dissimilarities may be due to the use of different techniques of palatoplasty. In their study, they used von Langenbeck and VY pushback palatoplasty while in our study surgeon used Bardach and von Langenbeck technique. Considering the finding that mHB scores are more negative, the transverse correction using rapid palatal expanders is needed and should be completed before performing secondary bone graft in order to guarantee stabilisation of the dental arch at a correct width (Yakob et al., 2018).

The present study found this scoring system having very good inter and intra-examiner agreement. A very few studies have been done using the mHB index previously. Among them most of the studies are about the reliability and validity of this index (Pegelow et al., 2019; Chaudhry et al., 2018; Yakob et al., 2018; Baraka et al., 2017; Dobbyn et al., 2015; Dobbyn et al., 2012; Manosudprasit et al., 2011; Wangsrimongkol and Jansawang, 2010; Ali et al., 2006). It can be noted that, reliable kappa value of mHB in this study was also consistent with previous studies.

According to literature, only one study found that evaluated treatment outcome using mHB scoring system using 3D digital models; reported a total mHB score of -6.9 among 30 virtual models (Asquith et al., 2012). The sample size of present study is quite large than previous studies and also first time evaluating the treatment outcome on LS3DM in three populations together.

5.4 Evaluation of Treatment Outcome Based on Maxillary Arch Dimension

The outcome of treatment of UCLP after cheiloplasty and palatoplasty can also be assessed based on maxillary arch dimension.

Thus the present study also assessed 255 LS3DM to evaluate the treatment outcome of non syndromic Malaysian, Bangladeshi and Pakistani UCLP children based on maxillary arch dimension. We have measured ICW, IMW, and AD of the maxilla of all the subjects.

A reliable finding in patients with repaired UCLP is constriction of the maxillary arch, with shortened maxillary AD and narrowing of ICW and IMW. How much of this is directly related to the nature of the primary surgery has been fiercely questioned (dos Santos et al., 2015). This is more severe in the medial and anterior regions and can be attributed to medial displacement of the palatal segments, especially the minor segment (da Silva Filho et al., 1992). In the mixed dentition, the degree of maxillary arch constriction in patients with repaired UCLP is an important factor when considering the impact of primary surgeries on growth (dos Santos et al., 2015; Carrara et al., 2016; Cassi et al., 2017).

Relatively similar mean dimension of ICW was found in Malaysia, Bangladesh and Pakistan; 26.88mm, 26.61mm and 26.69mm respectively. These findings indicating to the similar outcome on the anterior region of maxilla among all three populations. Besides, the dimension of ICW observed in the present evaluation is in agreement with findings from other studies (Wahaj and Ahmed, 2015; dos Santos et al., 2015; Gopinath et al., 2017) and it may be associated with the severe constriction of the anterior region in UCLP subjects. Conversely, some authors reported relatively larger ICW and stated the less severe constriction of the anterior region heading to more favourable treatment outcome (Lewis et al., 2008; Zinah et al., 2011). This outcome should be preferred, as early management of transverse deficiencies in UCLP subjects usually requires a greater amount of anterior maxillary expansion with segment rotation, secondary to the collapse of the buccal segment on the cleft side.

The mean dimension of IMW in Malaysia, Bangladeshi and Pakistani was 45.24mm, 42.89mm and 43.33mm respectively. The IMW dimension of Bangladeshi subjects was the smallest than other two populations. On the other hand, the mean dimension of AD in Malaysia, Bangladeshi and Pakistani was 29.81, 29.06 and 27.06 respectively. The AD dimension of Pakistani subjects was comparatively smaller than other two populations. The racial difference in the craniofacial morphology may justifies this differences.

First study had been reported by Gopinath et al. (2017) in Malaysia that assessed treatment outcome by measuring maxillary arch dimension, however the study was conducted on 48 dental casts of UCLP only. Treating with only one type of cheiloplasty (Millard technique) and palatoplasty (VY pushback technique), treatment of alveolar bone grafting and starting of orthodontic care were the notable disparities from present study yet the age group was similar. That study assessed the maxillary arch dimensions only and compared the measurement with healthy non cleft control group found ICW was significantly larger among control group. The mean dimension if ICW, IMW and AD of their study was 26.9mm, 46.7mm and 29.3mm respectively.

Interestingly, the findings of previous study is coincide with our outcomes of Malaysian subjects.

So far only one study had been found reporting the Pakistani UCLP patients that assessed treatment outcome by measuring maxillary arch dimension on 16 dental casts of UCLP with the age between 14 to 16 years (Wahaj and Ahmed, 2015). This study assessed the ICW (26.7 mm) and IMW (40.9mm) only and compared the measurement with a healthy non-cleft control group. According to Wahaj and Ahmed, (2015), ICW was significantly smaller among the cleft group. The mean dimension of ICW of the maxillae was 26.3 mm in the cleft group which is relatively similar to our findings. The IMW was smaller than the value of our sample by 3mm which indicates towards less maxillary constriction (more favourable). This differences may be due to inconsistency in the selection of age group, surgical technique and sampling bias as well.

The methodology used in the present study evaluated a 3D image method to measure the maxillary arch dimension. The particularities of our study from previous studies were the higher sample size and the use of LS3DM. Moreover, the most vital variances was that our study evaluated not only the maxillary arch dimension but also the effects of multiple factors on maxillary arch dimension which is important for the orthodontist as well as surgeon for the treatment plan and also facilitated the treatment outcome. Moreover, it should be noted that, no reported data till to date has found on Bangladeshi population evaluating treatment outcome using maxillary arch dimension. According to the literatures, narrowing or shortening of ICW was a consistent finding of UCLP children as well (Cassi et al., 2017; dos Santos et al., 2015; Wahaj and Ahmed, 2015; Garib et al., 2013; Lewis et al., 2008). ICW was most affected variable among CLP children followed by IMW (Koshikawa-Matsuno et al., 2014). An overview of global comparisons of ICW, IMW and AD is shown **Table 5.**1. The pattern of descriptive data indicated that our results values fell within the range of other populations worldwide.

Table 5.1 Mean dimension of ICW, IMW and AD of maxilla of global and present study

Author	Population	Sample size	Method	Measurement	Mean(SD) mm
Gopinath et al. (2017)	Malaysia	UCLP: 48	Dental casts	ICW IMW AD	26.9 (4.3) 46.7 (6.0) 29.3 (4.9)
Cassi et al. (2017)	Italy	UCLP: 20	Dental casts	ICW IMW (D)	25.7 (4.2) 35.5 (4.8)
Carrara et al. (2016)	Brazil	UCLP:114	3D dental models	ICW	26.9 (2.5)
Dos Santos et al. (2015)	Brazil	UCLP: 72	Dental casts	ICW IMW	26.0 (3.01) 45.6 (4.10)
Wahaj and Ahmed, (2015)	Pakistan	UCLP: 16	Dental casts	ICW IMW	26.3 (4.0) 40.9 (3.7)
Helio¨ vaara et al. (2014)	Finland	UCLP: 68	Dental casts	ICW IMW (D)	23.3 (2.9) 24.4 (3.0)
Zinah et al. (2011)	Iraq	UCLP:30	Dental casts	ICW IMW	27.89 (3.09) 43.64 (2.84)

Lewis et al. (2008)	England	UCLP: 30	2D photographs	ICW	27.08 (4.09)
				IMW	43.64 (3.84)
Garrahy et al. (2005)	Caucasian	UCLP:16	Dental casts	ICW	24.35 (2.44)
				IMW (D)	28.90 (2.92)
				AD	23.99 (2.85)
Present Study	Malaysia	UCLP: 85	LS3DM	ICW	26.88 (5.04)
				IMW	45.24 (4.76)
				AD	29.81 (5.75)
	Bangladesh	UCLP: 85	LS3DM	ICW	26.61 (4.33)
				IMW	42.89 (5.48)
				AD	29.06 (5.72)
	Pakistan	UCLP: 85	LS3DM	ICW	26.69 (5.70)
				IMW	43.33 (4.66)
				AD	27.06 (5.26)

D: deciduous; LS3DM: Laser scanned 3D digital model

It has to be considered that in UCLP patients, narrow upper arch is mostly seen which is a result of surgical treatment. Anterior part of the maxillary arch of UCLP subjects is affected by the cheiloplasty, which causes a restrictive shaping effect. The dimensions of maxillary dental arches and measurements of cleft width play an important role in deciding the treatment plan for UCLP patient. Accordingly, expansion of the anterior part of the maxillary arch could be beneficial (Dogan et al., 2019; Carrara et al., 2016; Liao et al., 2005; Nollet et al., 2005). Orthopedic expansion of patients with UCLP, with a stress in the anterior section of the palate, would be beneficial in order to provide needed space for the tongue and allowing for normal growth and development.

5.5 Association of Multiple Factors on Treatment Outcome Based on Dental Arch Relationship and Maxillary Arch Dimension

Logistic regression analyses were carried out to observe the associations of each congenital (UCLP type, UCLP side, family history of CLP, family history of Class III malocclusion), and post natal treatment (cheiloplasty, palatoplasty) factor with dental arch relationship (treatment outcome). Multiple linear regression analyses were carried out to observe the associations between each congenital and post natal treatment factor and maxillary arch dimension (treatment outcome).

5.5.1 Congenital Factors

Gender (male/female)

The present study found more males (59%, 52% and 52% in Malaysia, Bangladeshi and Pakistani respectively) were affected with cleft than females. Literature also states that incidence of cleft is more in males than female (Dixon et al., 2011; Bhalaji, 2012; Arshad et al., 2017).

Male UCLP subjects were significantly associated with unfavourable dental arch relationship using GY in the Bangladeshi population though Malaysian and Pakistani UCLP subjects did not show any significant associations using any index. Additionally, this factor also did not show any association with maxillary arch dimension in any population.

The transverse dimension of the maxilla comparatively smaller in female and larger in male mainly at the posterior region (da Silva Filho et al., 1992). The smaller is the transverse dimension of the maxilla the lesser will be cleft interference in the posterior part of the maxilla. Greater cleft interferences in the posterior region during maxillary growth in male resulted with more unfavourable dental arch relationship (da Silva Filho et al., 1992). This report coincides with our result. However, due to lack of enough data in literature regarding this issue, it is unjustified to make a statement that the differences in transverse dimension in a different gender of maxillary arch is an absolute factor contributing to the unfavourable dental arch relationship in Bangladeshi UCLP patients.

UCLP type (complete/incomplete)

Complete UCLP cases means hard tissue structures and soft tissue structures of the soft palate, hard palate, alveolus and lip totally failed to fuse with each other. The treatment for complete UCLP are more complicated compared to incomplete UCLP (Kulewicz and Dudkiewicz, 2010; Yamanishi et al., 2011).

In this study, type of UCLP did not show any association with dental arch relationship with any population. However, it showed statistically significant association with maxillary arch dimension in Bangladeshi population.

The subjects having complete type of UCLP resulted in shorter AD of maxillary arch dimension of Bangladeshi population in the multiple linear regression analysis. It was speculated in study that complete cleft has a strong association with other independent variable such as palatoplasty which may contribute more towards unfavourable treatment outcome due to denudation of palatal bone and excessive scar tissue formation at that particular area (Zin et al., 2017). Additionally study also showed that the patients having complete UCLP have more altered maxillary arch dimension due to the loss in the continuity of the alveolar ridge and supra position of the lateral segments on the cleft side (Dogan et al., 2019). These statements might provide the justification behind the association between complete UCLP and unfavourable AD of maxilla.

According to Ross (1970), the mucoperiosteal denudation of the palatal bone was an important inhibiting factor of maxillary growth in surgical procedure for complete UCLP cases then followed by the excessive scar tissues formation at the denuded palatal bone and the undermining of soft tissue during palatal repair which can inhibit the forward growth of the maxilla results shortening of AD dimension.

UCLP side (right/left)

Only Pakistani UCLP subjects showed the significant associations with dental arch relationship using EI. Left sided UCLP subjects had unfavourable effect on dental arch relationship. Yet maxillary arch dimension had not any significant association with side of UCLP in any population. We could not compare this result with other studies or similar studies because none of them found this factor as precise factor for dental arch relationship and maxillary arch dimension as well.

Nevertheless, higher distribution of left sided UCLP were observed in all the populations in this study. Worldwide studies done by researchers also reported that the left side involvement in UCLP cases were found to be of higher prevalence than the right side (Wilson, 1972; Kim and Baek, 2006; Zreaqat et al., 2009; Nagase et al., 2010; Gallagher et al., 2017). However the etiology of this phenomena is still not well understood (Gallagher et al., 2017).

The more frequent occurrence of UCLP on the left side suggests directional rather than fluctuating asymmetry. Directional asymmetry defines a trait that systematically occurs more often on one side or the other during development. Directional asymmetry may be related to a variety of underlying control processes (e.g., genetic variation, environmental insult) (Weinberg et al., 2006). In contrast, fluctuating asymmetry describes random variation, in which a trait would be expected to occur with equal frequency on the right or left side. This process suggests nonspecific insults to development. Facial directional asymmetry is also more common among relatives of individuals with UCLP compared with the general population, but not for relatives of individuals with bilateral clefts (Miller et al., 2014). It is possible that among multiple genetic pathways controlling facial development, some have fluctuating and some have directional asymmetry.

Family history of cleft

From the results of this study, we found that family history of cleft is the predictors of favourable or unfavourable dental arch relationship in Malaysian (using EY and mHB scoring system) and Bangladeshi (using mHB scoring system) UCLP subjects. The subjects who had no family history of cleft showed favourable dental arch relationship; that means the positive family history of cleft significantly affect the dental arch relationship. However, Pakistani subjects did not showed any association with dental arch relationship. Moreover, this factor was also not statistically associated with maxillary arch dimension in any population.

Family history of cleft is in a higher risk of having a baby with a cleft in some way (Klotz et al., 2010). A rate of recurrence of cleft condition in next generation is depend on a number of factors that are consistently constant in an individual family including the number of family members with clefts, their relationship to family members with clefts, sex of the affected individuals, and the type of cleft (Klotz et al., 2010). Figueiredo et al. (2015) found that maternal family history of clefts as well as having other biological children with a cleft were highly associated with increased risk. In a study, in CLP mothers, the same type of cleft was found in 70% of the boys and 18% of the girls. Yet, in fathers with CLP, no statistically significant difference was observed between the numbers of girls and boys with CLP (Kot and Kruk-Jeromini, 2007). The cleft type in a child depends not only upon the cleft type present in the mother or father, but also upon the sex of the child (Peterka et al, 1996). Autosomal fetal genes make the major contribution to risk of recurrence, with little additional contribution from heritable aspects of the maternal phenotype (Leslie and Marazita, 2013). Nevertheless, it was not possible to compare our results with others due to lack of data regarding associations of this variable with treatment outcome. Future studies are needed in other populations in order to determine the cause of it.

Family history of Class III malocclusion

According to the Angle classification, class III malocclusion is defined as the lower molar mesially positioned relative to the upper molar with no specifications in regards to the line of occlusion (Angle, 1899). A Class III jaw relationship suggests that the mandible has acquired a more mesial position in relation to the maxilla and/or cranial base (Angle, 1899). Class III problems may arise due to deficient growth of maxilla in the downward and forward direction and more forward growth or reduced downward growth of mandible (Proffit et al., 2007).

In this study, only 7 (8.2%) Bangladeshi subjects had family history of Class III malocclusion while 29 (34.1%) Malaysian subjects had family history of Class III malocclusion. However, no record was found regarding this factor among Pakistani subjects.

Interestingly, present study found a large number of family history of Class III malocclusion among Malaysian UCLP subjects, which is uncertain. Because Class III malocclusion can be caused by mandibular prognathism and/or maxillary retrognathism. It could be noted that Malay ethnic group had the high prevalence of Class III malocclusion in previous studies (Woon et al., 1989; Chew, 2006; Sunil and Dhanraj, 2019). Therefore, these results should interpret with precaution.

However, family history of Class III malocclusion was not significantly associated with dental arch relationship and maxillary arch dimension in all the population of this study, yet this variable was correlated with dental arch relationship in previous studies (Alam et al., 2008; Kajii et al., 2013).

The present study provided information that congenital factors are associated with dental arch relationship in Malaysian (family history of cleft using EI and mHB scoring system), Bangladeshi (gender using GY, family history of cleft using mHB scoring system), Pakistani (UCLP side using EI) populations. Congenital factors were also associated with larger and narrower maxillary arch dimension (AD) in Bangladeshi (UCLP type) population.

5.5.2 Post-natal Treatment Factors

Multi-population studies are very important to explain which procedures give the best treatment results as well as the esthetic and functional quality of the treatment outcome. The results of this study demonstrated that despite differences in the surgical techniques used, some of the treatment protocols produced similar treatment outcomes for the dental arch relationships and maxillary arch dimension as well.

In this study, all the subjects underwent two different techniques of cheiloplasty and palatoplasty. The choice of different techniques of cheiloplasty depends on the surgeon’s preferences and severity of cases as well. Millard technique and modified Millard technique of cheiloplasty was the treatment of choice for all the populations in the present study. In modified Millard technique, there is a rotation advancement flap yet no rotation flap is carried out in original Millard technique which is the basic difference between Millard and modified Millard technique of cheiloplasty (Murthy et al., 2016).

Regarding palatoplasty, all the subjects were treated with either the Bardach technique or von Langenbeck technique palatoplasty. In von Langebeck technique, two incisions are carried out; lateral and medial where medial incision is sutured leaving the lateral incision open. On the other hand, two triangle flap is rasied including greater palatine vessels followed by suturing, repositioning and anchoring of lateral edge is carried out in Bardach technique (Murthy et al., 2016).

The finding of this current study demonstrated that the Millard technique of cheiloplasty had the favourable effect on dental arch relationship and maxillary arch dimension as well. Millard technique of cheiloplasty was significantly showed a favourable outcome of dental arch relationship than the modified Millard technique in Bangladeshi (using GY and EI) and Pakistani (using EI) subjects. Furthermore, present study found, subjects with Millard technique of cheiloplasty had larger ICW of maxilla compared to modified Millard technique of cheiloplasty in Malaysian UCLP subjects.

Furthermore, this study also demonstrated that the von Langenbeck technique of palatoplasty had the favourable effect both on dental arch relationship and maxillary arch dimension. That means Bardach techniques of palatoplasty was responsible for the unfavourable dental arch relationship (using GY, EI and mHB scoring system) in all populations and also for the narrower maxillary arch dimension (ICW) in Malaysian and Bangladeshi populations.

It is recognized that poor growth of the maxillary region is related to the effects of primary repair surgery (Schilling et al., 2019), and this is of particular concern for the orthodontist who must correct dento-facial discrepancies during early adolescence. Although those patients who have displayed favourable facial growth may require only relatively routine orthodontic treatment, patients with unfavourable facial growth often need orthognathic surgery for complete correction of dento-facial discrepancies (Hay et al., 2018).

In the present study, constriction was slight in the molar region (IMW) and more pronounced in the anterior regions (ICW) of maxilla. This means that the influence of cleft and primary surgeries is markedly greater in the anterior region of the maxilla (da Silva Filho et al., 1992). Similar reduction of maxillary arch dimensions in children with repaired UCLP in different ages has been found previously (Robertson and Fish, 1975; Wada et al., 1984; Athanasiou et al., 1988; Kramer et al., 1996; DiBiase et al., 2002).

Unfavourable effects of modified Millard technique on maxillary growth has been reported previously. Kajii et al. (2013), reported that modified Millard with vomer flap had significantly unfavourable effect on the maxillary growth. Researches had revealed that modified Millard technique caused maxillary growth retardation (Li et al., 2006; Rousseau et al., 2013). Adetayo et al. (2019), did not found any significant differences between the Millard and Tennison–Randall's techniques of cheiloplasty among Nigerian UCLP subjects where both techniques showed a favourable outcome of dental arch relationship. In comparison with the present study, the modified Millard technique had a significant association with unfavourable growth patterns which can be attributed to the tension developed as a result of rotation advancement (Farronato et al., 2014). The greater lip tension is predicted to cause mainly dentoalveolar constriction rather than skeletal changes (Kuijpers-Jagtman and Long, 2000).

However, the skeletal changes comprising an anterior portion of the maxilla in antero-posterior and transverse dimension has also been reported (Normando et al., 1992).

The explanations for the association between maxillary antero-posterior deficiency and anterior maxillary constriction may rely on the fact that lip repair could cause continuous pressure on the anterior portion of the maxillary dental arch, influencing both the maxillary sagittal growth and the transverse dimension in the anterior region of the maxillary arch (Normando et al., 1992). The greater the lip tension after primary surgeries, the greater the maxillary sagittal deficiency and the constriction in the anterior region.

Narrow ICW of maxilla of Malaysian UCLP subjects was noted in the present study could be attributed to the scar tissue development following surgical repair procedures (Falzoni et al., 2016; Adetayo et al., 2019). It could also be due to the abnormal inferior position of the tongue as a result of the hyoid bone being positioned caudally in Malaysian UCLP infants (Rajion et al., 2006) that may have also contributed to maxillary constriction. Since it is known that under normal circumstances, the dorsum of the tongue that is anatomically and physiologically positioned against the palate at rest maintains the maxillary arch width by counteracting the contracting forces from the buccinator muscles (Ozbek et al., 2009). However, many more authors put the blame on the surgical scar as the main cause of maxillary constriction.

The primary aim of palatoplasty is to restore function and phonetics (Krause et al., 1976). von Langenbeck, Bardach technique, V-Y pushback techniques of palatoplasty have been used to achieve these goals for a few decades. However, with the introduction of new techniques, these techniques, such as two stage palatoplasty, alveolar extension palatoplasty are less practiced nowadays. Yet, they are still used by surgeons working in non-centralized cleft care units with no accountability.

The unfavourable effect of palatoplasty on speech, maxillary growth, upper dental arch, and dental anomalies has been extensively documented. Maxillary arch constriction is the major drawback of standard procedure of palatoplasty. Studies also have revealed that multiple surgeries as well as different techniques of surgeries of clefts inhibited the maxillary growth especially the anterior segment (Haque and Alam, 2015c). Dental arch growth and development in children with UCLP is influenced by the surgical technique employed (Carrara et al., 2018). A study has demonstrated that the timing of UCLP surgical intervention did not present significant effect on development of dento-facial skeletal structures (Priya et al., 2011). However, a large variation in the sample type and numerous confounding factors, such as the size of the defect, the extent of defect, timing of repair and most importantly growth response makes assessment very difficult (Schilling et al., 2019).

The use of von Langenbeck technique has resulted in better outcomes due to lower scar formation documented (Bishara and Mary Tharp, 1977). The findings of the current study also correspond with the findings of the study conducted by Sato et al. (2016) in relation to von Langenbeck technique. Another study also reported von Langenbeck technique had the favourable outcome where compared to VY pushback technique of palatoplasty (Arshad et al., 2018).

When a subject with cleft palate is treated with palatoplasty, maxillary growth may present variations (Pigott et al., 2002; Pradel et al., 2009; Dissaux et al., 2016). Pigott et al. (2002) compared three surgical techniques, namely: Cuthbert Veau, von Langenbeck, and medial Langenbeck. Subjects who underwent palatoplasty with von Langenbeck surgical technique presented better maxillary growth than those submitted to cleft palatoplasty employing Cuthbert Veau technique. In this regard, von Langenbeck technique was the one which presented the best results (Pigott et al., 2002).

On the other hand, the Bardach technique has been attributed to causing bigger scar formation which would manifest in the form of growth restriction. Fistula formation has also been associated as a drawback of this technique when performed to repair larger defects (Agrawal et al., 2009). However, interestingly, Rossell-Perry et al. (2017) reported no significant differences between two flap (Bardach technique) and one flap palatoplasty on dental arch relationship. Moreover, the patient treated with the Bardach technique achieved better normal speech (Bardach, 1995).

In view of the divergence between the results of the researches, it is suggested that the association between treatment outcome (dental arch relationship, maxillary arch dimension) and the effect of cheiloplasty and palatoplasty be better explored. Different surgical techniques are employed to observe the effect on maxillary growth, and it can be concrete from the results that treatment outcome of UCLP subjects is influenced by the surgical technique used.

The present study provided information that post natal treatment factors are associated with favourable and unfavourable dental arch relationship and also with larger and narrower maxillary arch dimension in all the three populations. These findings could warrant a modification of management protocols to ensure improvement in future cleft outcomes.

5.6 Tooth Size Asymmetry

Considering the requirement of exact evaluation of tooth size for achieving an esthetic, stable, and functional occlusal relationship, awareness about the variations in tooth size in patients with CLP may guide clinicians in orthodontics and accompanying dental treatment planning (Falzoni et al., 2016; Lione et al., 2013; Huang et al., 2002).

The purpose of this study was to evaluate whether the MD tooth dimension of CS differs from MD tooth dimension of NCS of maxillae among male and female UCLP subjects in three different populations.

Our findings showed that the MD dimension of PCI, PLI, DC, D1M, D2M, and P1M of CS in male and PLI, DC, D1M, D2M, and P1M of CS in female were significantly smaller than the NCS in Malaysians. On the other hand, the MD dimension of all the variables (PCI, PLI, DC, PC, D1M, D2M, and P1M) of CS in Bangladeshis (both male and female) and Pakistanis (both male and female) were found significantly smaller than NCS. Antonarakis et al. (2015), reported that the PCI, PLI, and P1M are significantly smaller in the CS than in the NCS of maxillae. Dos Santos et al. (2015), studied on Brazilian-Caucasian UCLP subjects, found the MD dimension of PLI of CS was significantly smaller than the NCS of maxillae though only three variables (PCI, PLI, and P1M) were included in that study. Jordanian UCLP subjects demonstrated that the MD dimension of PLI of CS was significantly smaller than NCS of maxillae. However, that study also found a larger MD dimension of PC and P1M on CS than NCS of maxillae (Rawashdeh et al., 2007). A recent study done on Polish UCLP subjects found no significant association between the CS and NCS of maxillae (Sękowski et al., 2019). These results indicate that the racial bias of the MD dimension of the tooth in UCLP subjects.

MD tooth size played a vital role in getting proper orthodontic diagnosis and treatment planning which leads to a satisfactory outcome. The evaluation of tooth size in UCLP subjects was always a topic of interest and necessity as well due to have compromised maxillary arch and tooth size (Akcam et al., 2014). MD tooth size was the most used variable to evaluate tooth size ratio in UCLP subjects (Antonarakis et al., 2015). Still, a lack of evidence was observed on the tooth size of UCLP subjects in Malaysian, Bangladeshi and Pakistani populations.

Orthopedically or orthodontically untreated UCLP patients who are in the mixed denti tion show different upper arch morphology with maxillary constriction (Falzoni et al., 2016; Lione et al., 2013; Huang et al., 2002). As the result of the reduced maxillary arch dimension, crossbite is an early and common malocclusion in children with UCLP.

For UCLP patients, investigators reported that anterior crossbite ranges from 7% to 64% and posterior crossbite ranges from 30% to 97%. But in only cleft palate patients, the reported frequencies are lower, ranging from 14% to 27% for anterior crossbite and 22% to 37% for posterior crossbite. Subsequent to the presence of the cleft, reduction in the maxillary interdental width and tooth width is generally observed.

The present study evaluated the associations of races and gender with the MD dimension of the tooth of both CS and NCS of maxillae and revealed the significant associations among Malaysian, Bangladeshi and Pakistani UCLP subjects with PLI, DC, PC, D2M and P1M of CS and D2M of NCS of maxillae. Only a study found that study on only 40 cleft subjects of Europeans and Asians; evaluated the MD dimension of the only P1M; described larger MD dimension among Asian than European (Echtermeyer et al., 2017). To the best of authors' knowledge, this is the first report comparing results among three different populations at a time. Thus it was not possible to compare our findings with others.

Regarding the effects of gender on the MD dimension, only the D2M showed significant associations with the MD dimension of both CS and NCS of maxillae. Male subjects had larger tooth size than female subjects in all populations. This corresponds to the findings of Rawashdeh et al. (2007), in Jordan population; the only study found in literature.

Various researchers evaluated the MD dimensions of UCLP subjects previously but did not evaluate the effect of factors together with multi-population. Their study was based on a single population. However, for the first time, the present study evaluated the MD dimension of both CS and NCS of maxillae; utilized larger sample size, 3D digital models and also evaluated the association between MD dimensions with multiple factors.

The null hypothesis was rejected because significantly smaller MD dimension tooth size of CS than NCS of maxilla was found in all populations using LS3DM. Races and gender also showed significant associations with MD dimensions of CS and NCS of maxillae.

CHAPTER 6

CONCLUSION

Present study analysed 255 cases of Malaysian, Bangladeshi and Pakistani UCLP children who underwent primary surgical repairs. This is the first study to assess the treatment outcomes based on dental arch relationship (using GY, EI and mHB scoring system) and maxillary arch dimension (ICW, IMW and AD) on LS3DM in all the three populations. This multi-population study also evaluated the effects of multiple congenital and postnatal factors on treatment outcome based on dental arch relationship and maxillary arch dimension. Furthermore, this three-dimentional study measured the MD tooth size asymmetry between CS and NCS of maxilla in male and female of three populations and evaluated the association of gender and races on it.

6.1 Dental Arch Relationship

6.1.1 GOSLON Yardstick (GY)

1. The mean GOSLON score of Malaysian, Bangladeshi and Pakistani UCLP children was 2.97, 3.40 and 3.09 respectively using LS3DM.

2. The distribution of favourable and unfauvorable dental arch relationship were 58 and 27 respectively in Malaysian; 45 and 40 respectively in Bangladeshi and 55 and 30 respectively in Pakistani UCLP children using LS3DM.

3. There was a significant association between von Langenbeck technique of palatoplasty and favourable dental arch relationship in all three (Malaysian, Bangladeshi and Pakistani) populations. Additionally, there was a significant association between female UCLP subjects, Millard technique of cheiloplasty and favourable dental arch relationship in Bangladeshi UCLP children.

6.1.2 EUROCRAN Index (EI)

1. The mean EUROCRAN score for the dental arch relationship of Malaysian, Bangladeshi and Pakistani UCLP children using LS3DM was 3.07, 2.66 and 2.56 respectively. The mean EUROCRAN score for the palatal morphology of Malaysian, Bangladeshi and Pakistani UCLP children was 2.21, 2.07 and 2.07 respectively.

2. The distribution of favorable and unfavorable dental arch relationship were 28 and 57 respectively in Malaysian; 35 and 50 respectively in Bangladeshi and 37 and 48 respectively in Pakistani UCLP children using LS3DM.

   There was a significant association between von Langenbeck technique of palatoplasty and favourable dental arch relationship in all three (Malaysian, Bangladeshi and Pakistani) populations. Adiitionally, the negative family history of cleft had a significantly favorable effect on the dental arch relationship in Malaysian; Millard techniques of cheiloplasty had a significantly favorable effect on the dental arch relationship in Bangladeshi and Pakistani UCLP children; right sided UCLP had a significantly favorable effect on the dental arch relationship in Pakistani UCLP children.

6.1.3 mHB Scoring System

1. The mean total mHB score of Malaysian, Bangladeshi and Pakistani UCLP children was -9.98, -8.76 and -6.57 respectively using LS3DM.

2. The distribution of favorable and unfavorable dental arch relationship were 43 and 42 respectively in Malaysian; 52 and 33 respectively in Bangladeshi and 56 and 29 respectively in Pakistani UCLP children using LS3DM.

3. This study revealed that the subjects with von Langenbeck technique of palatoplasty had a significantly favorable effect on the dental arch relationship in all three (Malaysian, Bangladeshi and Pakistani) UCLP children using LS3DM. Adiitionally, the negative family history of cleft had a significantly favorable effect on the dental arch relationship in Malaysian and Bangladeshi UCLP children.

6.2 Maxillary Arch Dimension

6.2.1 Inter-Canine Width (ICW)

1. The mean dimension of ICW of Malaysian, Bangladeshi and Pakistani UCLP children was 26.88 mm, 26.61 mm and 26.69 mm respectively using LS3DM.

2. This study found that the Millard technique of cheiloplasty had a significantly larger ICW in Malaysian UCLP children using LS3DM. Additionally, von Langenbeck technique of palatoplasty had a significantly larger ICW in Malaysian and Bangladeshi UCLP children. Howevr, no significant association was found between multiple factors and ICW in Pakistani UCLP children. There was no significant association observed on ICW statistically between three populations.

6.2.2 Inter-Molar Width (IMW)

1. The mean dimension of IMW of Malaysian, Bangladeshi and Pakistani UCLP children was 45.24 mm, 42.89 mm and 43.33 mm respectively using LS3DM.

2. No significant association was found between multiple factors and IMW in any populations (Malaysian, Bangladeshi and Pakistani) using multiple linear regression analysis.

3. There was signicicant association observeved on IMW between three populations. Malaysian vs. Bangladesh and Malaysian vs. Pakistan showed significant association with each other in terms of IMW.

6.2.3 Arch Depth (AD)

1. The mean dimension of AD of Malaysian, Bangladeshi and Pakistani UCLP children was 29.81 mm, 29.06 mm and 27.06 mm respectively using LS3DM.

2. This study found that the subjects with complete UCLP had a significantly shorter AD in Bangladeshi UCLP children using LS3DM. However, no significant association was found between multiple factors and AD in any Malaysian and Pakistani UCLP children using LS3DM.

3. There was signicicant association observeved on AD between three populations. Bangladesh vs. Pakistan and Malaysian vs. Pakistan showed significant association with each other in terms of AD.

6.3 Tooth Size Asymmetry

1. There was significant difference between the tooth size (MD) on the cleft and non-cleft sides of the maxilla among male (PCI, PLI, DC, D1M, D2M and P1M) and female (PLI, DC, D1M, D2M and P1M) non-syndromic UCLP children in Malaysian population.
2. There was significant difference between the tooth size (MD) on the cleft and non-cleft sides of the maxilla among male (PCI, PLI, DC, PC, D1M, D2M and

P1M) and female (PCI, PLI, DC, PC, D1M, D2M and P1M) non-syndromic UCLP children in Bangladeshi population.

3. There was significant difference between the tooth size (MD) on the cleft and non-cleft sides of the maxilla among male (PCI, PLI, DC, PC, D1M, D2M and P1M) and female (PCI, PLI, DC, PC, D1M, D2M and P1M) non-syndromic UCLP children in Pakistani population.
4. There was significant associations between tooth size (MD) of the cleft and non-cleft sides of the maxilla and gender (CS D1M, NCS D1M) and races (CS PLI, CS DC, CS PC, CS D2M, CS P1M and NCS D2M) in non-syndromic UCLP children among the three different populations.

CHAPTER 7

LIMITATIONS AND RECOMMENDATIONS

7.1 Limitations of the Study

Although the research has reached its aim, however, there were some unavoidable limitations. Because of insufficient amount of data from other centre, this study was conducted from single centre. In a future study we have plan to do multi centre study in multi population after collection of sufficient amount of data from other centre with large sample size.

The design of present study, limits the discussion to a specific instance. There is a need for longitudinal assessment of CLP from infancy to adulthood. To monitor the effects of treatments in relation to the initial set of complications and to assess the effects in the patterns of growth from young age to adulthood multiple additional factors are needed to be considered.

Role of surgeon's skill, timing of repair, and the severity of cleft should also be critically assessed as they can play an important role in altering the treatment outcome. Furthermore, nasolabial, speech and psychosocial assessments have their own significance and play an important role in patient well-being as a whole.

7.2 Recommendations

Further study is recommended so as to have an evenly distributed sample for each factor in order to allow more identification of association between independent variable factors and dental arch relationship. Additional independent variable factors such as using of pre orthopaedic appliances, presence of lateral incisor and two-stage or one-stage surgery performed were recommended to be include in further studies so as to assist the surgeons in predicting their treatment outcome for optimal treatment plan and care for the patients.

These findings were achieved from Malaysian, Bangladeshi and Pakistani UCLP children. May be these findings are different in other population. We encourage other population also to do same study to explore the precise factors that are responsible for dental arch relationship and maxillary arch dimension. For future studies, we advise to increase the number of subjects for more distinct results.

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APPENDICES

APPENDIX A ETHICAL CLEARENCE OF PRESENT PROJECT

UNIVERSITI SAINS MALAYSIA APEX JEPeM JAWATANKUASA ETIKA PENYELIDIKAN MANUSIA

Jawatankuasa Etika
Penyelidikan Manusia USM (JEPeM)
Human Research Ethics Committee USM (HREC)

Universiti Sains Malaysia
Kampus Kesihatan,
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8th January 2018

Dr. Sanjida Haque,
School of Dental Sciences,
Health Campus,
Universiti Sains Malaysia,
16150 Kubang Kerian, Kelantan.

JEPeM Code : USM/JEPeM/17100564
Protocol Title : Treatment Outcome Based on Congenital and Postnatal Treatment Factors in Children with Non-syndromic Unilateral Cleft Lip and Palate (UCLP): A Multi-population Study

Dear Dr.,

We wish to inform you that the Jawatankuasa Etika Penyelidikan Manusia, Universiti Sains Malaysia (JEPeM-USM) reviewed your proposed ethical application during its regular meeting on 14th December 2017 (Meeting No. 376). Your study has been assigned study protocol code USM/JEPeM/17100564 which should be used for all communication to the JEPeM related to this study.

As a result of the review, the decision of the committee is ***MINOR MODIFICATION***. Recommended revisions and/or clarifications are summarized in the 'conclusion and recommendations' part in the provided attachment.

Please note that revisions requested by the JEPeM-USM should:

1. Be integrated into a revised STUDY PROTOCOL and related documents in one printed copy
2. Be SUMMARIZED in a cover letter indicating in which page of the revised study protocol the respective revision may be found;
3. Modified part should be underlined and **bold**.

Please note that the cut-off date for submission of revised study protocol is on **20 February 2018**. Also, please note that resubmissions can only be accepted within 30 working days from the date of this letter. Failure to respond within 30 working days from the date of this letter will inactivate the application and study protocol will be archived. Subsequent submissions will be processed as initial review. Should you have any questions or clarifications regarding the abovementioned recommendations, please contact the undersigned through the JEPeM Secretariat at 09 7672352/2354 or jepem@usm.my.

CERTIFIED BY: NPRA MALAYSIA National Pharmaceutical Regulatory Agency (NPRA) | FERCAP Forum for Ethical Review Committees in Asia & Western Pacific Region

APPENDIX B TURNITIN REPORT

Treatment outcome on congenital and post natal treatment factors in children with nonsyndromic unilateral cleft lip and palate: A multi-population study using three dimensional digital model

ORIGINALITY REPORT

17%	14%	12%	13%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.catholic.ac.kr Internet Source	4%
2	jocpd.org Internet Source	2%
3	Submitted to Universiti Sains Malaysia Student Paper	1%
4	Yang Li, Bing Shi, Qing-Gao Song, Hui Zuo, Qian Zheng. "Effects of lip repair on maxillary growth and facial soft tissue development in patients with a complete unilateral cleft of lip, alveolus and palate", Journal of Cranio-Maxillofacial Surgery, 2006 Publication	1%
5	www.steveenglehart.com Internet Source	1%
6	Submitted to Higher Education Commission Pakistan	1%

APPENDIX C ACHIEVEMENTS

(THE VICE-CHANCELLOR AWARD SCHEME)

USM UNIVERSITI SAINS MALAYSIA APEX™

Pejabat Naib Canselor
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Canselori

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Date : 3 October 2017

Our Ref. : P-SGD0012/17(R)

Ms. Sanjida Haque
School of Dental Sciences
Universiti Sains Malaysia

Dear Ms. Sanjida Haque,

VICE-CHANCELLOR'S AWARD 2017

On behalf of the University, I would like to congratulate you for being conferred the Vice-Chancellor's Award.

The University may consider extending this award for the consecutive year (s), up to a maximum of two (2) years based upon satisfactory progress of your graduate works. You are required to apply for the extension at least two months before the expiry date of the current period of this award.

2 This Award covers the following:

(a)	**Duration**		
	From : 1 October 2017	To . 30 September 2018	
(b)	**Maximum period of funding (Please submit extension application before this funding expires)**		
	36 months (3 years)		
(c)	**This vice-chancellor's award covers**		
	Monthly Allowances	Tuition Fees	Examination Fees
	RM3,000.00	As charged **(Effective from Semester 1, 2017/2018)**	As charged **(Subjected to VC Award period).**
	Other fees are to be borne by the candidate		

3. Please kindly refer to Appendix for details for the terms and conditions of this offer.

4. If you wish to accept this Award, please kindly complete and submit the **Vice-Chancellor's Award Acceptance Declaration Form** to the Institute of Postgraduate Studies (IPS) before 13 October 2017.

THIS IS TO CERTIFY THAT

SANJIDA HAQUE

HAS BEEN AWARDED

VICE-CHANCELLOR AWARD 2017/2018

PROFESSOR DATUK DR. ASMA ISMAIL, FASc
Vice-Chancellor
UNIVERSITI SAINS MALAYSIA

APPENDIX C ACHIEVEMENTS

(PUBLICATION ACHIEVEMENT AWARD)

APPENDIX C ACHIEVEMENTS

(BEST PRESENTER AWARDS)

USM UNIVERSITI SAINS MALAYSIA APEX™

CERTIFICATE OF ACHIEVEMENT

1st Place in Oral Presentation
Clinical & Health Sciences Category

Won by

DR. SANJIDA HAQUE

Paper Title

Assessment of treatment outcome based on the age, types of clefts and effects of the different techniques of surgeries in Malay unilateral cleft lip and palate children

Co-Authors

Mohd Fadhli Khamis, Mohammad Khursheed Alam, Wan Muhamad Amir Wan Ahmed

at the

CONFERENCE ON MEDICAL AND HEALTH SCIENCES
(2ND ICMHS – 23RD NCMHS)
IN CONJUNCTION WITH
2ND TRANSLATIONAL CRANIOFACIAL CONFERENCE
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BEST ORAL AWARD

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SANJIDA HAQUE

for winning the

1st PRIZE (CLINICAL SCIENCES)

for the presentation on

Effects of Various Factors on Maxillary Arch Dimensions in Unilateral Cleft Lip and Palate Children: A Multi-population Study

at the

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Prof. Dr. Rosline Hassan
Deputy Chairperson
3RD ICMHS & 24TH NCMHS 2019

50 YEARS OF LEADING KNOWLEDGE FOR CHANGE

LIST OF PUBLICATIONS

1. Haque, S., Khamis, M.F., Alam, M.K., Ahmed, W.M.A.W. (2019) The reliability and validity of the measurements in unilateral cleft lip and palate laser scanned 3D dental casts. *Pesqui Bras Odontopediatria Clin Integr*, 19:e5051.

2. Haque, S., Khamis, M.F., Alam, M.K., Ahmed, W.M.A.W. (2020) Effects of Multiple Factors on Treatment Outcome in the 3D Maxillary Arch Morphometry of Unilateral Cleft Lip and Palate Children. *J Craniofac Surg*, (6):e534-e538.. IF: 0.785.

3. Haque, S., Khamis, M.F., Alam, M.K., Ahmed, W.M.A.W. (2020) A multi-population unilateral cleft lip and palate children: Three-dimensional tooth size in relation to gender and races. Orthodont Craniofac Res, (**Accepted**). IF: 0.946.

4. Haque, S., Khamis, M.F., Alam, M.K., Ahmed, W.M.A.W. (2020) An investigation of 3d maxillary arch morphometry of unilateral cleft lip and palate children. *J Craniofac Surg*, (**Accepted**) IF: 0.785.

5. Haque, S., Khamis, M.F., Alam, M.K., Ahmed, W.M.A.W. (2020) The assessment of 3D digital models using GOSLON Yardstick index: Exploring confounding factors responsible for unfavorable treatment outcome in multi-population UCLP children. *Cleft Palate Craniofac J*, (**Under Review**) IF: 1.471.

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LIST OF CONFERENCE PAPERS

1. Haque, S., Khamis, M.F., Alam, M.K., Ahmed, W.M.A.W. (2019) Effects of Various Factors on Maxillary Arch Dimensions in Unilateral Cleft Lip and Palate Children: A Multi-population Study. [3rd ICMHS and 24th NCMHS 2019, August, 2019)]

2. Haque, S., Khamis, M.F., Alam, M.K., Ahmed, W.M.A.W. (2019) Cheiloplasty and Palatoplasty have Detrimental Effect on Maxillary Arch of Unilateral Cleft Lip and Palate Children: A Myth or A Fact! [2nd Postgraduate Research Day /15th Students Scientific Conference, School of Dental Sciences, Universiti Sains Malaysia, April 2019]

3. Haque, S., Khamis, M.F., Alam, M.K., Ahmed, W.M.A.W. (2019) Surgeries Unfavorably Effect Maxillary Arch of Unilateral Cleft Lip and Palate Children: A 3D Study. [18th ANNUAL scientific meeting of Malaysian section IADR & 20th annual general meeting. March 2019]

4. Haque, S., Khamis, M.F., Alam, M.K., Ahmed, W.M.A.W. (2018) The performance of 3D laser scanned models in unilateral cleft lip and palate research. [6th Global Higher Education Forum 2018, October, 2018]

5. Haque, S., Khamis, M.F., Alam, M.K., Ahmed, W.M.A.W. (2018) Assessment of treatment outcome based on the age, types of clefts and effects of the techniques of surgeries in Malay unilateral cleft lip and palate children. [2nd ICMHS and 23rd NCMHS 2018, September, 2018]

6. Haque, S., Khamis, M.F., Alam, M.K., Ahmed, W.M.A.W. (2018) Different surgeries are the predictor of treatment outcome of unilateral cleft lip and palate children: A multi-population study. [Health Science Symposium 2018, May, 2018]

7. Haque, S., Khamis, M.F., Alam, M.K., Ahmed, W.M.A.W. (2018) Effects of Post Natal Treatment Factors in the Treatment Outcome of Non-Syndromic Unilateral Cleft Lip and Palate Children: A Multi Population Study. [2nd Postgraduate Research Day /15th Students Scientific Conference, School of Dental Sciences, Universiti Sains Malaysia, February 2018].