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Palatal morphology in unilateral cleft lip and palate patients: association with infant cleft dimensions and timing of hard palate repair

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Ethical implications:

The Scandcleft protocol for the present study was approved by the local Ethical Committee (journal number: 1997/4121). Informed consent was signed by the parents of all subjects participating at the time of inclusion. Permission to access data was granted by the regional Data Protection Agency (n.1-16-02-616-15). Anonymization of data was secured by using the random trial ID numbers for identification. The research protocol was designed in accordance with the ethical principles outlined in the Declaration of Helsinki (World Medical Association, 2013).

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ABSTRACT:

Objectives: To assess the impact of cleft severity and timing of hard palate repair on palatal dimensions in unilateral cleft lip and palate (UCLP) children.

Setting and Sample Population: Single center analysis within a multicenter RCT of primary surgery; 122 UCLP randomized to early hard palate closure (EHPC) at 12 months or delayed hard palate closure (DHPC) at 36 months; 28 frequency-matched controls.

Methods: Linear measurements of palatal height, width and length were performed on 116 digital models of UCLP subjects (8.21 years, SD= .53) and 28 models of non-cleft individuals (8.44 years SD= .72). Cleft dimensions at infancy (mean 1.8 months) were considered.

In a pilot study, shell-to-shell distances between the 3D cleft palate objects and a reference mesh were calculated and differences between the groups assessed. Morphological differences were visualized using color mapping.

Results: Compared to controls, UCLP subjects presented a higher palate at the level of the anterior scar ($p=.002$), but generally a lower palate in the middle region ($p<.001$). Comparing UCLP subgroups, the DHPC subjects showed a flatter palate posteriorly ($p=.048$) and the EHPC group exhibited more transversal constriction ($p=.003$ at M1 level). 3D analysis revealed a shallower palate in the DHPC group both in the middle ($p=.002$) and the posterior part ($p=.008$). Anterior cleft severity correlated negatively with palatal height ($p=.01$).

Conclusions: UCLP palates differ from controls in width and height. DHPC may represent an advantage for the transversal dimension, but a disadvantage for palatal height. Infant cleft dimensions partially explain differences in palatal height.

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Introduction

Previous studies have shown that cleft patients present a narrower and more irregular palatal vault than controls and that the height of their hard palate is reduced irrespectively of the type of the cleft [1-3]. Description of the palatal vault is considered an important parameter in cleft audit and was introduced as a separate score in the EUROCRAN project (2000-2004). The EUROCRAN index comprises assessment of dento-occlusal relations and assignment of a palatal score, composed of three categories based on palatal height, shape and morphology [4,5] [6,7]. The cleft team's interest in the anatomy of the palate refers to the hypothesis that it may have an influence on speech, oral function in general, and biomechanics of the orthodontic expansion. Furthermore, palatal scarring may be related to growth restriction [8].

In relation to speech, few studies have investigated the correlation between articulation and palatal vault morphology. Okazaki and co-authors found that children with cleft palates had a narrower and shallower palatal morphology than controls already at age 4-5 years, which was associated with an increased frequency of speech errors in the spectrum of retracted oral articulation[9]. Available research, based on phonetic transcription and electropalatographic data (EPG), confirms that children with cleft palates have increased tongue-palate contact, which affects vowel and consonant production[10]. Radiographically, an increased contact surface and predominant use of the dorsal part of the tongue are frequently observed in individuals with cleft palates [11]. From an anatomical point of view, the palate acts as a spatial reference for the tongue and provides tactile/feedback information furthering learning and control of specific tongue shapes [12]. Moreover, the height and morphology of the mouth's anatomical roof may affect oral function in general, for example during swallowing [13] and breathing [14,15].

To clinicians working with expansion (e.g. in case of crossbite), palatal height is critical to the design of the expansion device; thus, application of transversal forces at different heights, with respect to the centre of resistance of the teeth and the maxilla, changes significantly the biomechanical system and the expected stability of the result [16-18].

Previous studies have investigated the relation between palatal morphology and the surgical protocol adopted for hard palate closure. A study comparing six cleft centres showed that patients with a maxillary and facial growth pattern close to normal values also had a higher palatal vault [19]**.** Bakri and co-authors suggested an association between height of the palatal vault and surgical method employed [20]**.** Based on the same material, a study where speech was investigated as outcome showed that individuals with a higher palatal vault also had the best articulation results [21].

To the authors' knowledge, no studies have addressed how patient-specific intrinsic factors, e.g. cleft dimensions at birth, interact with the iatrogenic effects of surgery to determine palatal morphology[1].

The overall aim of the present study was to reveal differences in palatal dimensions in UCLP subjects who were randomized to early versus delayed hard palate closure, considering cleft dimensions at infancy. The specific objectives were to:

1) Develop a standardized morphometric analysis of palatal dimensions
2) Compare palate morphology in cleft and non-cleft individuals to establish where and how much a cleft palate deviates with respect to a normal reference palate
3) Assess the impact of variation in timing of hard palate repair.

Material and methods:

Subjects: UCLP infants (N=122) participating in a multicentre RCT, the Scandcleft, and operated in a single surgical centre at the Department of Plastic Surgery-University Hospital in Copenhagen-Denmark. were included. All patients received surgery of the lip and soft palate at age 3-4 months. Repair was accomplished using a modified Millard technique with McComb rhinoplasty and a posteriorly based vomer flap (ad modum Gothenburg). Patients were then randomized for hard palate closure at 12 (EHPC) or 36 months (DHPC). Inclusion criteria, randomization method, and trial design have been reported by Semb and co-authors [22] and the surgical technique described in detail by Rautio et al. [23] Surgery was performed by two senior high-volume surgeons (more than 50 cleft newborns' primary surgeries/year), calibrated according the Scandcleft protocol.

Plaster casts were collected according to trial protocol, at 8 years of age before bone grafting and orthodontic intervention. Casts were digitized with a table-top scanner

(3Shape D2000 Copenhagen-Denmark) and the digital models were then generated (Ortholab, Poland). We analysed 116 digital models (57 in EHPC, 19 females and 38 males; 59 in DHPC, 16 females and 43 males). The participants' mean age was 8.21 years (SD= .53); Fig. 1 depicts the participant flow.

Data regarding infant cleft dimensions, measured on digital baby models (mean age =1.8; SD = 1.5; range: 0.4-4.2 months), were available from a previous study; the method used for analysis has been described in detail in a technical note [24]. For this analysis, we used linear measurements of cleft dimensions between the alveolar segments (anterior cleft or G-L), at the level of the maxillary tuberosities (posterior cleft or tt'), and the ratio between cleft surface and palatal surface (3D-Infant Cleft Severity Ratio, 3DICSR).

A reference group of digital models from individuals without malocclusion and not needing orthodontic treatment was available at the Department of Orthodontics at University of Ljubljana-Slovenia. A sample size calculation indicated that for an expected 1.5 mm difference in palatal height with a standard deviation of 1.7 mm, a minimum number of 21 subjects would be needed in each group with an alpha error of 5% and a beta error of 10%. The reference group included digital casts from 28 Slovenian subjects frequency matched with respect to age (mean: 8.44 years; SD= .72), sex (9 girls and 19 boys), and ethnicity. All cleft patients from the single surgical centre participating in the RCT were included.

Two-dimensional standardized linear measurements on a 3D object:

The digital models were imported as STL files in the Mimics software (Mimics v19.0, Materialise -Belgium) for analysis. Proceeding distally from the deciduous canines to the first permanent molars, we identified anatomical landmarks at the midpoint on the palatal gingival contour for all teeth (Table 1 and Fig. 2). The cleft side was considered correspondent to the left side in the reference group since in the majority of UCLP cases, the cleft is localized on the patient's left. To define a sagittal plane, a midpoint (Mid) was marked as the most antero-superior point on the incisal papilla, allowing for a maximum of 0.5 mm correction in cases where the incisors, and therefore the papilla, were very tilted. A coordinate system composed of three reference planes was established, and we mapped the palatal depth on the cleft side, the non-cleft side (left

and right for the reference group) and along the sagittal plane at all dental levels (Fig. 2).

Finally, palatal width was measured as the distance between landmarks on correspondent teeth and palatal length as the distance between the Mid and the posterior reference plane.

A complete list of points, planes and measurements is reported in Table 1.

Three-dimensional assessment (pilot study)

Using a method previously described [24] , we calculated the palatal volume by applying a region-growing algorithm and a Boolean algebra operation. For each UCLP patient, the palatal volume, delimited by the perimeter of the anatomical landmarks and the horizontal and posterior reference planes, was aligned with the same "comparator" reference volume, chosen as representative of the reference group: for this reference patient, the 2D values describing palatal height were very similar to the median values of the reference group.

The alignment of each cleft to the "comparator" was performed according to surface-based STL registration: a mask was generated from the "comparator". Thereafter, alignment was performed as a semiautomatic procedure using, in sequence, two standardized filters for global (minimal distance: 1 mm) and local (maximal distance: 3 mm) registrations (Fig. 4 Supplementary).

For a subgroup of 70 cases (35 randomly selected cases in each surgical group), the aligned STL models were imported into a 3D mesh-processing software (MeshLab JS 16.01-University of Pisa, Italy), allowing for calculation of the Hausdorff distance, defined in computer graphics as the largest distance between two correspondent points of two objects in a metric space [25]. Hausdorff distances were calculated between the aligned UCLP and control meshes and qualitatively visualized by colour mapping (Fig. 3). The procedure was repeated after identification of four regions of interest. First, the total central palate (middle third of the palate) was identified. Using a standardized procedure, this part was then cut divided into an anterior central, a middle central and a posterior central part.

After applying the Hausdorff filter, a new mesh represented by the cloud of the Hausdorff points on the cleft model was generated and the cloud to "comparator" mesh distance was calculated using the filter "distance from a reference mesh". Data from the latter distance algorithm were used to define the area under the curve. The median, the range (min and max), and the quartiles could be used for a proxy quantification of the shell-to-shell distance for each of the four regions of interest.

Statistical methods:

Intra-examiner and inter-examiner reproducibility assessments were performed based on repeated measurements of 30 cases for the intra-examiner and 15 cases for the inter-examiner reproducibility assessment with at least three weeks in between. Intra-class correlation coefficients (ICC) were computed, and the technical error of the method (TEM) was assessed using the Dahlberg formula[26]. Furthermore, Bland-Altman plots were inspected to identify systematic errors[27]. The hypothesis of no systematic difference between sample means for repeated measurements was tested using a paired t-test.

For the 2D measurements, analysis of variance (ANOVA) was applied to assess the crude differences between the groups. Interpretation of pairwise comparisons was based on the Tukey test (adjusted P-value).

Finally, adjustments for covariates representing infant cleft dimensions were performed in a linear regression model.

For the 3D datasets, the groups' means were compared using an unpaired samples t-test for each region of interest and for each quartile.

The analysis was performed using STATA software version 14.1 (Stata Corp, LP, College Station, Texas, USA). Statistical significance was reported at a .05 confidence level.

Ethical implications:

The Scandcleft protocol for the present study was approved by the local Ethical Committee (journal number: 1997/4121). Informed consent was signed by the parents

of all subjects participating at the time of inclusion. Permission to access data was granted by the regional Data Protection Agency (n.1-16-02-616-15). Anonymization of data was secured by using the random trial ID numbers for identification. The research protocol was designed in accordance with the ethical principles outlined in the Declaration of Helsinki (World Medical Association, 2013).

Results:

Reliability assessment

The ICC revealed an excellent intra-examiner and inter-examiner reproducibility, ranging from .933 (CI:817;977, respectively) to .997 (CI:.993;.999, respectively). The TEM was below .21 mm for the intra-examiner assessment and below .38 mm for the inter-examiner assessment. Minor systematic bias among sets of repeated measurements could be identified for M1 Transversal Intra: .17 mm (CI:-.25;-.11) and for Arch length Inter: .34 (CI:-.55,-.13), M2 height cleft Inter: .15 (CI:.15;.38), M3 height non-cleft Inter: .22 (CI:.00;.44), Midpoint (Mid) height Inter: .26 (CI:.10;.42). The complete results concerning the reproducibility assessment and the Bland-Altman plots are shown in Supplementary material (Table I-II and Bland-Altman).

Two- dimensional linear measurements on the digital models in a coordinate system (palatal height, width and length):

Cleft patients in both groups presented a higher palate than the reference group at the level of the canines (ant. height cleft) (p=.002) and at the level of the incisal papilla (Mid) (p<.001), whereas in general the palate was lower at the level of the first deciduous molar (M_1) (p<.001) and the second deciduous molar (M_2) (p<.001).

For the EHPC group, the posterior height approximated that of the controls, while the DHPC tended to have a flatter palate in this region than EHPC (p= .048). Regarding the transversal width of the palate, we observed significant differences between UCLP patients and the reference group (p< .001), but also between surgical groups (p= .003 at M1 level); the EHPC group showed the narrowest palatal dimensions at all antero-posterior levels.

Cleft patients in both groups had shorter arch length than controls (p<.001). We observed a trend that the group who received DHPC presented with a longer arch length (p=.057). The complete results of the ANOVA and post-hoc multiple tests are reported in Table 2.

When cleft dimensions were used as covariates, anterior cleft size at infancy correlated positively with anterior palatal height in the cleft side (p= .007) and negatively with posterior height in the non-cleft side at M3 (p=.010) and at posterior level (p=.013). Similarly, the 3DICSR [24] was important for determining M3 height (p=.006), whereas cleft size at the level of the tuberosities played a significant role in the analysis of anterior height in the non-cleft side (p= .011) and arch length (p= .004).

A supplementary analysis was conducted adjusting for operator during the first stage and the second stage of surgery; but the role of those covariates was non-significant for all the dependent variables, and therefore they were removed from the model (data not shown).

The complete results of the adjusted analysis and the 95% CI are reported in Table III-Supplementary material.

Three-dimensional assessment (pilot study)

The group who received DHPC presented in general with a larger shell-to-shell distance than the group who received EHPC at the levels of middle central (p=.002), posterior central (p=.008) and total central palate (p= .01). An example of qualitative visualization of the shell-to-shell distances between cleft patients and the "comparator" representative of the reference group is reported in Fig. 3. Table 3 offers further details regarding distance mapping: the description of the main distances between Hausdorff point clouds and control reference meshes and the results of the comparison between the surgical groups for each quartile.

Discussion:

The results of the present study show palatal morphometric differences between cleft patients operated according two different protocols of hard palate closure and in relation to non-cleft controls. The method was based on linear measurements of maximal palatal

height, length and width at different antero-posterior levels and appeared robust with good intra-examiner and inter-examiner reproducibility.

Summarizing our findings, before orthodontic treatment and bone-grafting intervention, an 8-year-old UCLP child will present a lower palatal roof in the middle part of the palate than a child without a cleft. However, for UCLP patients, the palatal roof will tend to be higher than the roof of reference non-cleft palates in the anterior region, corresponding to the scar. These findings are in accordance with the results shown by Smahel[1] and Ruskova[28]. Compared with their studies, our study benefits from a homogeneous material collected within the context of an RCT of primary surgery. Moreover, patients were operated by the same surgical team and palatal morphology was evaluated on standardized models collected at age 8 years, before undertaking orthodontics or bone-grafting interventions. Furthermore, in our study, we focused on the influence of the surgical timing and identified some differences between EHPC (at 12 months) and DHPC (at 36 months). Concerning height of the palatal vault, DHPC showed a shallower palate in the posterior region. Regarding transversal dimensions: UCLP patients in both groups presented a narrower palate than controls, though less so in patients who received delayed hard palate closure. Their palatal width was almost similar to that of the controls in the posterior regions. Regarding arch length, UCLP subjects who received delayed hard palate closure (DHPC) tended to have longer arches.

The results of the analysis based on 2-dimensional (2D) linear measurements were confirmed by explorative 3D assessment of a subsample of patients. Through distance mapping, 3D assessment may better depict true differences between subgroups as the surface of operated cleft palates appears “bumpy” and irregular; features that may easily escape simple 2D height measuring.

The 3D assessment revealed that the distance from the “comparator” shell was larger in the DHPC group than in the EHPC group at all central palate levels. Even if distance mapping and colour visualization provide no information about horizontal and vertical distance components, we can assume from the information obtained by the 2D assessment that the central palate is in general shallower in DHPC than in EHPC cases.

The role of the tongue during speech and oral function may explain these morphological differences. Furthermore, we also need to consider the possibility that further transversal growth, undisturbed by surgical scars, could take place in DHPC subjects.

We could speculate that the tongue's palatal relation and the extent of tongue/palatal contact differs between cleft individuals, depending on the timing of closing of their hard palates. Previous studies reported a relatively high occurrence of retracted oral articulation in 5-year-old subjects who received delayed hard palate closure [29,30]. This is in accordance with the Scandcleft report on articulation errors. The report was based on registration at age 5 years and showed that the group who received delayed hard palate closure had a lower percentage of correctly pronounced consonants (PCC score) [31]. Referring to developmental theory, the authors posit that the differences may be explained by the cleft persisting for longer time.

Interestingly, we also found a flatter palatal morphology after DHPC than after EHPC, which could be associated with a different tongue/palate contact relation and a dominant use of the dorsal part of the tongue for longer time in DHPC [32]. The latter could also explain the good arch width observed in the posterior regions for the DHPC group. Future research should investigate if persistency of articulation errors at later stages is associated with different palatal morphology [10].

In a previous study assessing occlusal differences between the two surgical groups and the association of occlusal scores with cleft dimensions at birth, we found a higher number of dental crossbites in EHPC than in DHPC, corroborating the results of the present study (Botticelli et al. ysubmitted). From the orthodontic point of view, the results of the present study confirm the need for palatal expansion in both clefts groups[33], and suggest that this need is even higher for those patients whose hard palate was closed early. Previous studies of the effect of early treatment of skeletal crossbite suggest a positive association between expansion and an increase of palatal volume [34].

This paper pilots a technique for 3D data extraction of distances between two solids. We are currently improving and validating the method before it will be applied to the full dataset. It has been previously shown how the development of recent 3D imaging techniques like mirroring and alignment/registration with geometric morphometrics (GMM) and principal component analysis (PCA) allows description of palatal volume and 3D shape analysis of the palate to identify patterns for specific malocclusions[35,36].

Asymmetries in transversal dimensions and shapes of the palatal volume have been illustrated with simpler methods in cleft [33] and non-cleft [37] crossbite patients, and the influence of oral breathing habits on palatal height has been elucidated through differences in palatal volume and shape [14].

This is the first study aiming to quantify the distance between the palatal vaults of a cleft and a reference individual for a number of regions of interest. For this purpose, distance mapping seems appropriate [38]. We chose to use a single individual representative of the reference group as a "comparator" instead of a compound image of the reference group. The current technique for averaging is based on point-to-point alignment which requires extensive processing to remove noise at several steps. This may significantly affect reliability and we therefore deselected this approach for this study. Better algorithms for generating compounds are currently being investigated. Further development of this method will be using colorimetric mapping to help the clinician in assessing palatal morphology based on a qualitative index, inspired by the EUROCRAN palatal scoring.

The standardization of the surgical protocol and the homogeneity of the surgical team may be considered advantages from a methodological perspective; still, this design may also limit generalization of our results to other patient populations.

Conclusions:

Subjects born with unilateral cleft lip and palate display large morphological variation in palatal height and shape. 2D and 3D morphometric analysis showed that before orthodontic intervention and bone grafting, the palate of a young cleft subject is typically higher at the level of the anterior scar but shallower in the middle region and transversally narrower than the palate of a reference group of non-cleft individuals. A surgical protocol with delayed hard palate closure at three years of age (DHPC) favours the transversal dimensions but may lead to a shallower palatal morphology than hard palate closure performed at one year of age (EHPC). Increased cleft severity at birth was negatively associated with palatal height and antero-posterior palatal length.

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Legends to the figures:

Figure 1.

Flow chart diagram (CONSORT) illustrating final retention of the subjects participating in Trial 1 in the Scandcleft project included in the present analysis

Figure 2.

Linear measurements on the digital models at 8 years of age. Anatomical markers on the teeth, coordinate system, mapping of maximal palatal height on the cleft (left side for the controls), non-cleft (right side for the controls) and sagittal plane at different antero-posterior levels defined by the mesio-distal position of the teeth.

Figure 3.a and 3.b

Examples of colour-mapping to illustrate variability within the sample in early and delayed hard palate closure. For case 1 to 4 in each group the right, left, back and top views are represented. On the left side, the quality-coded algorithm of the distances

shows mapping of correspondent points from the minimal distance (red) to the maximal (blue).

Table 1. Landmarks and planes and standardized linear measurements of palatal height width and length

	Definition
Landmarks	
Mid *(anatomical)*	The most antero-superior point on the inter-incisal papilla
C *(anatomical)*	Middle point of the palatal gingival contour of the deciduous canine in the cleft side or the left side for the control group
C'*(anatomical)*	Middle point of the palatal gingival contour of the deciduous canine in the non- cleft side or the right side for the control group
M_1 *(anatomical)*	Middle point of the palatal gingival contour of the first deciduous molar in the cleft side or the left side for the control group
M_1' *(anatomical)*	Middle point of the palatal gingival contour of the first deciduous molar in the non-cleft side or the right side for the control group
M_2 *(anatomical)*	Middle point of the palatal gingival contour of the second deciduous molar in the cleft side or the left side for the control group
M_2' *(anatomical)*	Middle point of the palatal gingival contour of the second deciduous molar in the non- cleft side or the right side for the control group
M_3 *(anatomical)*	Middle point of the palatal gingival contour of the first permanent molar in the cleft side or the left side for the control group
M_3' *(anatomical)*	Middle point of the palatal gingival contour of the first permanent molar in the non-cleft side or the right side for the control group
D *(anatomical)*	Most distal point of the palatal gingival contour of the first permanent molar in the cleft side or the left side for the control group
D' *(anatomical)*	Most distal point the palatal gingival contour of the first permanent molar in the non- cleft side or the right side for the control group
Planes	
Reference horizontal plane	Defined by C'-D-D'
Reference posterior plane	Perpendicular to Ref. horizontal through D-D'
Reference sagittal plane	Perpendicular to Ref. horizontal and posterior through Mid
C *plane*	Parallel to ref. posterior passing through C
C' *plane*	Parallel to ref. posterior passing through C'
M_1 *plane*	Parallel to ref. posterior passing through M_1
M_1' *plane*	Parallel to ref. posterior passing through M_1'
M_2 *plane*	Parallel to ref. posterior passing through M_2
M_2' *plane*	Parallel to ref. posterior passing through M_2'
M_3 *plane*	Parallel to ref. posterior passing through M_3
M_3' *plane*	Parallel to ref. posterior passing through M_3'

Palatal Height Measurements	
C *height*	Intersection of C plane with the palatal vault contour
C' *height*	Intersection of C' plane with the palatal vault contour
C' mid *height*	Intersection of the Ref. sagittal plane with the palatal vault contour at C' level
M_1 *height*	Intersection of M_1 plane with the palatal vault contour
M_1' *height*	Intersection of M_1' plane with the palatal vault contour
M_1 mid *height*	Intersection of the Ref. sagittal plane with the palatal vault contour at M_1' level
M_2 *height*	Intersection of M_2 plane with the palatal vault contour
M_2' *height*	Intersection of M_2' plane with the palatal vault contour
M_2 mid *height*	Intersection of the Ref. sagittal plane with the palatal vault contour at M_2' level
M_3 *height*	Intersection of M_3 plane with the palatal vault contour
M_3' *height*	Intersection of M_3' plane with the palatal vault contour
M_3 mid *height*	Intersection of the Ref. sagittal plane with the palatal vault contour at M_3' level
Palatal Width Measurements	
Anterior *transversal*	Distance C-C'
M_1 *transversal*	Distance M_1-M_1'
M_2 *transversal*	Distance M_2-M_2'
M_3 *transversal*	Distance M_3-M_3'
Palatal Length Measurements	
Arch Length	Distance Mid-Reference posterior plane (taken on the Reference sagittal plane)

Footnote to the table: "C" indicates the canine level, "M_1"indicates the first deciduous molar level, "M_2" indicates the second deciduous molar level, "M_3" indicates the first permanent molar level.

Table 2:

Inter-group differences between controls and the two surgical groups. Level of significance p=.05. Secondary post-ANOVA tests. For each variable mean and SD are reported in each group.

Morphometric measures	C:Controls (SD)	A: EHPC-12 months (SD)	B: DHPC-36months (SD)	ANOVA	**Post-ANOVA tests-**
Ant. Height cleft	3.48 (1.38)	5.03 (1.53)	4.76 (1.63)	.002*	C< (A=B)
Ant. Height mid	4.48 (1.35)	4.31 (1.52)	4.58 (1.65)	.316	A=B=C
Ant. Height non - cleft	3.66 (1.33)	3.53 (1.77)	3.69 (1.72)	.522	A=B=C
Ant. transversal	25.74 (1.86)	20.19 (2.79)	21.49 (3.42)	.072	A< (B=C) (A<B; P=.025*)
M1 height cleft	10.29 (1.93)	7.93 (2.10)	7.75 (1.68)	<.001*	(A=B) <C
M1 height mid	10.43 (1.70)	8.16 (1.99)	8.20 (1.69)	<.001*	(A=B) <C
M1 height non-cleft	9.98 (1.94)	7.82 (1.70)	7.86 (2.02)	<.001*	(A=B) <C
M1 transversal	28.27 (1.89)	23.77 (3.03)	25.25 (2.45)	.006*	A<B<C (A<B; P=.003*)
M2 height cleft	13.05 (1.60)	10.05 (2.44)	9.96 (1.79)	<.001*	(A=B) <C
M2 height mid	13.22 (1.65)	11.01 (2.04)	10.55 (1.92)	<.001*	(A=B) <C
M2 height non-cleft	12.94 (1.65)	10.36 (1.71)	9.90 (1.89)	<.001*	(A=B) <C
M2 transversal	31.51 (2.06)	28.55 (2.99)	29.80 (2.63)	<.001*	A<B<C (A<B; P=.031*)
M3 height cleft	12.03 (1.86)	10.89 (2.41)	10.56 (2.72)	.051 (trend)	A=B=C
M3 height mid	12.29 (1.80)	11.90 (2.01)	11.38 (2.54)	.307	A=B=C
M3 height non-cleft	12.16 (1.70)	11.27 (2.05)	10.63 (2.41)	.022*	(B<C)=A (B<C; P=.006*)

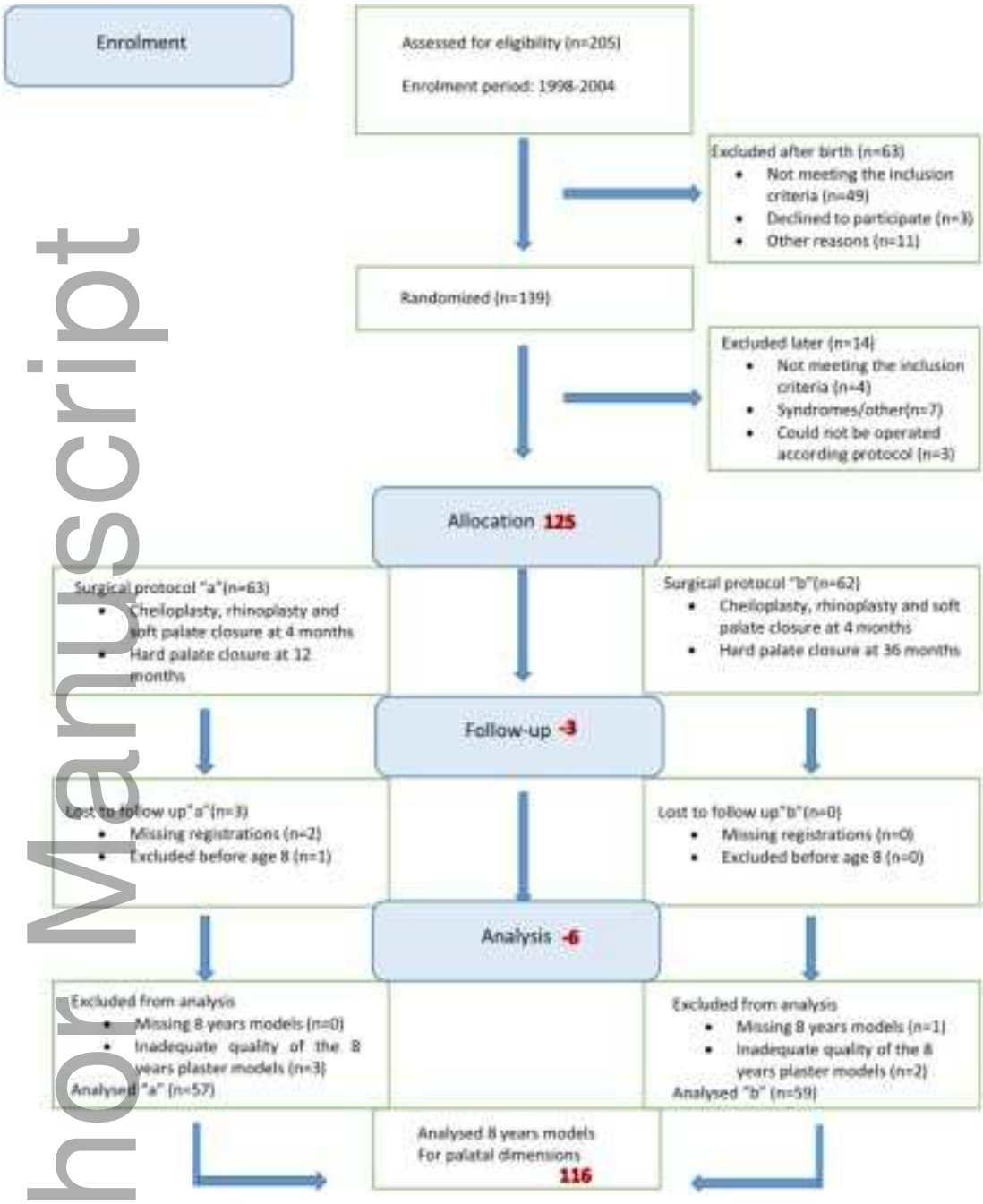
M3 transversal	35.07 (1.89)	34.11 (3.20)	35.24 (2.88)	.115	A<(B=C) (A<B; P=.049*)
Post height cleft	11.41 (1.98)	10.58 (2.12)	10.19 (2.53)	.145	(B<C)=A (B<C; P=.050*)
Post height mid	11.73 (1.90)	11.47 (2.05)	10.94 (2.69)	.439	A=B=C
Post height non-cleft	11.52 (1.78)	10.81 (2.14)	10.32 (2.62)	.138	(B<C)=A (B<C; P=.048*)
Midpoint height	.79 (.54)	1.58 (1.06)	1.44 (0.87)	<.001*	(A=B)>C (B<C; P=.001*)
Arch length	34.76 (1.93)	30.17 (2.47)	31.04 (2.47)	<.001*	(A=B) <C (Trend for A<B P=.057)

Footnote to the table: * indicates significance for the unadjusted P-value. Interpretation after adjustment for multiple comparison by Tukey test.

Table 3.

Regions of Interest	Anterior Palate Signed Distance					Middle Palate Signed Distance					Posterior Palate Signed Distance					Central Palate Signed Distance				
	Min		Med		Max	Min		Med		Max	Min		Med		Max	Min		Med		Max
Quartiles	**q0**	**q1**	**q2**	**q3**	**q4**	**q0**	**q1**	**q2**	**q3**	**q4**	**q0**	**q1**	**q2**	**q3**	**q4**	**q0**	**q1**	**q2**	**q3**	**q4**
EHPC	**-2.43**	**-0.61**	**-0.09**	**0.47**	**2.42**	**-3.48**	**-1.80**	**-1.32**	**-0.83**	**0.89**	**-2.10**	**-0.63**	**-0.21**	**0.14**	**1.39**	**-3.39**	**-1.25**	**-0.63**	**0.09**	**2.49**
Std Dev	1.60	0.94	0.87	0.84	1.19	1.23	0.76	0.68	0.63	0.78	1.19	1.13	1.18	1.21	1.43	1.13	0.74	0.70	0.69	1.14
DHPC	**-3.09**	**-1.09**	**-0.52**	**0.29**	**3.11**	**-4.26**	**-2.46**	**-1.94**	**-1.24**	**1.22**	**-3.89**	**-2.16**	**-1.67**	**-1.00**	**1.35**	**-4.51**	**-1.93**	**-1.20**	**-0.29**	**2.90**
Std Dev	3.36	0.90	0.61	0.99	3.73	2.15	1.09	0.96	0.94	3.55	3.76	3.11	2.97	2.23	2.93	2.52	0.87	0.98	1.03	2.33
P value (t-test)	*.293*	*.034**	*.023**	*.426*	*.302*	*.063*	*.004**	*.002**	*.034**	*.588*	*.009**	*.008**	**.008*	**.009*	*.944*	*.019**	**.001*	*.012**	*.094*	*.522*

3D Assessment: Inferential Statistics for early (EHPC-at 12 months) and delayed hard palate closure (DHPC-at 36 months). Values based on the signed distances between UCLP patients' digital models (examined mesh) and correspondent points on the digital model of a control patient (reference mesh).



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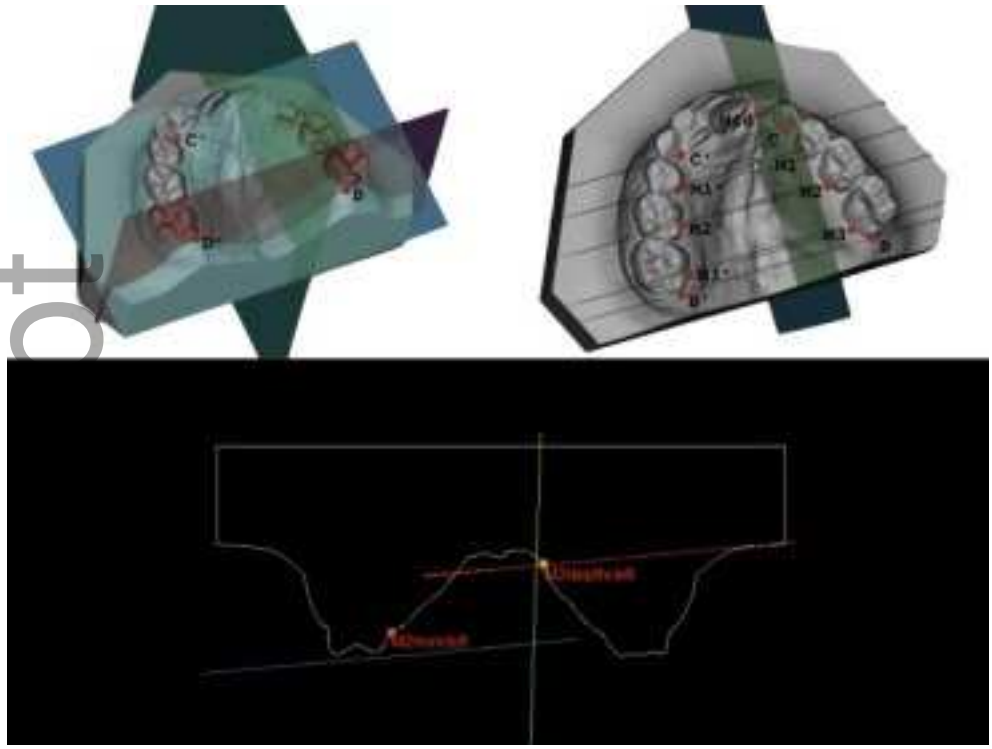

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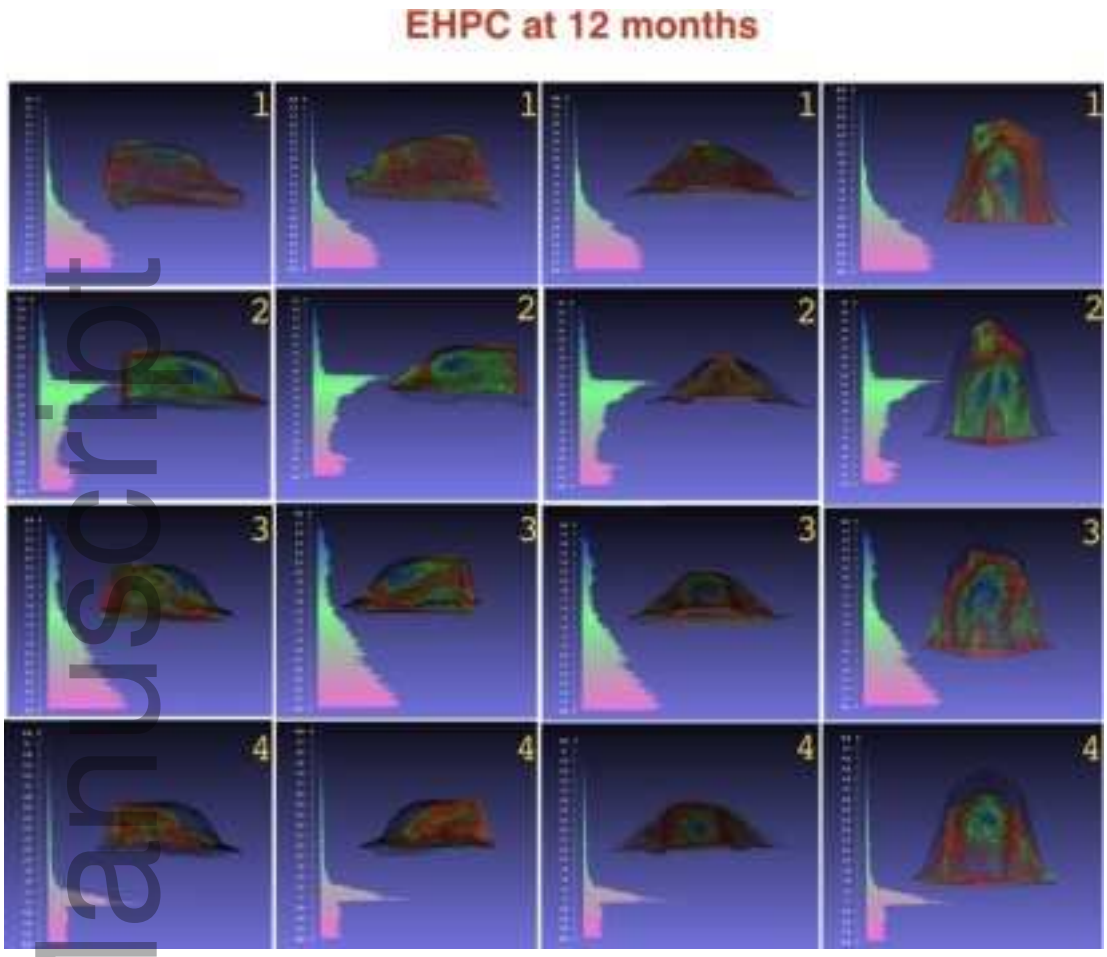

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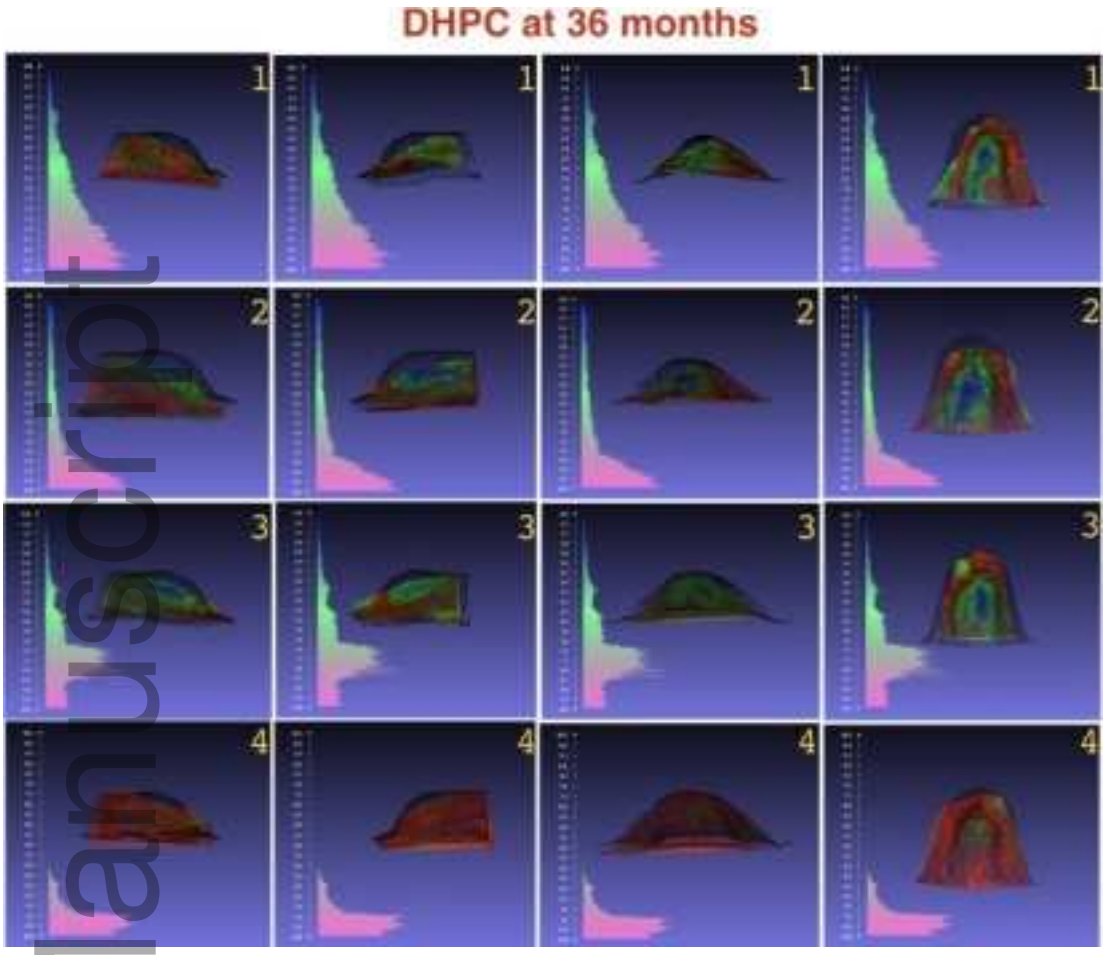

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