Evaluation of Cleft Volume as a Predictor of Alveolar Bone Graft Success

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A thesis submitted in partial fulfillment for the Degree of Master of Science in Orthodontics.

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Abstract

Objective: To determine if bony fill of alveolar clefts after alveolar bone grafting (ABG) was correlated with initial cleft volume and other factors.

Materials and Methods: Case records were retrospectively selected for this pilot study according to protocols approved by Institutional Review Boards from three sites. Inclusion criteria were: 7-14 years-of-age at time bone grafting, unilateral cleft of the maxillary alveolus, pre-and ≥3-month post-ABG surgery cone-beam computed tomography images (CBCTs). Exclusion criteria were: diagnosed underlying diseases or syndromes, ABG previously failed or used to support implants or prostheses, bilateral clefts, and orthodontic expansion prior to ABG. 3D masks of alveolar cleft sites before and after ABG were extracted from CBCTs and used to calculate original and residual cleft volumes (mm^3). Bony fill of the cleft site (%) was calculated by: (initial–residual cleft volumes/initial cleft volume) x100 and tested for correlation with case-specific factors. Statistical analysis for binary factors was performed using Student's t-tests, and linear regression was utilized for continuous factors. Statistical significance was defined as $p<0.05$.

Results: Records from 13 cases (6 females, 7 males) met inclusion and did not meet exclusion criteria. Inter- and intra-rater reliabilities for calculating cleft volumes were excellent, with the intraclass correlation coefficient (ICC)=0.96 and 0.93, respectively. Mean bony fill was 47.6±27.6% overall and significantly larger ($p<0.01$) for females (67.5±24.9%) compared to males (30.6±16.4%) and significantly larger ($p=0.01$) for right-sided clefts (74.9±28.5%) compared to left-sided clefts (35.5±17.3%). Initial cleft volume versus bony fill (%) was inversely correlated ($R^2=0.21$, $p=0.11$) overall and the relationship was accentuated in cases without tooth structure exposed in the cleft ($R^2=0.37$, $p=0.12$) and type I cleft shape ($R^2=0.35$, $p=0.06$). Extractions performed at the time of ABG, presence of exposed teeth in the cleft, and age at time of ABG were not found to influence bony fill significantly.

Conclusions: Increased bony fill of alveolar clefts after ABG was related to smaller initial cleft volume and being female compared to male.

I. Introduction

Orofacial clefts, including cleft lip, cleft palate, and cleft lip and palate (CLP), are one of the most common craniofacial conditions in the world. In most cases the causes of clefts are multifactorial, involving both genetic and external factors.[1] The incidence of cleft lip with or without cleft palate is approximately 1:1000 and varies between races, with the highest incidence in Asian and Caucasian populations and the lowest in African populations.[2] Patients with clefts require multidisciplinary management from birth to adulthood to facilitate a fully functional craniofacial complex. Nasoalveolar molding or lip adhesion surgery or both, is or are frequently performed from 1 week to 3 months of age to reduce the size of the cleft and provide greater nasal symmetry. Lip repair is typically completed at around 3 months of age, and palatoplasty follows at 9-18 months. Alveolar bone grafting (ABG) is traditionally completed at around ages 8-12 years and is an essential step in management of cleft patients, as around 75% of CLP patients present with an alveolar cleft[3,4]

Historically, alveolar bone grafting was completed prior to the eruption of all the deciduous dentition and at the time of lip or palate repair, around 0-24 months. This procedure was termed primary alveolar bone grafting (PABG) and aimed to consolidate the soft and hard tissue procedures into one surgery, and potentially improve psychosocial outcomes. More recently, PABG has fallen out of favor due to poor long-term graft survival, maxillary retrusion and underdevelopment, and poor occlusal outcomes. Instead, secondary alveolar bone grafting (SABG) is done around 8-12 years of age.[5] SABG, was first reported by Boyne and Sands in 1972.[6] It has been continuously refined since then, and has now become the gold standard treatment option for patients with alveolar clefts.[4] SABG is ideally performed during the mixed dentition and most commonly uses autologous bone, often from the iliac region. It aims to stabilize the maxillary arch by unifying the alveolar segments and allowing tooth

eruption.[7] If successful, SABG also closes any residual oronasal communication and provides support to the alar base, improving facial symmetry.[8] Patients commonly undergo orthodontic treatment prior to the graft to align the alveolar segments and facilitate access to the surgical site. After the graft, the volume and distribution of bone in the cleft must be assessed to ensure adequate bridging of the bony segments across the alveolar cleft and adequate bony support of teeth adjacent to the cleft that will erupt or be moved orthodontically into grafted bone.

There are many factors that may contribute to the success or insufficiency of alveolar bone grafts including surgical timing, type of bone graft, size of the graft, surgical technique, age, gender, and stage of tooth eruption.[8-11] These factors have been studied extensively but not made explicit or incorporated into treatment protocols. While some studies have found a correlation between pre-surgical cleft size and SABG success, others have found no statistically significant correlation.[11-13] The literature contains reports of up to 94% success rates of SABGs, but reported rates vary significantly and are likely subject to bias, as elaborated in the paragraphs below. Due to the extremely high burden of care placed on these patients, it is important to aim to minimize complications and increase success rates of these procedures. Further research is needed to establish standardized protocols that increase success rates of SABG and improve care for patients with clefts worldwide.

Prior to the advent of three-dimensional (3D) imaging modalities, studies used two-dimensional (2D) images such as occlusal, panoramic, or periapical radiographs to evaluate clefts and grafted sites. Cleft care teams around the world published studies using scoring systems such as the Berglan or Kindelan system to evaluate success, correlating interdental height or bony fill of the cleft site with success or insufficiency.[14,15] These 2D images of a three-dimensional site have tremendous limitations including distortion, magnification differences, superimposition of bilateral structures, inability to analyze the horizontal dimension, and difficulty of identifying anatomic landmarks.[14]

Using 2D images also often overestimates the amount of bone present in comparison to 3D methods such as cone-beam computed tomography images (CBCTs).[4] In recent years, CBCTs have been more commonly used to assess alveolar bone defects before and after grafting. By using 3D volumetric analysis of the defect, providers can examine conditions surrounding the cleft, estimate how much bone may be needed for grafting, and assess the quality and quantity of bone present after grafting.[16] This may decrease total operative time, costs, and morbidity while leading to better treatment outcomes.

One of the debated topics in managing alveolar clefts is orthodontic preparation for the ABG, due to its effect on cleft volume and shape. Increased volume is commonly believed to affect graft outcome negatively, although studies have shown conflicting results. While some studies have shown that alveolar cleft width influences the success of alveolar bone grafting and wider clefts are more prone to resorption [11,17,18], others have found that the preoperative size of the cleft does not affect the outcome of the bone fill.[7,12,19,20] Long et al. evaluated models, periapical radiographs, and occlusal radiographs to determine cleft width at its narrowest point and aimed to correlate pre-surgical cleft width with alveolar bone attachment of teeth adjacent to the grafted cleft site.[17] They found a significant, but low, negative correlation between cleft width and bony attachment in the proximal and distal segments, (R^2=0.11 and 0.22, respectively) after a mean radiographic follow up of 3.1 years. Another study by van der Meij et al., investigated the influence of cleft width on the fate of bone grafts in patients with early secondary bone grafting, late secondary bone grafting, and tertiary bone grafting (bone grafting at a later stage, median age 20 years, 2 months).[18] Cleft width in this study was defined as the smallest distance from the lesser to the greater alveolar segment measured along the tangent of both segments. They found a weak but significant relationship (R=-0.29) between cleft width and success of bone graft, with wider grafts being more prone to failure (p=0.04). A recent study by Padwa et al. in 2024 identified specific outcome predictors for alveolar bone graft success in a large sample of 722 patients with 900 alveolar cleft sites.[11] They used CBCTs to analyze vertical bone level and

labiopalatal thickness at the cervical, middle and apical thirds of the graft site and found that larger bony defects (mesial-distal distance ≥ 7.5mm) significantly increased the risk of failure (p=0.001). Studies looking at volumetric assessment of cleft sites, to date have found less of a correlation. Linderup et al. investigated bony fill volumetrically 1 year post-operatively in n=32 patients who received mandibular symphyseal bone grafts. They found an average of 87% bony fill that was not related to size of the alveolar defect pre-operatively.[12] Another volumetric study by Oberoi et al. found an average of 84% bony fill after SABG in both unilateral (n=17) and bilateral (n=4) cleft lip and palate patients, but no influence of size of preoperative defect on alveolar bone graft success.[19] A systematic review looking at cleft width and volume found 23 studies published between 1994-2020 that met their criteria, which included 13 retrospective studies with numbers of participants ranging from 15 -90 and totaling 1021, with age range of 6 – 17 years and averaging 10 years at time of SABG. However, due to lack of standardized protocols and lack of consistent outcome measures, these authors concluded that there was insufficient evidence to correlate preoperative cleft size with SABG outcomes.[7] Because of these differing results, there is no consensus regarding how or when orthodontic preparation for the ABG, which can result in cleft size expansion, should be performed.[21] Understanding the relationship between cleft volume and ABG success could influence clinical decision-making regarding pre-surgical orthodontics to prepare for ABG surgery.

Because of the controversies surrounding the correlation between initial cleft defect and outcome of ABG, some have suggested a more individualized approach to treatment based on cleft morphology. Yu et al. characterized five types of alveolar cleft morphologies based on 120 CBCT images (Figure 1).[22] They then aimed to correlate initial cleft defect morphology with SABG outcome, as the morphology of the alveolar clefts are often complex and irregular. Using both continuous and categorical evaluation methods, they evaluated both bony bridging and bony fill rate after alveolar bone grafting and found significant correlations between type I and IV morphology clefts and successful SABG

outcomes. In both morphologies, the shape is like a funnel with a larger labial defect compared to palatal and larger nasal defect size compared with the occlusal. Type IV differs in that it narrows more significantly in the middle of the defect. Prior to this, cleft width was most commonly used to evaluate cleft defects pre-surgically, but this method failed to assess the labial-palatal dimension of the cleft, which often shows a high amount of resorption after grafting[23]. Utilizing this classification method to evaluate alveolar clefts prior to surgery could help inform an individualized surgical approach to increase success of grafting results. Extraction of supernumerary teeth or orthodontic treatment prior to SABG may be able to transform a highly irregular cleft morphology into a more regular one, increasing chances of success. While the morphological classification method is straight forward and easy to apply, more research is needed to assign increased success rates to certain cleft morphologies.

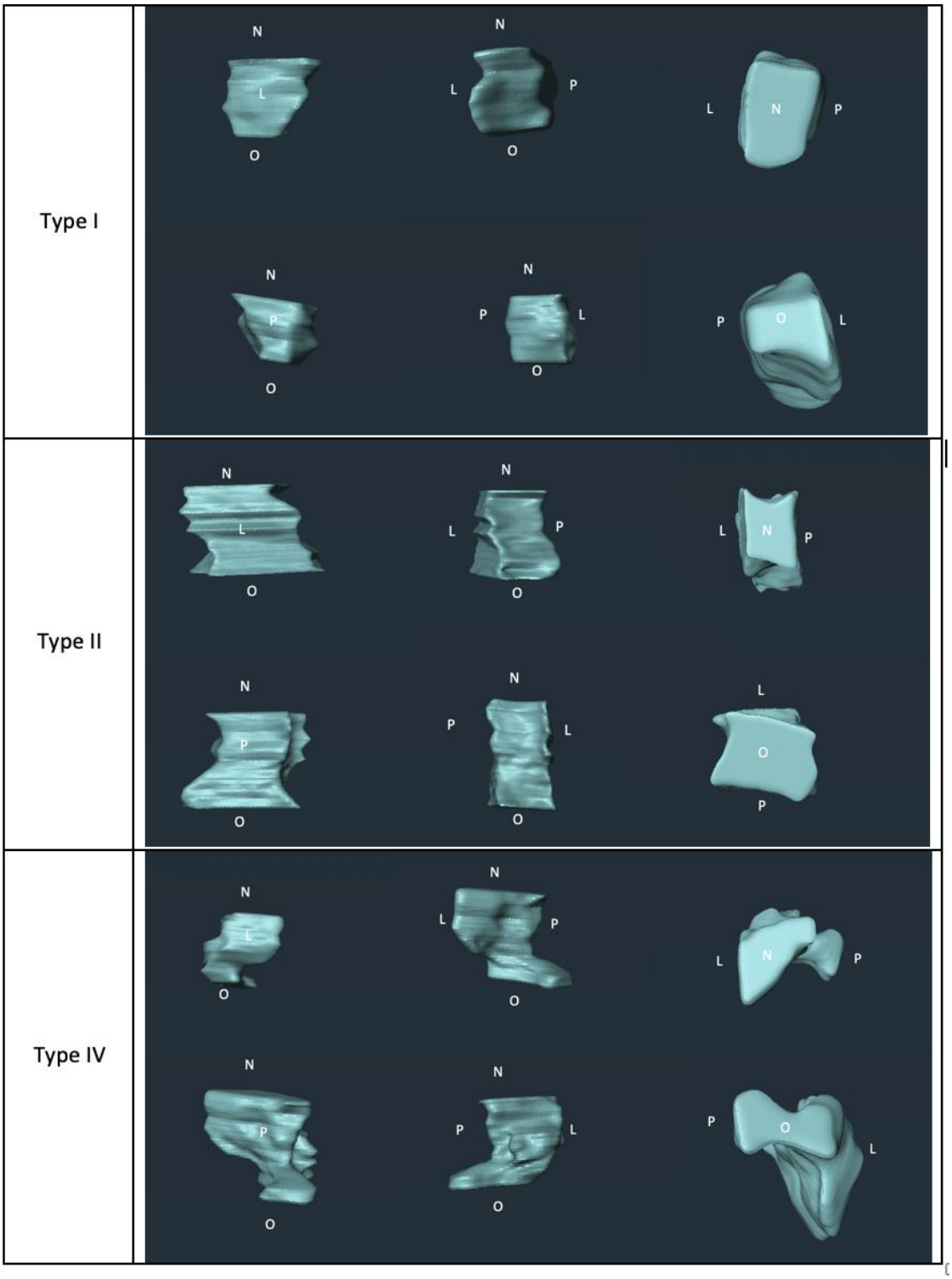

Figure 1. Classification of alveolar cleft morphology adapted from Yu et al. 2022[22]. Type I, prism type morphology (labial (L) defect ≥ palatal (P) defect; nasal (N) defect size ≥ occlusal (O) defect size); type II prism type (labial defect ≥ palatal defect; nasal defect < occlusal defect); type IV, funnel type (relatively narrow defect in the middle).

While many studies use CBCTs to evaluate alveolar bone grafting, no standard method of assessment has been clearly defined. Standardization of image acquisition parameters, field of view, anatomical boundaries for area of interest, and segmentation method is also absent between studies,[12] making comparison of results between studies difficult.

To solve the aforementioned problems, the current study developed a clinically relevant protocol to analyze alveolar cleft volume prior to bone grafting and residual alveolar cleft volume after bone grafting. Subtraction of the residual cleft volume from the initial cleft volume allowed calculation of a percentage of the cleft that was successfully grafted. Additionally, each post-ABG CBCT was examined for evidence of continuous bony bridging of the segments. Correlation of the bony fill percentage with case-specific factors, such as cleft size and shape, were tested. Thus, a protocol was developed and tested as a step towards increasing the success rate of alveolar bone grafts and improving care for patients with clefts. In the future, this pilot study could grow to a multi-center study and help further develop protocols that increase success rates of alveolar bone grafts. To address the previously described lack of evidence to support protocols associated with secondary alveolar bone grafting, this research addressed the following aims:

1. Correlate the bony fill percentage with initial cleft volume, cleft shape, absence/presence of exposed teeth in cleft, and extraction during secondary alveolar bone graft surgery.
2. Test for sex differences and cleft-side differences in the bony fill percentage.

The null hypotheses to be tested were that neither initial cleft volume, initial cleft shape, cleft side, presence of teeth in cleft, extractions during surgery nor sex had significant effects on percentage bony fill of the cleft site.

II. Materials and Methods

The protocol for this study was approved by the Oregon Health & Science University (OHSU) Institutional Review Board (*STUDY 00025484)*, the University of California San Francisco (UCSF)-Fresno

Community Health System Institutional Review Board (*STUDY 2023032)*, and the Valley Children's Hospital (VCH) Institutional Review Board (*STUDY* 2560, Appendix A). This was a retrospective study that involved clinical records from pediatric patients with unilateral clefts of the maxillary alveolus, with or without clefting of the secondary hard palate, who had alveolar bone grafting in the cleft site and presented to the OHSU Orthodontics Clinic and the private orthodontic practice of BH for treatment. As part of their orthodontic treatment, subjects had CBCTs taken prior to and following alveolar bone grafting. Patients treated in the private practice were associated with cleft teams at UCSF-Fresno Hospital or Valley Children's Hospital-Madera.

Case Selection

Records of patients who presented with unilateral clefts of the maxillary alveolus were screened for eligibility. Inclusion criteria were records from patients between the ages of 7 and 14 years old at the time of ABG with pre-and post-surgical CBCT Digital Imaging and Communications in Medicine (DICOM) files, with the post-surgical CBCT at least 3 months after alveolar bone grafting. Exclusion criteria were records from patients with diagnosed underlying diseases or syndromes, previous alveolar bone grafting that was insufficient, unavailable CBCTs, children above age 14 or below age 7 years at time of bone grafting, bilateral cleft patients, patients who received alveolar bone grafts to support implants or prostheses, and patients who had orthodontic expansion prior to bone grafting. Three centers participated by providing de-identified imaging files. The centers were:

1. OHSU School of Dentistry, Department of Craniofacial Sciences, Division of Orthodontics (Drs. Laura Iwasaki, Bruce Havens, Jeff Nickel, Saulo Sousa Melo)
2. UCSF Fresno Children's Hospital, Fresno, CA (Dr. George Zakhary)
3. Valley Children's Hospital, Madera, CA (Dr. Matthew Hiersche)

A target accrual of records from 40 cases was anticipated, with each center identifying cases that met the inclusion and did not meet exclusion criteria. At each center, archived data that met research criteria were stripped of meta-data using de-identification software (DICOM Anonymizer Pro, v2.0.15, NeoLogica, https://www.neologica.it/eng/Products/DICOMAnonymizerPro) and assigned a research identification number (ID #). Research data were stored on an OHSU research server accessible to site investigators. All research-related protocols were conducted at OHSU by OHSU personnel. Pre-surgical CBCT images were visualized using commercial software (AMIRA 3D, v2022.1, Thermo Scientific, https://www.thermofisher.com/us/en/home/electron-microscopy/products/software-em-3d-vis/amira-software.html) to measure maxillary dentoalveolar cleft dimensions (linear and volumetric). Post-grafting images were evaluated to determine whether or not bony bridging of the cleft segments was present.

Defining Cleft Region of Interest

CBCTs were viewed using AMIRA software and thresholding was completed based on the surrounding alveolar bone to identify what was and was not hard tissue in the cleft site after grafting. Landmarks were defined to determine the superior, facial, inferior, and palatal limits of the alveolar cleft, in accordance to the protocol developed by Stoop et al. 2023 (Figure 2).[24] The superior limit was determined to be the axial slice at the level of the nasal floor at the mesial of the maxillary 1st molar on the non-cleft side (Figure 2B and 2C). The inferior limit was determined to be the axial slice at the level of the most superior portion of the cementoenamel junction (CEJ) of the central incisor on the cleft side. Four landmarks were identified in every third axial slice (0.3 mm slice thickness) from the superior to inferior limits of the cleft, and interpolation was used to fill the volume between analyzed slices. The facial limit of the cleft volume was defined using medial-facial (MF) and lateral facial (LF) landmarks and drawing a line between MF-LF to connect the lesser and greater segments of the alveolar ridges (Figure 2A). Since prior studies have shown the palatal region of the bony defect to have the greatest

interobserver variability, the region of interest was defined using the first 8 mm of the alveolar process extending palatally perpendicular to the MF-LF line from MF to define the medial-palatal (MP) and from LF to define the lateral-palatal (LP) landmarks (Figure 2A). This approach was based on previous research showing a minimal necessary maxillary alveolar ridge width of 8 mm at the location of the canine.[25]

Volume Calculation

The pre-ABG cleft volume and post-ABG residual cleft volume were calculated using a defined protocol (see below). The percentage of the initial cleft that was successfully grafted was calculated using the following formula:

(Initial cleft volume- residual cleft volume/initial cleft volume) x 100.

Protocol

3D models of initial and residual cleft volumes (Figure 2D) were created from a series of 2D masks defining the initial or residual cleft according to the protocol below.

<u>Creating the Cleft Mask</u>

1. Select all DICOM files to open CBCT in 3D in the software program (AMIRA)
2. Navigate to the multiplanar view and identify and record superior and inferior axial slice number in all 3 planes of space
    a. Inferior border of the Piriform aperture superiorly (Figure 2B)
    b. Mesial of maxillary 1st molar posteriorly on the non-cleft side (Figure 2C)
    c. Cementoenamel junction of the incisor closest to the alveolar cleft inferiorly (Figure 2D)
3. Navigate to project view of the CBCT file
    a. Select volume rendering → create to generate a data file
        i. Drag and adjust the colormap to change the amount of soft tissue and bone visible until just necessary bony structures are visible
    b. Select “ROI box” from the original file drop down menu
        i. Select desired region of interest (ROI) encompassing the alveolar cleft site using mouse pointer and hand tools, being careful to not adjust vertical borders of ROI to preserve same slice number
    c. Select extract subvolume → create from the original data file
        i. Press the dropdown arrow next to >Data at the bottom left of the toolbar
        ii. In the ROI drop down menu, select “ROI box” and push “apply”
            1. This will open a new data file in the upper left map
4. Navigate to segmentation view
    a. Scroll to the above slice numbers identified in multiplanar view at the location of the mesial of the 1st molar and piriform aperture (step 2)
    b. Make sure cropped file is selected at top left (should default to this)

c. Select brush tool and change to 3 voxels
d. Check the box for “enable masking” at the bottom right of the properties box
e. Adjust masking until the bone and teeth are white and everything else, including the cleft site are purple
f. Use the brush to draw the facial boundary of the cleft (Figure 2A), connecting the medial and lateral bony segments together between landmarks medial-facial (MF) and lateral-facial (LF)
g. Measure with an 8mm ruler from the facial boundary palatally to the medial and lateral sides of the cleft and mark each of these to identify landmarks medial-palatal (MP) and lateral-palatal (LP) (Figure 2A)
h. Use the lasso tool to connect the facial boundary line to the two marked palatal points on the medial and lateral sides of the cleft (Figure 2A)
i. Scroll 5 slices down and repeat steps f-h until at the slice number that correlates with the CEJ of the cleft side incisor (identified in step 2)
j. Press CTRL+I to interpolate (this will fill in the slices in between)
k. Under materials, make sure the inside box is checked for 2D and press the plus button under selection to change the color of material (select desired color)

5. Return to project view
    a. Under new file (file name.labels) select generate surface > create
    b. Check the box next to compactify and make sure the minimum edge length is set to 0.4 and then press “apply”
        i. This will create another data file in the map
            1. Select the surface editor button under properties to create a surface view in the map
        ii. Select draw style –outlined
        iii. Export the data as a stereolithography (STL) binary file

Defining cleft shape

Pre-operative cleft shape was defined using the classification system from Yu et al. [22]

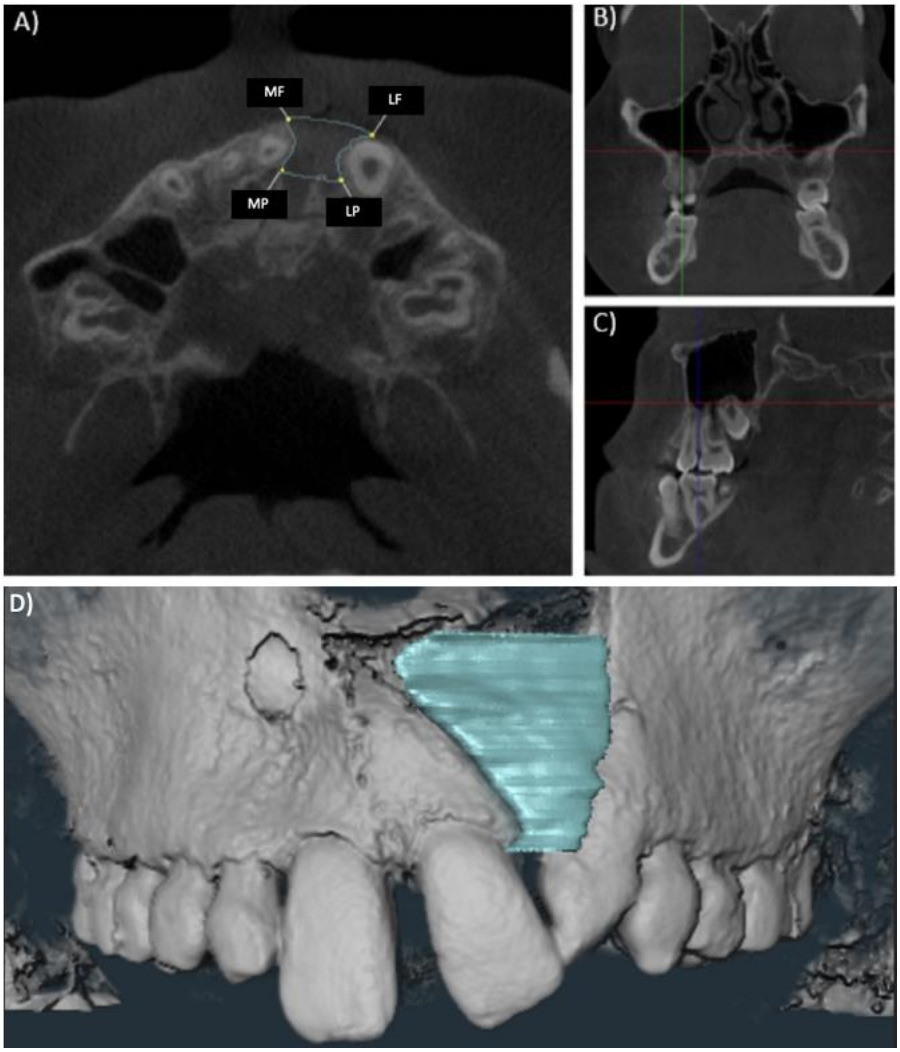

Figure 2. Display of landmarks used to define the alveolar cleft **A)** Axial CBCT slice showing identification of the most medial-facial border (MF) and most lateral-facial border (LF) of the alveolar cleft. The medial-palatal landmark was placed 8 mm palatal to medial-facial and the lateral-palatal landmark was placed 8 mm palatal of lateral-facial. **B)** Coronal and **C)** Sagittal slices at the mesial of the maxillary 1st molar of the non-cleft side showing identification of the most superior portion of the alveolar cleft (red lines) at the lower border of the nasal floor on the non-cleft side. **D)** Facial view of 3D cleft mask, extending superiorly from the lower border of the nasal floor and inferiorly to the CEJ of the cleft side central incisor.

Calculating Volume

1. Select surface area volume from the drop-down menu on the data file in software (AMIRA)
2. Scroll down and push "apply"
    a. A new data file should appear
    b. Select spreadsheet- show → volume will be displayed

Statistical Analysis

All CBCT data sets were evaluated separately by two examiners. Both were trained and calibrated prior to performing the process. Generation of the 3D mask of the alveolar cleft site and volumetric measurements were performed three times. Measurements were made twice within a 2-month interval by the first examiner (EG) and once by the other examiner (BH). Separate spreadsheets were used to record the measurements to avoid bias. To assess inter-rater and intra-rater reliabilities, the two investigators measured and remeasured five sets of pre- and post-ABG CBCT scans and calculated volume and percentage of bony fill for each set. The reliabilities of the measurements within the first rater and between raters were analyzed using intra-class correlation coefficients (ICCs). Data analysis included descriptive statistics of means $\pm$ SD and t-tests for sex, extractions at the time of grafting, exposed teeth in the cleft, and cleft sidedness. Regression analyses was performed with the independent variables of pre-surgical cleft volume and age, and the dependent variable of percent bony fill at $\geq$ 3 months post-surgery. Significance was defined as $p<0.05$.

III. Results

An initial screen for VCH and UCSF-Fresno patients with a facial cleft in the practice of BH between 2008 and 2022 produced 216 records. Of these records, 11 records (10 from VCH and 1 from UCSF-Fresno) met inclusion and did not meet exclusion criteria. A total of 55 current patients with clefts treated in the OHSU orthodontic clinic were screened for qualification. Two patients met inclusion and did not meet inclusion criteria. A total of 13 cases from all centers were included in this study. Mean age ± standard deviation was 10.1 ± 1.7 years. There were 6 females (46%) and 7 males (54%) included in the sample. No significant age differences were found between females and males ($p=0.65$). Four cases (31%) had right-sided clefts and nine cases (69%) had left-sided clefts. Twelve out of thirteen cases (92%) had bony bridging after grafting (Table 1). Right-sided clefts showed significantly greater bony fill

(%) than left-sided clefts (p=0.01), with no significant difference in size of clefts between groups (p=0.36).

Inter- and intra-rater reliabilities for calculating cleft volumes were excellent, where ICC=0.96 and 0.93, respectively.

The pre-operative cleft volumes ranged from 169 to 1455 mm^3 with a mean of 639 ± 343 mm^3. All but two ABGs were completed using iliac crest bone, while in the other two cases allograft with bone-morphogenetic protein (BMP) was used. ABGs were performed by three different surgeons. In one case, orthodontic alignment was done prior to ABG and no orthodontic expansion was done prior to ABG in any of the cases. Six cases had extractions completed at the time of ABG. Post-operative cleft volume ranged from 11 to 1370 mm^3, with a mean of 375 ± 354 mm^3 (Table 1).

Initial cleft volume versus bony fill (%) was inversely correlated (R^2=0.21, p=0.11) overall (Figure 3) and the relationship was accentuated in cases with no tooth structure exposed in the cleft (R^2=0.37, p=0.12; Figure 4) but not in cases with teeth present in the cleft (R^2=0.02, p=0.57; Figure 5). Mean bony fill was 47.6 ± 27.6% overall and significantly larger (p<0.01) for females (67.5 ± 24.9%) compared to males (30.6 ± 16.4%) and significantly larger (p=0.01) for right-sided clefts (74.9± 28.5) compared to left-sided clefts (35.5±17.3; Figure 6). Extractions performed at the time of ABG, and age at time of initial imaging were not found to influence bony fill (Table 2).

Eleven of the thirteen clefts were type I prism type morphology, with the labial defect size ≥ the palatal defect size and the nasal defect size ≥ the occlusal defect size (Figure 1). One cleft was type II prism type morphology with the labial defect size ≥ the palatal defect size and the nasal defect < the occlusal defect size. One cleft was type IV funnel type morphology with a significantly narrow defect in the middle. When bony fill (%) versus initial cleft volume was considered for type 1 initial clefts shapes only, there was an inverse correlation that was stronger than for the overall sample (R^2=0.35; Figure 7). Cleft 3D masks were superimposed on CBCTs to visualize initial and residual defects (Figure 8).

Table 1. Case Demographics: Age (years) at time of ABG surgery, sex, cleft side, cleft shape, and cleft volume pre- and post-surgery.

Case	Sex	Age	Cleft side	Cleft Shape Type	Cleft site volume (mm^3)	
					Pre-surgery	Post-surgery
1┼[a]	Female	11.4	Right	II	740	31
2[b]	Female	9.0	Right	I	169	11
3*¥[c]	Female	8.2	Right	I	626	151
4*[a]	Female	8.5	Left	IV	207	91
5[c]	Male	13.2	Left	I	419	188
6¥[b]	Female	9.9	Left	I	1098	549
7¥[b]	Male	8.9	Left	I	596	363
8¥[a]	Male	9.0	Left	I	702	438
9[a]	Male	13.1	Right	I	644	423
10¥[a]	Female	8.8	Left	I	406	268
11[a]	Male	8.9	Left	I	539	393
12[x]	Male	11.5	Left	I	706	600
13¥[a]	Male	10.9	Left	I	1455	1370
Average ± SD		10.1 ± 1.7			639 ± 343	375 ± 354

Where: * indicates allograft, all others had iliac crest grafts; ┼ indicates orthodontic alignment pre-surgery; ¥ indicates extractions during surgery; [a,b,c] indicates different surgeons, and [x] indicates no bony bridging.

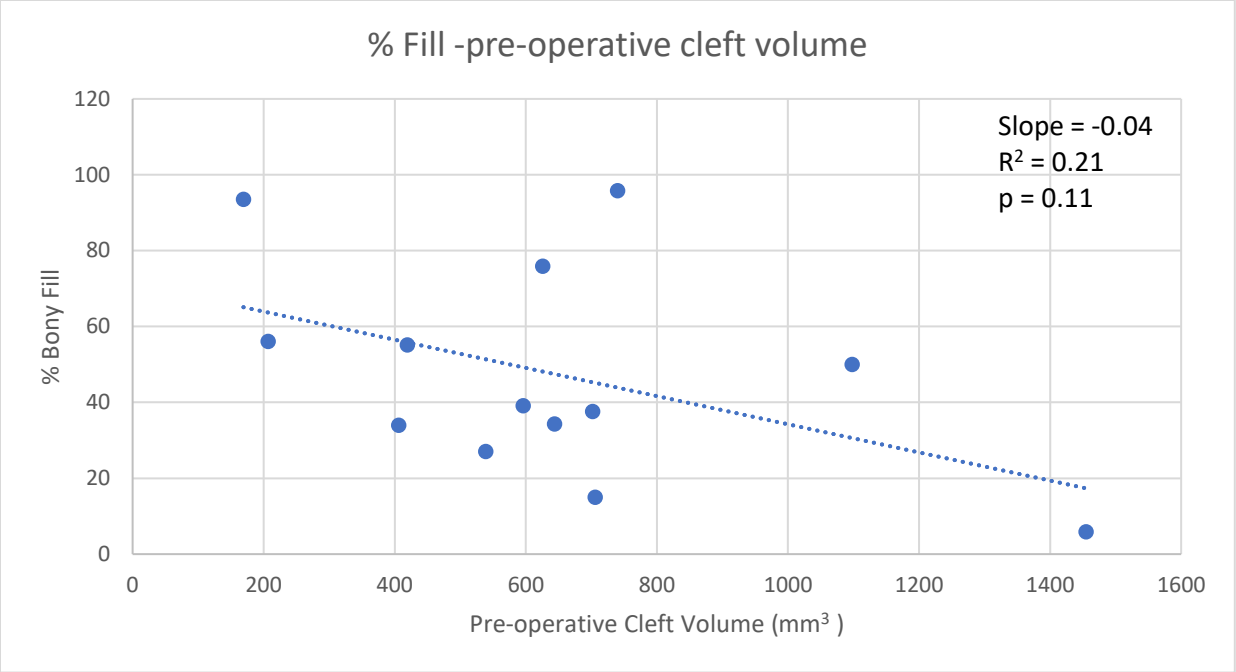

Figure 3. Relationship between pre-operative cleft volume and % bony fill after alveolar bone graft overall.

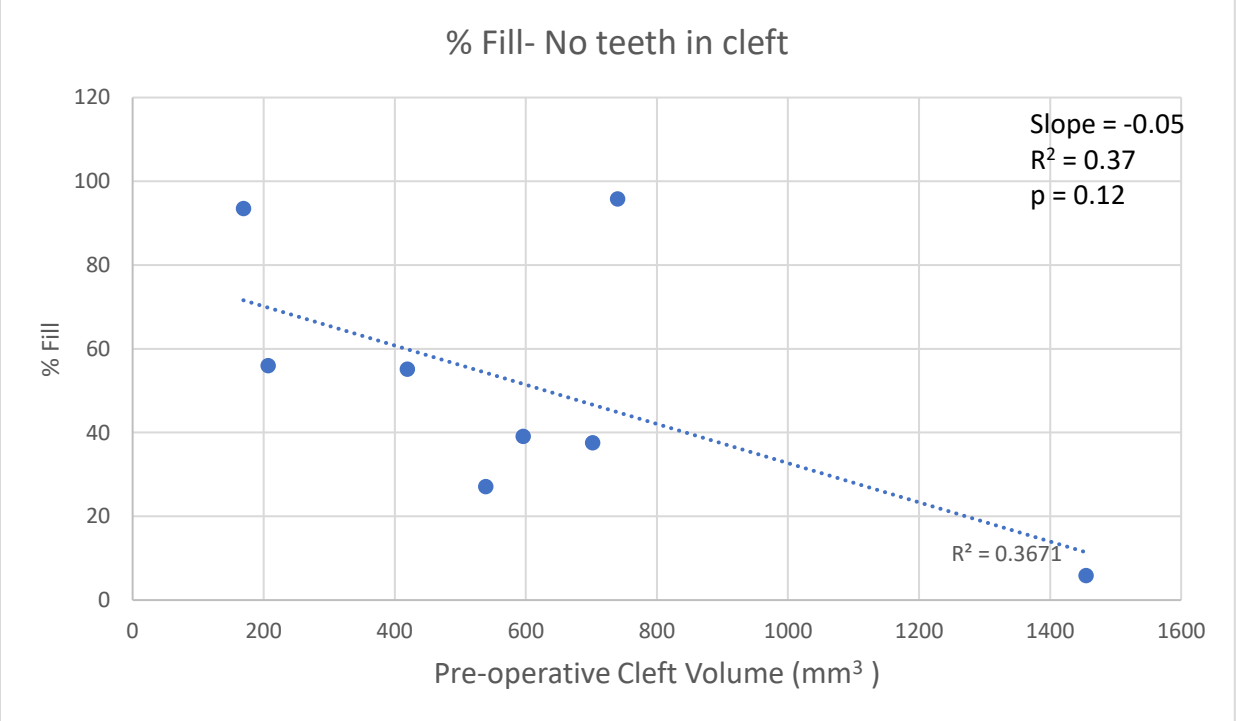

Figure 4. Relationship between pre-operative cleft volume and % bony fill after alveolar bone graft in cases with no teeth in the cleft site.

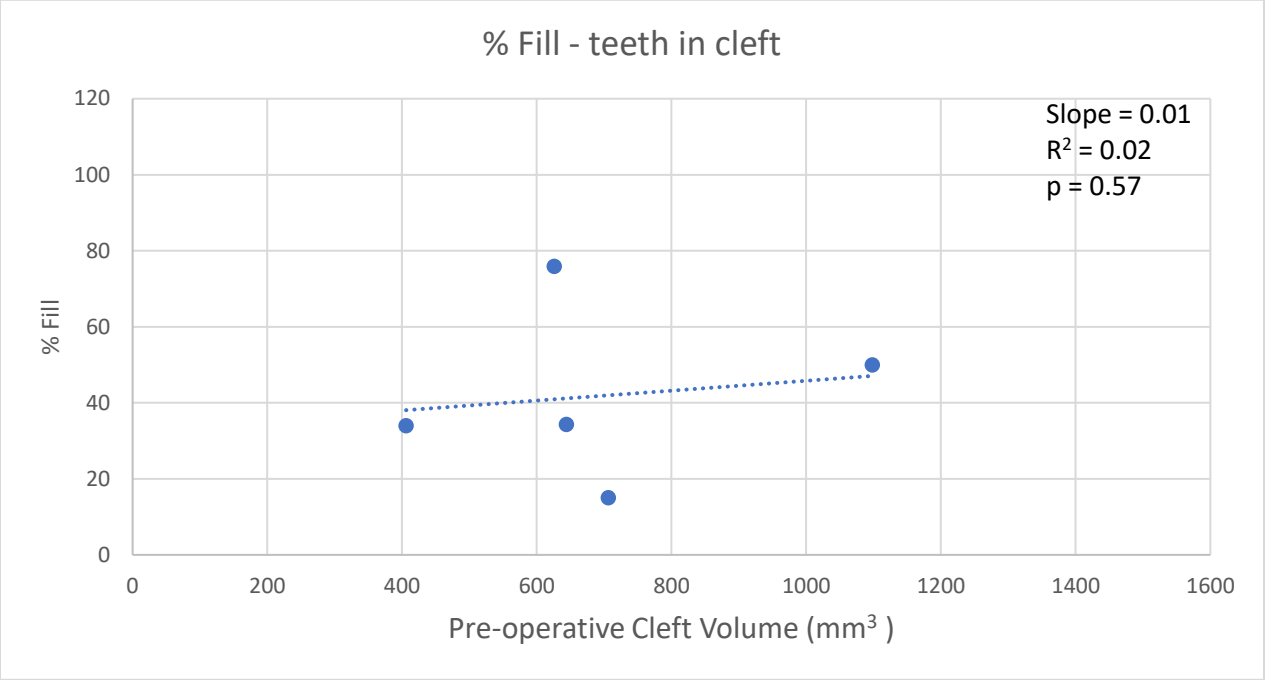

Figure 5. Relationship between pre-operative cleft volume and % bony fill after alveolar bone graft in cases with teeth in the cleft site.

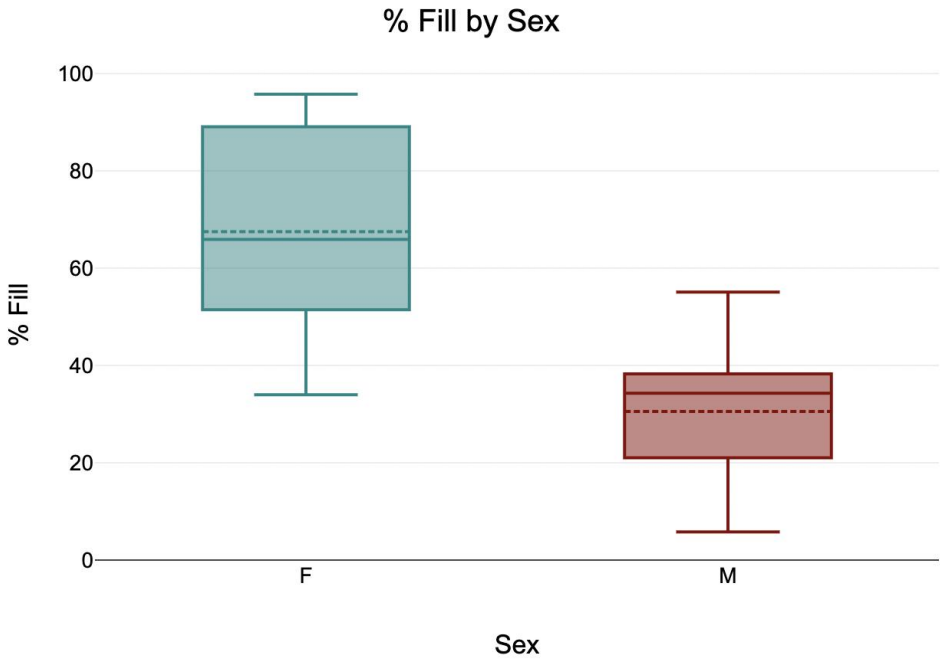

Figure 6. Percentage bony fill of cleft site by sex where F=female and M=male. Dashed line in box plot indicates mean values for the data set and solid line indicates median values. Vertical lines indicate maximum and minimum values and boxes indicate the middle 50% of data from quartile 1 to quartile 3 There were significant differences between % bony fill in male and female groups ($p<0.01$).

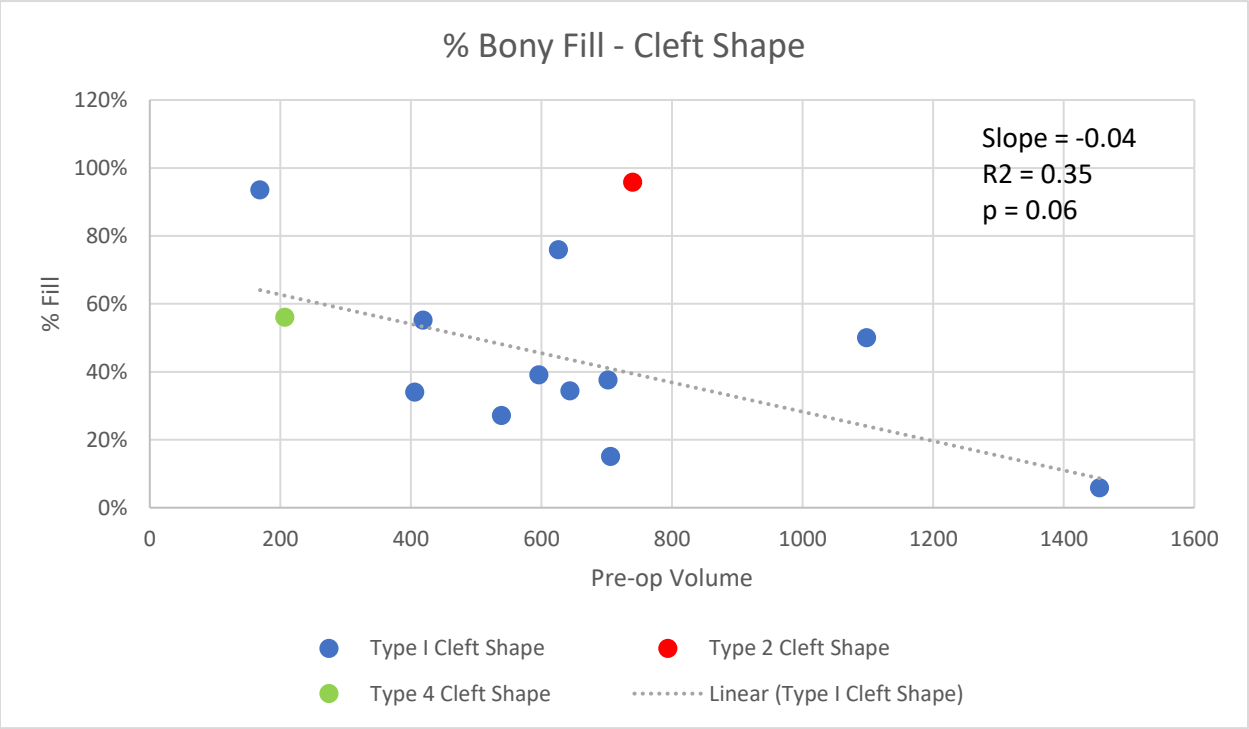

Figure 7. Relationship between pre-operative cleft volume and % bony fill sorted by cleft shape. Regression for type I cleft shape.

		Mean (% bony fill) ± standard deviation	p-value
Sex	Female	67.5± 24.9	<0.01*
	Male	30.6 ± 16.4	
Cleft side	Left	35.5 ± 17.3	0.01*
	Right	74.9 ± 28.5	
Teeth in cleft	Yes	41.8 ± 22.7	0.57
	No	51.3 ± 31.3	
Extractions during ABG	Yes	40.4 ± 22.8	0.42
	No	53.8 ± 31.5	

Table 2. Descriptive statistics of sex, cleft side, teeth exposed in cleft, extractions during bone grafting with means ± standard deviations. * denotes statistical significance less than 0.05.

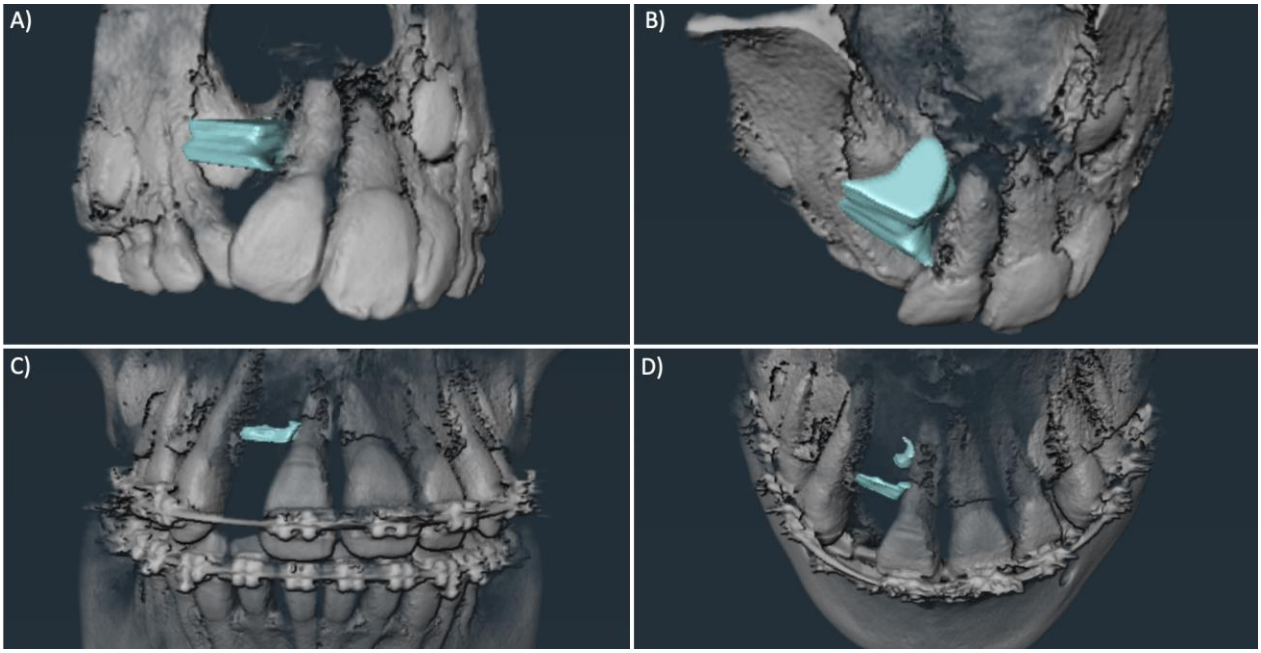

Figure 8. Case 2 images **A)** Anterior view of the cleft site pre-alveolar bone graft. **B)** Superior view of the cleft site pre-alveolar bone graft. **C)** Anterior view of the cleft site post-alveolar bone graft. **D)** Superior view of the cleft site-post alveolar bone graft show the bony defect remaining at the CEJ.

IV. Discussion

The aim of this study was to determine if bony fill of alveolar clefts after alveolar bone grafting is correlated with initial cleft volume and other factors. Percentage bony fill was calculated based on initial and residual cleft volumes using 3D CBCTs from archival patient records. Designing a pilot study to identify a 3D measurement protocol was necessary to confirm efficacy, reliability, and inform future clinical protocols regarding treatment of patients with alveolar clefts. It proved difficult to obtain a large sample with records that consisted of a complete set of pre- and post-graft CBCTs, as protocols at the institutions involved in the study did not routinely take CBCTs on these patients until more recently. Although the number of cases was small for generalizable conclusions, the results show trends important for further investigation.

Many studies have evaluated metrics of ABG success in patients with clefts, but using 2D images to look at cleft width was the most commonly utilized parameter used to characterize the initial defect in the past literature.[17,18] While width is an important factor, it fails to recognize the multi-dimensionality of the defect as it exists in the facial complex. The success of an ABG can be defined in many ways, but it must consider the ultimate goal of maximizing the improvement of both function and esthetics of the patient's craniofacial complex. Surgical success may be defined as bridging of maxillary segments and repair of an oronasal fistula with elimination of any communications between the nose and mouth, but this does not necessarily mean an intact alveolus to support the dentition has been achieved. Orthodontic treatment to achieve a functional occlusion and esthetic result may not be possible if a bony defect remains surrounding the dental roots. Therefore, this current method of volumetric analysis of the cleft site more comprehensively captures the condition of the repaired alveolus and whether any remaining deficits need further intervention to allow orthodontic movement of teeth without compromising their periodontal health.

CBCT volumetric analysis is becoming the method of choice for evaluation of alveolar bone defects, but standardized and reproducible protocols are lacking.[14,19,26] Previous studies often used different anatomical boundaries to define the alveolar defect or different segmentation methods (slice thickness, number of measured slices), making it difficult to compare variables across studies.[12] An aim of the current study was to simplify the identification of anatomical landmarks to define the cleft region in a way that would be reproducible for future studies. Although manually defined, this method showed high reproducibility and eliminated the limitations encountered with studies dependent on the contralateral alveolar bone for segmentation, which may not be feasible in cases of asymmetry.[14]

In the current study, the mean pre-operative cleft volume was 639 mm^3. This was similar to the average volume found in a 2009 study by Oberoi et al[19] of 610 cubic mm^3. Mean bony fill was 47.6%, indicating a resorption rate of 53%. This resorption rate was greater than values reported by 2D imaging

studies, but comparable to rates found in conventional CT studies.[20,27] 2D imaging studies have reported higher success rates of alveolar bone grafting (up to 95%), but are inferior in evaluating the bony support of the teeth adjacent to the cleft and fail to display resorption along the facial-palatal axis.[19,26,28] With the consensus for evaluation alveolar bone graft success shifting to 3D imaging, bony fill rates will likely be lower than with conventional 2D imaging, which tend to overestimate bone present,[29] but the architecture of the bony defect and volume and thickness of the bony bridge will be much more clearly reflected.

Pre-operative cleft volume was analyzed in association with percentage of bony fill and an inverse relationship was found, with larger initial clefts showing less bony fill (R^2=0.21, p=0.11). This relationship was accentuated in cases with no tooth structure in the cleft (R^2=0.37, p=0.12) and in type I cleft shapes (R^2=0.35, p=0.06). While these correlations were not statistically significant, it is promising that a substantial amount of the variability in bony fill outcomes can be explained by pre-operative cleft volumes, even in this small sample size. Previous studies have shown conflicting results regarding the effect of initial cleft size on bony fill, but differing methodologies make comparisons difficult. A 2D study by Long et al. and a 3D study by van der Meij et al. found cleft width to have an influence on alveolar bone graft success, with wider clefts being more prone to resorption.[17,18] Volumetric studies have failed to show an effect of the volume of the pre-operative defect on the outcome of bony fill.[7,12,19] The studies by Oberoi and Linderup both included pre-surgical expansion in all subjects, which they stated allowed approximation of wide cleft defects. In the current study, pre-alveolar bone graft expansion was not completed in any cases. A recent study by Roohani et al. defined a critical size defect of 810 mm^3 for iliac crest grafts and 885 mm^3 for allografts with bone morphogenetic protein, above which there were significantly higher graft failure rates.[30] Our study included two clefts over this threshold, but not enough to definitively identify a lower success rate. Different anatomic landmarks were used to define the cleft region in the previous studies, which could explain the discrepancy in results compared to the

current results. The current study is the first known to suggest a correlation between initial cleft volume and bony fill. Thus, further studies are needed to substantiate this finding.

A significant difference in mean bony fill in females (67.5 ± 24.9%) compared to males (30.6 ± 16.4%, $p<0.01$) was found. Although most previous studies showed no correlation between sex and success of alveolar bone grafting[19,31,32]; Aurouze et al. found a statistically significant association, with girls having a 3.79-times greater chance of graft success than boys ($p=0.0253$).[33] The reason for this sex-difference is unclear and could be confounded by other variables such as hygiene, periodontal infection, flap tension, skill of the surgeon, and bony support of teeth prior to grafting.[32,34] Studies have also found larger facial dimensions, higher bite force and chewing frequency, and better masticatory performance in male adolescents compared to female adolescents.[35] Higher masticatory forces and frequencies could place more strain on the graft and lead to tissue fatigue, which could possibly explanation less graft success in males compared to females. Males and females have also been shown to have differences in oral microbiomes, although this has not been investigated in relation to alveolar bone graft outcomes.[36,37] We also found a significant difference in mean bony fill in right-sided clefts (74.9 $\pm$ 28.5%) compared to left-sided clefts (35.5 $\pm$ 17.3%, $p=0.01$). Previous studies have not shown an effect of sidedness on success of ABG, but some surgeons report greater difficulty grafting right-sided clefts compared to left-sided clefts.[38] Future studies with larger sample sizes are needed to corroborate the effect of initial volume, sex, and cleft sidedness on ABGs.

Limitations

While important trends were identified in this pilot study, due to the small sample size there was insufficient power. Power analysis (Table 3) using these pilot data showed the sample size needed to reliably detect the observed effect of initial volume, age, extractions, and exposed teeth in the cleft was N=40, N>100, N=80-100, and N>100, respectively. Another limitation of this study was expansion was completed in four cases between ABG and the post-surgery CBCT. This could have had effects on

the condition of the cleft site and healing. There was also a large variation in span of time between CBCTs (1.1-10.6 years). While all were taken more than 3 months after grafting, orthodontic traction on impacted teeth and alignment could introduce confounding variables in graft success or insufficiency. This was also a retrospective study with no defined treatment protocol. Because of this, we could not control for the type of treatment each patient received and the timing of the CBCTs.

Power	N1	N2	N	Detectable fill change (%)
0.8	10	10	20	29.3
0.8	20	20	40	20.3
0.8	30	30	60	16.5
0.8	40	40	80	14.2
0.8	50	50	100	12.7

Power	Sample Size N	Detectable Slope for Pre-surgical Volume	Detectable Slope for Age
0.8	20	0.049	9.7
0.8	40	0.034	6.7
0.8	60	0.027	5.4
0.8	80	0.024	4.7
0.8	100	0.021	4.2

Table 3: A) T-tests power analysis for study sample), and B) Regression power analysis for study sample (α=0.05, β=0.2)

Future Work

This novel method has the potential to provide craniofacial surgeons and orthodontists with valuable information that could help inform treatment protocols. To validate the findings of this study and confirm and identify additional variables affecting ABG outcomes, future studies with larger sample sizes should be conducted using the same methodology and ensuring standardization of treatment protocols. Other suggestions for future work could investigate the effect of sex on ABG success and consider differing masticatory forces and oral microbiomes between sexes. Finally, looking further into cleft shape characterization and identifying treatment needed to optimize the cleft for grafting could help improve clinical procedures.

V. Conclusions

In this retrospective pilot study, volumetric rendering and calculation using CBCTs and specialized software (AMIRA) was reproducible and practical to assess outcomes of alveolar bone grafting. Specifically, bony fill percentage post-surgery was:

1. Inversely correlated with initial cleft volume overall and more strongly for initial clefts without teeth present and for type I initial cleft shape, but not correlated with exposed teeth in initial cleft or extraction during secondary alveolar bone graft surgery.
2. Significantly higher for females than males.
3. Significantly higher for right-sided compared to left-sided clefts.

Although our data showed trends towards increased success in smaller volume clefts, female sex, and right-sided clefts, the null hypotheses could not be rejected due to insufficient power.

VI. Comprehensive Literature Review:

Cleft Overview

Orofacial clefts are among the most common congenital anomalies in the world. Cleft lip and palate (CLP) can vary in location and severity and may involve the lip, primary palate, secondary palate, and/or alveolus. The incidence of cleft lip with or without cleft palate (CLP) is around 1:1000 worldwide, with cleft palate occurring in 1:2500.[2] CLP presents more commonly in Asians and Caucasians than black populations and occurs more often in males than females in a 2:1 ratio. Clefts have been linked to both genetic and environmental factors. While many occur in isolation (61.6%), they can also be associated with other congenital anomalies or syndromes (38.4%), with more than 200 genetic syndromes showing an association.[2] Isolated cleft palates are more commonly associated with other defects than CLP. Environmental risk factors include smoking or alcohol use during pregnancy, pre-gestational and gestational diabetes, use of anti-convulsants, and nutritional deficiencies.[2] Maternal smoking during

pregnancy has been consistently shown to increase risk of both cleft lip with or without cleft palate and isolated cleft palate as high as 20%.[39]

Sequence of Treatment

CLP patients require multidisciplinary care from the time of birth throughout adulthood. Treatment protocols for management of these patients vary significantly throughout the world and even between cleft teams in the same regions.[39] Ideally, clefts are identified early on in pregnancy in order to educate parents and begin planning for treatment. Ultrasounds can detect CLP in utero as early as 16-24 weeks, with sensitivity improving in recent years up to 95%.[40]

Due to the deformities of the orofacial complex, CLP patients often experience difficulties with feeding, speech, hearing, and psychosocial development. These challenges require care from a multidisciplinary team of specialists working together to create an individualized treatment plan for the needs of the patient. Cleft care teams commonly consist of specialists in otolaryngology, plastic surgery, oral and maxillofacial surgery, pediatrics, speech language pathology, nutrition, and orthodontics.[41] As the child grows and develops, the involvement of different team members evolves to reflect the changing needs of the patient at each stage of development. Shortly after birth, patients are evaluated to ensure proper feeding and weight gain. Prior to surgical treatment to repair the cleft lip, the child must weigh at least 10lbs, have a hemoglobin of more than 10g/dL, and be more than 10 weeks of age according to the proposed "rule of 10s."[42] Millard suggested postponing repair until at least 3-5 months of age if possible.[43] Repair of the cleft palate generally occurs before the age of 18 months. Timing must take into consideration speech development as well as potential impairment of maxillary growth related to early surgery. While delaying palatoplasty can have negative effects on speech development, the earlier the surgery is performed, the greater the restriction of growth of the maxilla. This scar tissue contracture resulting from lip and palate repair, as well as the absence of midpalatal bone are thought

to restrict the maxilla in all three dimensions, sometimes leading to the need for orthognathic surgery later in life.[44]

Pre-and post ABG orthodontic treatment

Many patients with a cleft undergo orthodontic treatment prior to SABG to help optimize grafting conditions, while others have the graft prior to any orthodontic intervention. Arch expansion and alignment of cleft adjacent teeth can facilitate easier surgical access for grafting but may increase the size of the cleft.[12,13] In the mixed dentition stage around 8-12 years of age, patients with CLP usually present with anterior transverse collapse of the maxillary arch, anterior and posterior cross bite, and a class III malocclusion. A first phase of orthodontic treatment is often carried out to prepare patients for alveolar bone grafting. During this stage of treatment, expansion is commonly used to align the maxillary segments, and teeth are sometimes repositioned and de-rotated to allow easier surgical access to the graft site. Timing of the graft should consider eruption of the canine or ability to orthodontically move teeth into the site shortly after the graft, as failure to load the bone in the graft area could result in resorption and thinning of the bone in all dimensions.[45]

While secondary alveolar bone grafting was originally performed between 9-12 years of age, there has been controversy surrounding the ideal timing. Some studies have shown that grafting prior to lateral incisor eruption resulted in less graft resorption.[46] Dissaux et al. also looked at bone survival and tooth eruption after ABG and found that early ABG before lateral incisor eruption (5 years) resulted in greater bone survival in 3D volumetric analysis than before canine eruption (10 years).[47] This could indicate that the lateral incisor, if present, could be an additional consideration in graft timing. In patients without the lateral incisor, ABG should be delayed until the cleft-side canine is close to eruption.[4] Ideally, the graft should be placed at a time when the canine (or lateral) will erupt into the site within a year. This is estimated by the root of the tooth being 2/3 formed. In cases where patients have ectopically erupting canines or present later in life after eruption of the canine, timing is left up to

discretion of the provider or is planned as soon as possible.[45] When the ABG is performed after canine eruption, some studies have shown accelerated resorption of the root and patients require more prosthetic treatment.[4]

In a 2023 study surveying orthodontists affiliated with American Cleft Palate Craniofacial Association (ACPA)-approved cleft/craniofacial teams by Preston et al., 66 teams responded including 31 orthodontists, 17 of which had craniofacial fellowship training. 35.5% reported treatment involving maxillary expansion to align alveolar segments alone, 19.4% expanded for both anterior segment alignment and posterior crossbite correction, and 19.4% expanded for posterior crossbite correction, aligned maxillary anterior teeth with fixed appliances, and corrected anterior crossbite with fixed appliances and/or facemask. Altogether, 87.1% of orthodontists performed at least maxillary expansion to align the anterior segments.[21]

Graft Materials

The gold standard graft material used for SABG is iliac cancellous bone. This is due to the large amount of cancellous bone containing osteogenic cells and easy surgical access. Limitations of iliac bone are postoperative hip pain and scarring.[4] Other options include calvarial and tibial bone. Calvarial bone gained attraction due to the shared embryologic origin of membranous and alveolar bone. Tibial bone is often used for orthopedic surgeries involving trauma, but few have reported success of ABG with tibial grafts, and there is a risk of damage to the growing epiphyseal cartilage during harvest. A 1991 study by Kortebein reported a success rate of 89.8% with iliac cancellous bone and only 63% with calvarial corticocancellous bone.[48]

Allogenic freeze-dried bone grafts are another option for SABG, and are attractive as they eliminate the post-operative pain and donor site morbidity of autogenous grafts. Options include bovine-derived demineralized bone matrix (DBM) and recombinant human bone morphogenetic protein (rhBMP)-2. While some studies have shown no difference between success of iliac cancellous bone

grafts and allogenic bone grafts, others have shown increased success with iliac grafts.[49-51] In a study by Scalzone et al. 2019, autologous bone grafts showed statistically significant higher bone formation after 6 months when compared to rh-BMP2 grafts, but no statistically significant difference was noted after a 1 year follow up. Assuming clinical success is similar with allogenic grafts, the lower morbidity and shorter hospital stay involved must be weighed against the increased cost of the allogenic bone grafting procedure. Additional long term studies evaluating safety and efficacy of allogenic bone grafts are needed.

Cleft Shape

The morphology of alveolar bony defects in cleft sites can be extremely complex and variable. Evaluating the size and shape of the defect before and after grafting could lead to more individualized approaches to treatment and increased success rates when compared to traditional pre-established protocols. A recent study by Yu et al. developed a method of classification of alveolar cleft morphology and correlated this with success of SABG.[22] They found a significant correlation between initial cleft morphology and evaluation outcome, with a type I and IV funnel shaped cleft leading to better outcomes. Using a classification system like this, personalized treatment protocols could be developed for cleft patients to improve outcomes.

Assessment of Graft

Following alveolar bone grafting, it is essential to evaluate the quantity and quality of bone in the cleft site before proceeding with orthodontic tooth movement into the area. Prior to the advent of 3D imaging modalities, practitioners relied upon 2D periapical radiographs, panoramic images, or the surgeon's view intraoperatively to assess the graft.[45] 2D images of a three-dimensional site have tremendous limitations including distortion, magnification differences, superimposition of bilateral structures, and difficulty of identifying anatomic landmarks.[14] In recent years, cone beam computed tomography (CBCT) has been used to assess alveolar bone defects before and after grafting. By using 3D

volumetric analysis of the defect, providers can identify the condition surrounding the cleft, estimate how much bone may be needed for grafting, and assess the quality and quantity of bone present after grafting.[16] This may decrease total operative time, costs, and morbidity while leading to better treatment outcomes. While many studies use CBCTs to evaluate alveolar bone grafting, no standard method of assessment has been clearly defined. Standardization of image acquisition parameters, field of view, anatomical boundaries for area of interest, and segmentation method is also absent between studies.[12] Because of this, it is difficult to compare results between studies with any confidence.

Need for 3D Quantification

While some studies have shown that alveolar cleft width influences the success of alveolar bone grafting and wider clefts are more prone to resorption,[17,18,20] others have found that the preoperative size of the cleft does not affect the outcome of the bone fill.[7,12,19] Further research is needed to illuminate the connection between cleft morphology and success of secondary alveolar bone graft, as well as identify patient specific factors that may affect success of SABG.

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VIII. Appendices

Appendix A: OHSU Institutional Review Board Approval

APPROVAL OF SUBMISSION

May 24, 2023

Dear Investigator:

On 5/24/2023, the IRB reviewed the following submission:

IRB ID:	STUDY00025484
Type of Review:	Initial Study
Title of Study:	A study of the effects of alveolar cleft volume and success rate of alveolar bone grafting
Principal Investigator:	Jeff Nickel
Funding:	None
IND, IDE, or HDE:	None
Documents Reviewed:	• HIPAA Waiver • Protocol - A Study of the Effects of Alveolar Cleft Volume and Graft Success Rate

The IRB granted final approval on 5/24/2023. The study requires you to submit a check-in before 5/22/2026.

Review Category: Exempt Category #4

Copies of all approved documents are available in the study's **Final** Documents (far right column under the documents tab) list in the eIRB. Any additional documents that require an IRB signature (e.g. IIAs and IAAs) will be posted when signed. If this applies to your study, you will receive a notification when these additional signed documents are available.

Ongoing IRB submission requirements:

- Six to ten weeks before the eIRB system expiration date, submit a check-in..
- Any changes to the project must be submitted for IRB approval prior to implementation.
- Reportable New Information must be submitted per OHSU policy.
- Submit a check-in to close the study when your research is complete

Appendix B: Valley Children's Institutional Review Board Approval

Institutional Review Board

J Daniel Ozeran, M.D., Ph.D. IRB Chair

James Horspool, D.O. Vice Chair

irb@valleychildrens.org

9300 Valley Children's Place Madera, California 93636 (559) 353-3000 valleychildrens.org

November 30, 2023

Bruce Havens, MD Department of Surgery 9300 Valley Children's Place Madera, CA 93636

Initial Approval - Expedited Review HSC2560 - A Study of the Effects of Alveolar Cleft Volume and Success Rate of Alveolar Bone Grafting Study Risk Assignment: Minimal Risk Submission Date: 11/21/2023 Approval Date: 11/30/2023 Expiration Date: None

Dear Dr. Havens:

All documents for the above-referenced study were reviewed and approved via expedited review by the Valley Children's Healthcare Institutional Review Board on 11/30/2023.

The study was reviewed via expedited review and approved in accordance with regulations found at 45CFR46.110(5) and Subpart D 45CFR46.404.

Your request for a waiver of consent was approved in accordance with regulations at 45CFR46.116(f)(1).

A waiver of HIPAA Authorization is acceptable for the conduct of the study. 1. The study procedures do not adversely affect the rights and welfare of the individuals and pose minimal risk to their privacy, based on, at least, the presence of the following elements: a. An adequate plan to protect the identifiers from improper use and disclosure; b. An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless a health or research justification for retaining the identifiers was provided or such retention is otherwise required by law; c. Adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be

permitted by the Privacy Rule;2. The research could not practicably be conducted without the waiver; and3. The research could not practicably be conducted without access to and use of the protected health information.

In the future, if you wish to make subsequent changes to the study, they must be re-approved by the IRB prior to implementation of the changes.

It has been determined that this study does not require future continuing review, per the regulatory criteria set forth in 45CFR46.109(f)(1). Changes to the study must be reported promptly so the IRB can determine whether the protocol still meets this regulatory criteria, and all mandatory reporting obligations are still in effect. In the future, if you wish to make subsequent changes to the study, they must be re-approved by the IRB prior to implementation of the changes.

Please notify the board immediately of any proposed changes to the protocol, amendments, revisions, or any unanticipated problems involving risks to subjects or others in the protocol. If there are any serious or unexpected adverse events, please send a written response, as to your opinion whether it was study-related and whether it is safe to continue the study.

To ensure adherence to good clinical practice, the IRB may audit your study in the future. If you have questions, please do not hesitate to contact the IRB at (559) 353-5171. As soon as the study closes, please inform the IRB immediately with a summary report and submit a Study Retirement Form.

Sincerely,

Brian L. Baker, MLS, JD Institutional Review Board Valley Children's Healthcare

Valley Children's | HOSPITAL | MEDICAL GROUP | HOME CARE | FOUNDATION

Documents Submitted in Support of this Application: • Alveolar Bone Graft IRB application• Alveolar Bone Graft protocol• Alveolar Bone Graft Waiver

Appendix C: UCSF Fresno Institutional Review Board Approval

Human Research Protection Program Institutional Review Board (IRB)

IRB Exemption

June 9, 2023
To: George Zakhary, DDS, MD, FACS Department of Oral/Maxillofacial Surgery

From: Alan Rosa, MBA/HCM IRB Member

Study Title:

IRB No.: Ref No.: Type of Submission: Approval Date: Study Expiration: Funding Source: Initial IRB Approval Type: Category:

A Study of the Effects of Alveolar Cleft Volume and Success Rate of Alveolar Bone Grafting 2023032 001611377

New Study, Initial Submission June 9, 2023 June 8, 2024 None

Exempt Certificate 4

Human Research Protection Program Institutional Review Board (IRB)

IRB Exemption

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June 9, 2023

Regulatory Determinations Pertaining to this Approval:

4. The study was determined to be not greater than minimal risk and met all criteria for IRB approval under 45 CFR 46.111 and 21 CFR 56.111.

5. Waiver/alteration approved 45 CFR 46.116(f)

6. Waiver of HIPAA Authorization for Research/Subject Identification approved under 45 CFR164.508

Important Information for the Principal Investigator:

- It is the Principal Investigator's responsibility to ensure that all study personnel are properly trained for their roles in the study.

- It is the Principal Investigator's responsibility to ensure that the list of personnel in the IRB application is current and those listed as Key Study Personnel maintain current CITI Human Subjects Protection Training.

- It is the Principal Investigator's responsibility to report to the IRB any protocol violations, adverse events and other reportable events/items that meet the CHS reporting requirements.

 If this study has collaborating sites with their own reviewing IRBs, it is the Principal Investigator's responsibility to ensure that the collaborating sites have current IRB approval prior to engaging with them in any research activities, including sharing CHS data or samples with them.

 If the IRB has approved the study to enroll non-English speaking participants, the Principal Investigator must ensure that the consent method follows current CHS guidelines based on the IRB-approved method (Short Form Method vs. Preferred Method).

 You are responsible for ensuring that any required facility reviews and approvals are secured before implementing any modifications to the study protocol. If you have not already initiated the facility approval process, please contact CMCClinicalContentandResearch@communitymedical.org. **All changes to a study must receive CHS IRB approval before they are implemented.** Proposed changes to the protocol, or consent form, amendments, and revisions can be submitted for review and approval by completing the Post Approval Application in CyberIRB. Any deviations from the protocol, injuries to subjects, or any unanticipated problems involving risks to subjects or others in the protocol can be submitted for review and acceptance by completing the Adverse Event/Incident Report Application in CyberIRB. The only exception to the requirement for prior CHS IRB review and approval is when the changes are necessary to eliminate apparent immediate hazards to the subject (45 CFR 46.103.b.4, 21 CFR 56.108.a). If there are any serious or unexpected adverse events, written response must be submitted to the IRB within 10 days, and include your opinion whether it was study related and whether it is safe to continue the study. The written response can be reported by completing a Protocol

Deviation/Incident Report in CyberIRB. If the change will be a permanent change to the study, you must also submit a Modification form. Please provide the committee with a summary of any changes to the investigators' brochure, if applicable.
Expiration Notice: The CyberIRB system will generate a notification 60 days and 30 days prior to the expiration of this study's approval. However, it is your responsibility to ensure that an application for continuing review approval has been submitted by the required time. In addition, you are required to submit a study closeout report at the completion of the project by submitting a Post Approval Application or Renewal Application in CyberIRB.

Documents Reviewed and Approved with this Submission:

Title

CHS IRB Application Curriculum Vitae for PI and Sub-Investigators Human Subjects Research Training for PI and Sub-Investigators Data Collection Sheet Study Proposal

Version No. -

Signed/ Version Date 05Jun2023

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05Jun2023

To ensure adherence to good clinical practice, the IRB may audit your study in the future. Please direct all questions pertaining to this study to the IRB office at IRB@communitymedical.org.