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Congenital craniofacial deformities: Genetic and clinical aspects

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Congenital craniofacial deformities: Genetic and clinical aspects

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Editorial: Congenital craniofacial deformities: genetic and clinical aspects

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Editorial on the Research Topic
Congenital craniofacial deformities: genetic and clinical aspects

The Research Topic "Congenital Craniofacial Deformities: Genetic and Clinical Aspects" is a Frontiers Research Topic aimed to provide an opportunity for researchers and clinicians from different perspectives and areas to publish recent advances in investigating the genetic etiology and the treatment options for different congenital craniofacial deformities.

Caused by genetic diseases, chromosomal mutations, or abnormal embryonic development, congenital craniofacial deformities refer to the inborn anomalies of the skull, orbits, zygomatic bones, maxilla, and mandible. Facial soft tissue defects, including craniosynostosis, craniofacial fissure, dilated orbital distance, and craniofacial microscopic anomalies are also considered craniofacial deformities. In severe cases, they can even lead to intellectual disability and visual impairment. Craniofacial deformities are often accompanied by anomalies of the spine, trunk, limbs, and visceral transposition. The treatment of congenital craniofacial deformities is complex, and satisfying outcomes are still missing. Furthermore, the patient's psychological state and related social behavior also need more attention. Even though a lot of research has been carried out in the field of craniofacial development, the genetic etiology of congenital craniofacial deformities needs more investigation to reveal the role of specific genes and their synergistic effect during the development of the craniofacial skeletal system.

Cleft lip and palate is one of the most common congenital craniofacial deformities. For repairing cleft lip and palate, team approach should be carried out. Restorations of primary deformities and secondary dysfunctions are the main purposes in the treatment of cleft lip and palate.

In this Research Topic, presurgical intervention of primary cleft lip repair is focused by Yin et al. Outcomes by three dimensional evaluation of presurgical nasoalveolar molding (PNAM) therapy in patients with non-syndromic complete unilateral cleft lip and palate (UCLP) were presented. Their results demonstrated that PNAM therapy could help decrease the difficulties of cleft lip repair.

Rhinoplasty for patients with cleft lip is always a challenge to the surgeons, and narrow nostril deformities are the most troublesome. The study by Wei et al. developed an algorithm for surgical method selection for repairing narrow nostrils in patient with secondary cleft lip nasal deformities. It demonstrated that the width of the nasal floor and the length of the alar rim are critical elements for selecting the appropriate surgical method. Meanwhile, a review by Xu et al. focusing on the growth patterns of the nasolabial region following unilateral cleft lip primary repair was also included in this Research Topic.

The purpose of cleft palate repair is to reconstructing a normal velopharyngeal function of the patient. In this Research Topic, the study by Fan et al. compared the velopharyngeal morphology of patients with hard and soft cleft palate after Furlow and Sommerlad palatoplasty, and Mao et al. presented a review to introduce specific problems that are currently under-recognized in the diagnosis and treatment of marginal velopharyngeal inadequacy and provides guidelines for further exploration of standardized and reasonable intervention protocols for marginal velopharyngeal inadequacy.

A review about poor oral hygiene and high susceptibility to dental caries and periodontitis in patients with cleft lip and palate was presented by Wu et al. which concluded and updated probable causes underlying the association between cleft lip and palate and poor oral health.

Meanwhile, application of vertical transposition flap in closure for large facial soft tissue defects in children was reported by Feng et al. A case with hereditary sensory autonomic neuropathy was also reported by O'hagan-Wong et al. which demonstrated extensive oral trauma as one of the early signs of hereditary sensory autonomic neuropathy that should provoke a timely referral for neurological assessment.

This Research Topic targets the acquisition and dissemination of knowledge regarding to congenital craniofacial deformities to share knowledge from both the basic and clinical sciences. Briefly, this Research Topic provided researchers and clinicians from different perspectives and areas with a platform to discuss recent advances in the understanding of congenital craniofacial deformities. It also will provide readers with new insights and different viewpoints to stimulate further investigations in this broad research field.

Author contributions

HH: Writing – original draft, Writing – review & editing. JD: Writing – original draft, Writing – review & editing.

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Conflict of interest

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The circadian clock component BMAL1 regulates osteogenesis in osseointegration

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Congenital and developmental craniofacial deformities often cause bone defects, misalignment, and soft tissue asymmetry, which can lead to facial function and morphologic abnormalities, especially among children born with cleft lip and palate. Joint efforts from oral maxillofacial surgery, oral implantology, and cosmetic surgery are often required for diagnosis and treatment. As one of the most widely performed treatment methods, implant-supported cranio-maxillofacial prostheses have been widely applied in the course of treatment. Therefore, stability of peri-implant bone tissue is crucial for the long-term success of treatment and patients' quality of life. The circadian clock component brain and muscle aryl hydrocarbon receptor nuclear translocator-like protein 1 (BMAL1) was found to be involved in the cell fate of bone marrow mesenchymal stem cells, which were essential in the fixation of titanium implants. This study aimed to investigate the effect of BMAL1 on osteogenesis in osseointegration, providing a brand new solution to increase bone implant conjunction efficiency and implant stability, paving the way for a long-term satisfactory therapy outcome.

KEYWORDS

implant treatment, Bmal1 gene, osseointegration, osteogenesis, cell senescence, aging

Introduction

Cleft lip and palate (CLP) are one of the most common craniofacial congenital malformations in humans (1). It has been estimated lately that, with ethnic and geographic variation, approximately 1.5–1.7 of every 1,000 infants are born with CLP, which sorely hampers the development of important physiological functions, including breathing, swallowing, speech, chewing, and esthetics (2, 3). At the end stage of growth and development, in order to re-establish esthetics, phonetics, function, and self-confidence, rehabilitation of edentulous space should be the priority (4). Initially reported by Verdi et al., dental implant therapy gradually earned its place in the field of CLP treatment and rehabilitation (5). Severe clinical studies have verified its satisfying results and high long-term success rates (6–8).

Dental implants have been widely employed to restore the function and esthetics for dentition defect or edentulism, especially for youngster patients with congenital craniofacial deformities in an increasing number. The key to a successful dental implant therapy is to achieve direct and complete implant-to-bone contact, which has been defined as osseointegration (9). Following the placement of titanium implants, a series of biochemical reactions occur in the bone marrow, among which osteoprogenitor cells and osteoblasts play a vital role (10). Bone marrow mesenchymal stem cells (BMSCs) are recruited to implant surface and, subsequently, differentiate into osteoblasts. Osteoblasts can secrete bone matrix, directing the process of osseointegration. However, senility leads to changes in the bone marrow microenvironment. At the cellular level, aging impairs the osteogenic differentiation ability of BMSCs and encourages differentiation into adipose cells, leading to fewer osteoblasts and weaker osseointegration (11). Despite the donor's age, an aging bone marrow microenvironment also forces foreign transplanted mesenchymal progenitor cells to transform into adipocytes (12). Therefore, osseointegration in elderly individuals requires a longer period, which remains a clinical challenge. It is essential to study the age-related function of mesenchymal cells, so as to promote a curative effect of dental implants.

Interestingly, several recent studies have shown that the circadian clock system in mammals may influence the function and cell fate of mesenchymal cells (13–15). Brain and muscle aryl hydrocarbon receptor nuclear translocator-like protein 1, briefly BMAL1, is the core component of circadian clock system in mammals, functioning as the positive arm in the negative feedback regulation mechanism of circadian rhythm (16). Bmal1 gene knockout mice show reduced bone volume and lower bone density. Histological examination also demonstrates that deficiency of BMAL1 leads to osteocytes' decrease *in vivo* (14). The mechanism of aging process has been studied as well. The absence of Bmal1 results in a premature aging process and shortened lifespan in mice (17). Chen et al. found that BMAL1 was related to aging process in aged BMSCs. The expression level of BMAL1 decreased, while the aging of BMSCs hampered osteogenic differentiation (13). Moreover, follow-up studies have demonstrated that the regulation effect of BMAL1 might go through the Wnt pathway (18, 19).

Since BMSCs are the key to osseointegration, we hypothesized that BMAL1 might directly influence osteogenic differentiation of BMSCs among the implant–bone environment. In aged mice, downregulation of Bmal1 gene occurs naturally, impairing the integration between titanium implants and bone. Rescued expression of BAML1 at implant sites can promote local bone healing and obtain higher bone–implant contact ratio (BIC). Hence, in this study, we performed knockdown of BMAL1 of BMSCs to examine its effect on fate choice as well as investigated the overexpression results of lentiviral vector BMAL1 applied around titanium implants in aged mice.

Materials and methods

Animals and cell culture

All animal care and studies were approved by the Animal Research Committee of Sichuan University (Chengdu, China) and conducted in accordance with international standards. Young adult (1 month old) and aged (12 months old) C57BL/6 male mice were obtained from the Animal Centre of Sichuan University.

Young adult mice were used for primary extraction of mesenchymal cells. After the mice were sacrificed, the femurs and tibias of both sides were obtained and immediately immersed into phosphate buffer saline (PBS, Gibco) containing 10% penicillin–streptomycin (Liquid, Gibco). The epiphyses were cut off and the marrow cavities were syringed with a sterile medium using a #25-gauge needle. Cells were washed with PBS by centrifugation and then cultured in alpha minimum Eagle's medium (α-MEM, HyClone) with 10% fetal bovine serum (FBS, Gibco) and 1% penicillin–streptomycin. BMSCs were incubated at 37 °C with 5% CO_2, and the culture medium was exchanged every 2 days. When the confluence rate reached 80%–90%, BMSCs were detached by 0.25% trypsin and then passaged. BMSCs were employed for the subsequent research at passage 4 (18). For osteogenic induction, osteogenic medium was supplemented with the basic medium 10 mM β-glycerophosphate (Sigma), 50 µM ascorbic acid (Sigma), and 10 nM dexamethasone (Sigma).

BMAL1 knockdown

Bmal1 siRNA and negative control RNA were synthesized from Shanghai Sangon Biotech Co. (China). The sequence of Bmal1 siRNA is GCAAACUACAAGCCAACAU, the bases of which were shuffled for control siRNA. According to the manufacturer's protocol, the siRNA and Lipofectamine® RNAiMAX (Invitrogen) were dissolved in Opti-MEM (Gibco). The two transfection solutions were mixed and then incubated at room temperature in dark for 30 min. When the confluence rate of BMSCs reached 40%–50%, the culture medium was exchanged into α-MEM with 10% FBS without penicillin or streptomycin 2 h in advance. Then, the transfection mixture with Bmal1 siRNA or control siRNA was added into the culture medium. The knockdown efficiency was detected by quantitative reverse transcription polymerase chain reaction (qRT-PCR) after 12-h incubation. If BMAL1 was successfully knockdown, cells were applied for tests as described below.

CCK-8 assay

A cell counting kit-8 (CCK-8) (Beyotime, China) was used to measure the proliferation ability of BMSCs. At the time point of 1 and 3 days after being transfected with siRNA, cells were cultured into a 96-well plate in five duplicated wells. Then, a 100 µl CCK-8 working solution was added into each well.

After incubating for 2 h, absorbance of the culture medium was detected at 450 nm.

Assessment of senescence-associated β-galactosidase staining

A senescence-associated β-galactosidase (SA-β-gal) staining kit (Beyotime, China) was used to detect cell senescence of BMSCs. Passage 4 BMSCs were incubated in a six-well plate. After being transfected with siRNA, the medium was removed and cells were rinsed with PBS twice. Then, BMSCs were fixed with 4% paraformaldehyde and stained with a working mixture of β-galactosidase and X-Gal at 37 °C overnight in dark. Senescent cells were inspected with an optical microscope and counted in random field of vision.

RNA extraction and qRT-PCR

In the *in vitro* test, total RNA was isolated using Trizol Reagent (Invitrogen) 7 days after osteogenic induction. The total RNA was treated with DNase and then reverse transcribed *via* a PrimeScript RT reagent Kit (Takara). Real-time PCR was conducted in a 20-µl mixture using SYBR Premix Ex Taq (Takara) and LightCycler 96 (Roche). Bmal1 and osteogenesis-related genes such as Sp7, Runx2, and Bmp2 were examined quantitatively using the housekeeping gene GAPDH as baseline. The primers are shown in **Table 1** (18).

Alkaline phosphatase staining and protein assay

After 7 days of osteogenic induction, BMSCs were fixed with 4% paraformaldehyde and then incubated with a working mixture of BCIP/NBT (BCIP/NBT Alkaline Phosphatase Color Development Kit, Beyotime, China) for 15 min. Images were taken with the Epson Perfection V370 Photo Scanner. For the alkaline phosphatase (ALP) protein assay, the total protein of BMSCs was collected with a protein extraction kit (PE001, Sab-biotech) and quantitatively assayed using the BCA Protein Assay Kit (Beyotime, China). An alkaline phosphatase assay kit (Beyotime, China) was used for the protein assay. After reaction with 0.5 mM p-nitrophenyl phosphate for 10 min, absorbance of p-nitrophenol formed by hydrolysis was detected at 405 nm. The corresponding of ALP activity was converted according to the standard curve.

Alizarin Red S staining

After 14 days of osteogenic induction, BMSCs were fixed with 4% paraformaldehyde and stained with Alizarin Red S (ARS) solution (Solarbio, China). Images were taken with the Epson Perfection V370 Photo Scanner.

Implant surgery

The mouse Bmal1 sequence (NM_007489) was retrieved from GeneBank, and the lentiviral vector was obtained from GENECHEM Co. (China). Mice were divided into three groups: (1) young group: young adult mice without lentiviral vector injection; (2) aged group: aged adult mice without lentiviral vector injection; and (3) transfection group: aged adult mice with lentiviral vector injection. Rod-shaped titanium implants (commercial pure titanium, grade 4, SLA surface modification, 2 mm in length and 1 mm in diameter) were obtained from WEGO CO. (China). Mice were anesthetized through intraperitoneal injections of ketamine (70 mg/kg) and xylazine (10 mg/kg), and implants were inserted into the distal aspect of femurs as described by Xiang et al. (20) and Xue et al. (21). Briefly, after dissecting the skin and muscles, the implant sites were prepared by sequential drilling with 0.8/1.0 mm-diameter stainless-steel twist drills under continuous sterile saline irrigation. Then, one implant

TABLE 1 Primer sequences for qRT-PCR.

Primer	Forward	Reverse
Bmal1	5′-AACCTTCCCGCAGCTAACAG-3′	5′-AGTCCTCTTTGGGCCACCTT-3′
Gapdh	5′-ACTGAGGACCAGGTTGTC-3′	5′-TGCTGTAGCCGTATTCATTG-3′
Sp7	5′-TATGCTCCGACCTCCTCAAC-3′	5′-AATAGGATTGGGAAGCAGAAA-3′
Runx2	5′-GGTACTTCGTCAGCATCCTATCAG-3′	5′-GCTTCCGTCAGCGTCAACAC-3′
Alp	5′-AACCCAGACACAAGCATTCC-3′	5′-GCCTTTGAGGTTTTTGGTCA-3′
Dlx5	5′-CTGGCCGCTTTACAGAGAAG-3′	5′-CTGGTGACTGTGGCGAGTTA-3′
Col1a1	5′-TAGGCCATTGTGTATGCAGC-3′	5′-ACATGTTCAGCTTTGTGGACC-3′
Bglap	5′-TTGGTGCACACCTAGCAGAC-3′	5′-ACCTTATTGCCCTCCTGCTT-3′

qRT-PCR, quantitative reverse transcription polymerase chain reaction.

was press-fitted into the prepared hole (Figure 3A). In the transfection group, BMAL1 lentiviral vector was injected into the holes before implant insertion. Finally, the muscles and skin were sutured tightly with 5-0 nylon suture (Huawei, China) to protect the implant sites from the surrounding environment. Figures 3B,C show the representative actual and x-ray inspection of femurs with implants.

Identification of lentiviral vector transfection

To confirm the functionality of BMAL1 lentiviral vector transfection system in the peri-implant sites, the IVIS Spectrum imaging system (PerkinElmer, Inc.) (absorbance of 465 nm) and immunofluorescence labeling of GFP (Abcam)

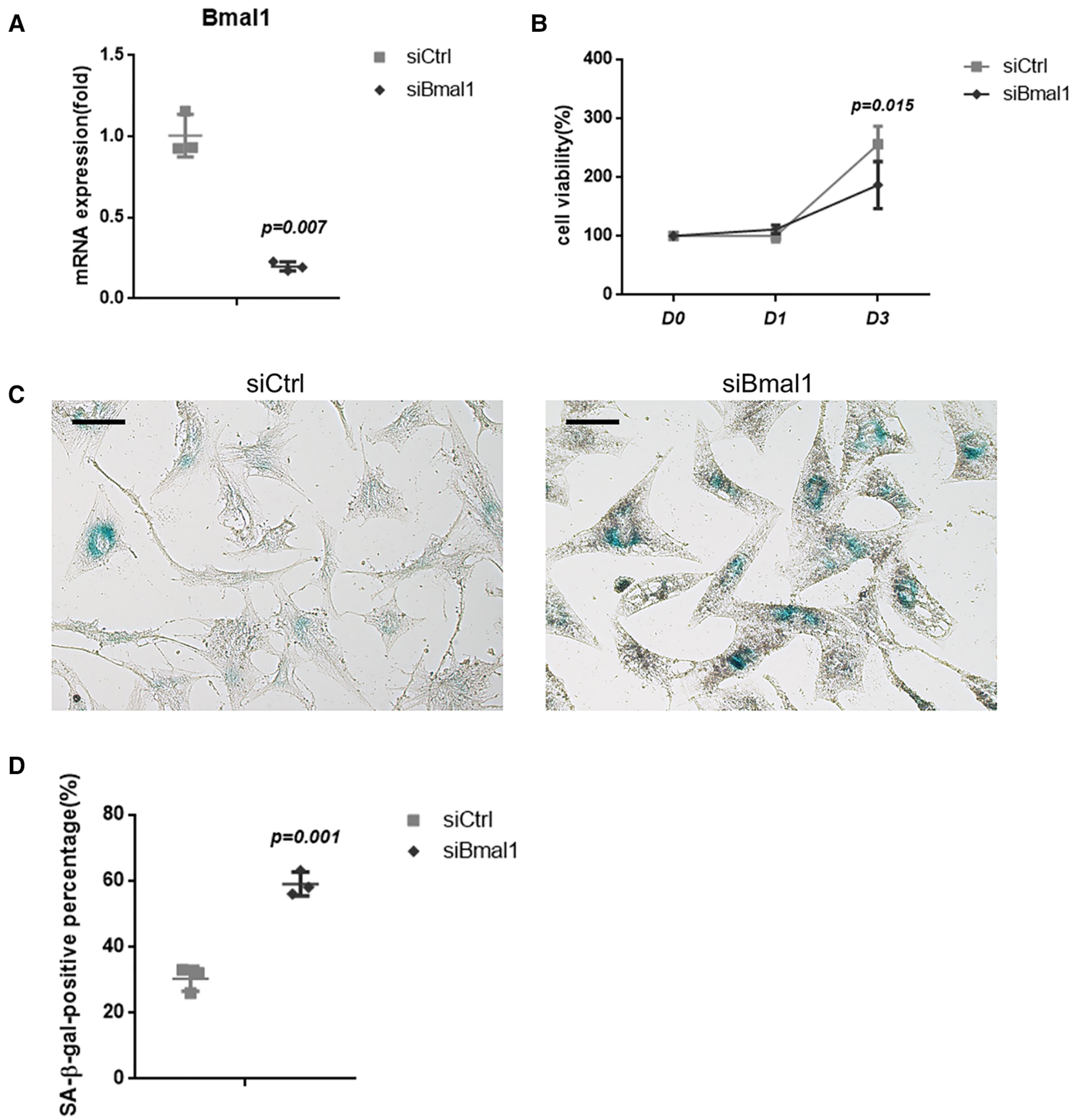

FIGURE 1
Depletion of BMAL1 accelerated cell senescence of BMSCs. (A) qRT-PCR test verified the knockdown efficiency of siBmal1. (B) Cell viability of BMSCs after siRNA treatment. (C) SA-β-gal staining images of BMSCs after siRNA treatment. Scale bar = 100 μm. (D) Quantitative analyses of SA-β-gal staining. BMSCs, bone marrow mesenchymal stem cells; qRT-PCR, quantitative reverse transcription polymerase chain reaction; SA-β-gal, senescence-associated β-galactosidase.

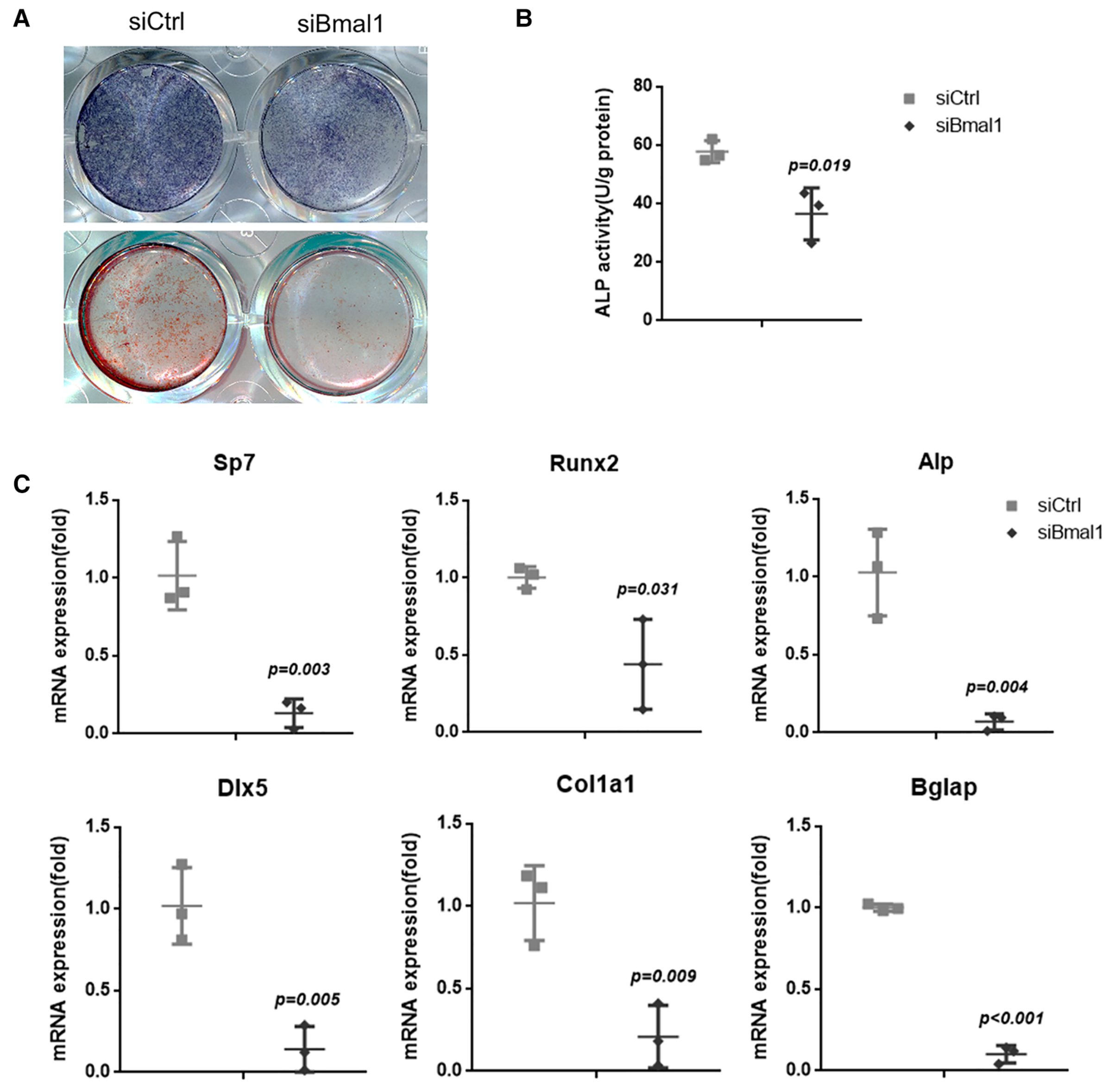

FIGURE 2
Knockdown of BMAL1 reduced osteogenic differentiation of BMSCs. (A) Representative images of ALP and ARS staining of BMSCs in siBmal1 and siCtrl group. (B) Quantitative analyses of ALP activity. (C) qRT-PCR analyses of the expression of osteogenesis-related genes (Sp7, Runx2, Alp, Dlx-5, Col1a1, and Bglap) 7 days after osteoinduction. BMSCs, bone marrow mesenchymal stem cells; qRT-PCR, quantitative reverse transcription polymerase chain reaction; ALP, alkaline phosphatase; ARS, Alizarin Red S.

were used to observe the expression of GFP in the transfection group at day 14 after the implant surgery.

Micro-CT analyses

Two weeks after implant surgery, femurs containing implants were harvested and scanned with a μCT 80 micro-CT system (SCANCO 50, Switzerland) at 8 μm resolution (90 kV, 200 μA, 500 ms integration time). A radius of μ20 m around implants was defined as the peri-implant site for volume of interest (VOI). After three-dimensional reconstruction, a few basic parameters were analyzed as follows: (1) BIC: bone–implant contact; (2) BV/TV: bone volume fraction; (3) Tb. N: trabecular number; (4) Tb. Sp: trabecular separation.

Histomorphometric analyses

The specimens were fixed with 4% paraformaldehyde, dehydrated with a graded series of ethanol solutions (60%, 80%, 90%, and 100%), and embedded in light-curing epoxy resin (Technovit 7200VLC, Hereaus Kulzer, Germany) for 1 week. Then, the specimens were sliced perpendicular to the long axis of the implants and sanding to about 50 μm thickness using a grinding system (Exakt Apparatebau, Germany). Sections were stained with Stevenel's blue and Van Gieson's Picrofuchsin stain (20), and images were taken under a light microscope (OLYMPUS BX43F, Japan). For histomorphometric analysis, BIC and BV/TV were measured using the NIH IMAGE J software (21). BIC was defined as the line percentage of the implant interface that directly contacts the bone. As for the BV/TV, it indicated the proportion of bone to total tissue volume around the implants.

Statistical analyses

All data were presented as mean ± standard error (SD). Statistical differences were calculated *via* Student's *t* test for independent samples or one-way ANOVA for multiple comparisons using SPSS 17.0 software (SPSS, Inc., Chicago, IL, United States). A *P* value of less than 0.05 was considered as a statistically significant difference.

Results

The knockdown of BMAL1 accelerated cell senescence of BMSCs

BMAL1 was knockdown in BMSCs to verify its effect on cell senescence. qRT-PCR tests showed the efficiency of BMAL1 knockdown (**Figure 1A**). CCK-8 assay demonstrated that deficiency of BMAL1 led to reduced cell proliferation capacity (**Figure 1B**). In the knockdown group, more blue-dyed products catalyzed by β-galactosidase were observed than another group under optical microscope *via* SA-β-gal staining (**Figure 1C**). It indicated that the knockdown of BMAL1 in BMSCs accelerated cell senescence. The counting result of senescent cells is shown in **Figure 1D**.

The knockdown of BMAL1 reduced osteogenic differentiation of BMSCs

The osteogenesis of BMSCs was examined with ALP staining after 7 days osteoinduction, which indicates reduced capacity of osteogenic differentiation in the knockdown group (**Figure 2A**). The quantitative analysis of ALP activity also showed the downregulated osteogenesis under BMAL1 deficiency (**Figure 2B**), and the ARS staining demonstrated the consistent result (**Figure 2A**). Moreover, qRT-PCR tests at 7 days after osteoinduction revealed that a few osteogenesis-related genes (Sp7, Runx2, Alp, Dlx-5, Col1a1, and Bglap) were downregulated significantly (**Figure 2C**). The results above indicated reduced osteogenic differentiation of BMSCs under BMAL1 depletion.

Transfection of BMAL1 promoted titanium implants osseointegration

To investigate the overexpression of BMAL1 around titanium implants in aged mice, micro-CT and histomorphometric analyses were conducted. First of all, immunofluorescence proved that GFP is expressed around the implant sites in the transfection group (**Figure 3D**). The three-dimensional reconstruction of the implant and newly formed bone tissue indicated that 2 weeks after implant surgery, bone–implant contact was obviously detected in the young group, while in the aged group, less bone–implant contact could be observed. After overexpressing BMAL1, samples in the transfection group exhibited increased BIC (**Figure 4A**). Histomorphometric analyses demonstrated likewise that the transfection of BMAL1 reversed bone–implant contact, which decreased while aging (**Figure 5A**). **Figures 4B** and **5B** show the calculation results of BIC. As

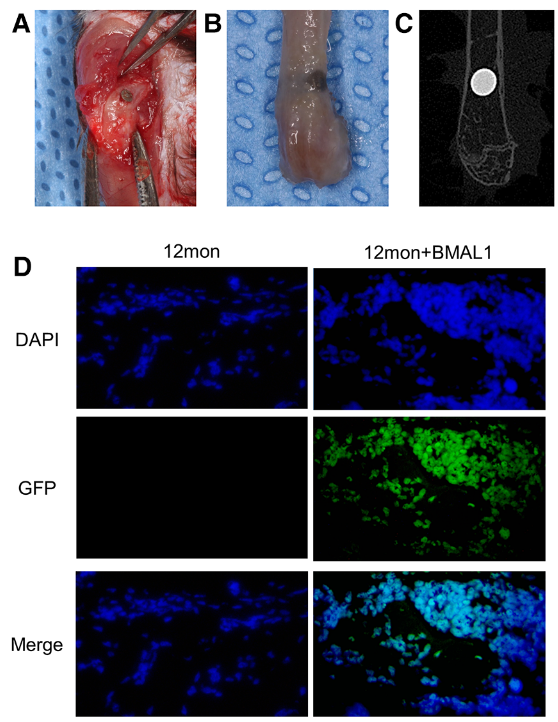

FIGURE 3
Representative images of implant surgery. (A) Titanium implants inserted into the distal end of femurs. (B) Representative image of femur with implant. (C) X-ray inspection of femur with implant. (D) Immunofluorescence proved positive expression of GFP in transfection group.

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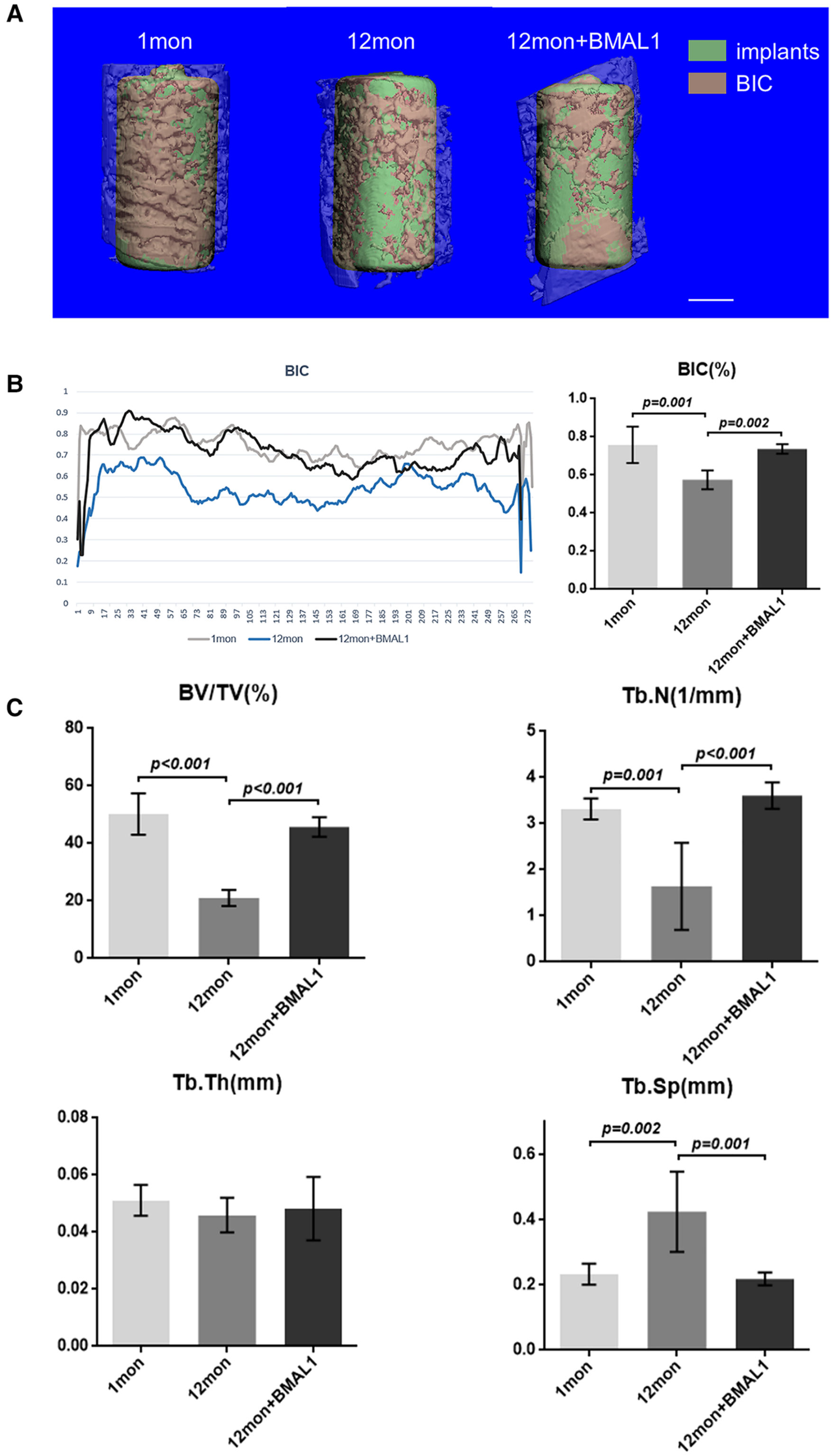

FIGURE 4
Micro-CT analyses of BIC and trabecular bone of femurs. (A) Representative 3D reconstruction images of peri-implant sites. Scale bar = 500 μm. (B) Representative liner graph and quantitative analyses of BIC rate. (*n* = 4) (C) Quantitative analyses of bone morphology parameters regarding BV/TV (%), Tb. N (1/mm), Tb. Th (mm), and Tb. Sp (mm). (*n* = 4). BIC, bone-to-implant contact; BV/TV, bone volume fraction; Tb. N, trabecular number; Tb. Sp, trabecular separation.

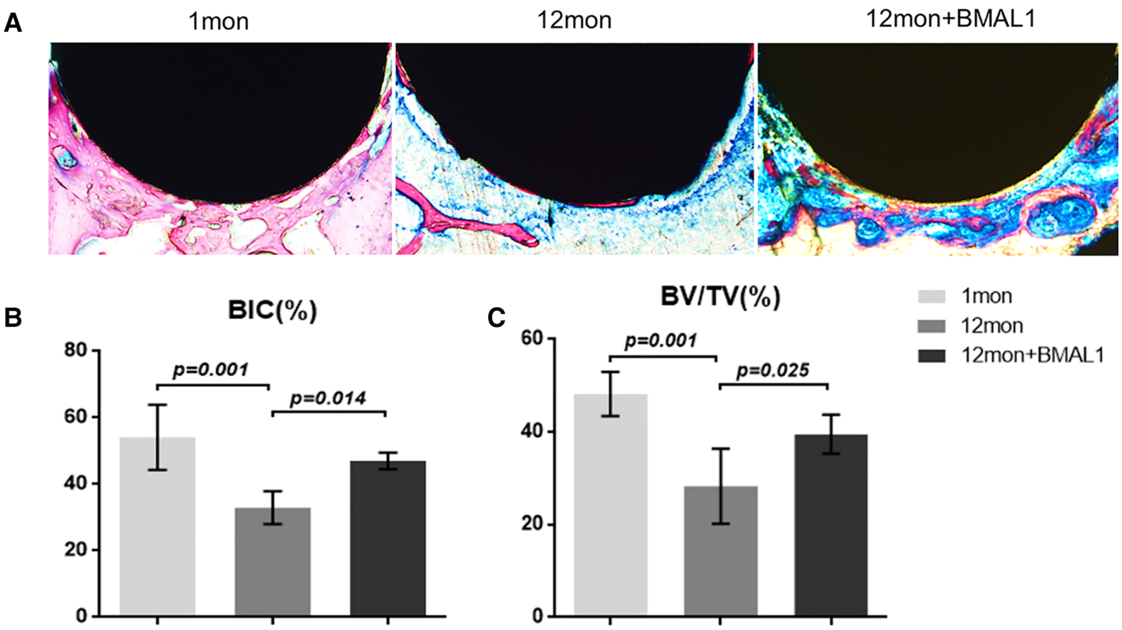

FIGURE 5
Histologic analyses of femurs with implants. (A) Representative image of histological sections after 2 weeks healing. (B,C) Quantitative analyses of BIC (%) and BV/TC (%), respectively, through histological images. (n = 4). BIC, bone-to-implant contact; BV/TV, bone volume fraction.

shown in Figure 4C, the BV/TV and Tb. N of mice femurs around implants in the aged group were significantly lower than that in the young group, but they increased in the transfection group. Otherwise, the Tb. Sp of mice femurs around implants in the aged group were significantly higher than that in the young group, but they decreased in the transfection group. Histomorphometric analyses demonstrated consistent results of BV/TV (Figure 5C). Results above indicated that overexpression of BMAL1 facilitates osseointegration, which decreases while aging.

Discussion

Implant treatment has become a mainstream of dental rehabilitation therapy in recent years. Despite the relatively high successful rate of implant therapy and a great number of surface modification techniques for titanium implants, osseointegration in certain individuals, such as the elderly, remains a challenge (22, 23). After the placement of implants, osteoprogenitor cells around the sites are recruited, differentiating into osteoblasts following the hemostasis and inflammatory phase (10). Osteoblasts derived from mesenchymal stem cells secrete extracellular bone matrix on the surface of implants and mineralize the matrix. Aging status, however, alters this process (11). In recent years, increasing amount of evidence shows that disruption of biorhythm can lead to various pathologies in different tissues (17, 24, 25). Simultaneously, interruption of circadian clock causes aging, clicking with the fact that BMAL1 has been reported as the key factor to aging, in addition to its effect on circadian rhythm in mammals (17, 26).

The effects of circadian clock proteins on bone metabolism and osteogenesis have been extensively studied, while the conclusion remains controversial though. Chen et al. found that gene and protein levels of BMAL1 in BMSCs decreased during the aging process, suggesting the potential impact of BMAL1 in osteogenesis, and it was confirmed by subsequent studies (13, 18). Related studies have been carried out in mice as well. Mice deficient of Bmal1 show low bone mass phenotype, meanwhile increasing bone resorption (14, 27). It has been reported that bone resorption can also be regulated by BMAL1 (28). However, another report has reached a contradicted conclusion (15). More detailed research on bone mass regulation should be carried on in the near future as a result. Interestingly, Zhuo et al. demonstrated that BMAL1 along with PER2, another component circadian clock protein, might play a synergistically negative role in bone metabolism. Qian et al. also reported this opposite effect (29, 30). Though a whole set of genes, including BMAL1, Per2, and Npas2, all have been reported to add up to the basic biorhythm regulation, BMAL1 can still be regarded as one of most important genes and studied most, according to earlier investigations, which is the reason we chose to lay our eyes on BMAL1 in this study. Same as the results of Chen et al., we herein demonstrated that knockdown of BMAL1 in mouse BMSCs decreased the osteogenic differentiation ability (Figure 2). In addition, the results in this study confirmed that deficiency of BMAL1 also influenced the cell aging status of BMSCs (**Figure 1**). These results suggested that BMAL1 might have an influence on bone metabolism around dental implants due to its key function of BMSCs in osseointegration under a common microenvironment.

As for osseointegration, few studies have focused on the function of circadian clock proteins in dental implants so far. Mengatto et al. conducted whole genome microarray analyses to evaluate the total RNA around implants in rats and provided evidence that the circadian rhythm system was involved in the establishment of osseointegration (31). The mentioned circadian clock genes, including Bmal1, Per2, and Npas2, act together as the positive and negative arms of the negative feedback mechanism. NPAS2 was proven to facilitate osseointegration of titanium implants through a neuroskeletal mechanism (32). However, as far as we know, this study is the first on the effect of BMAL1 in osseointegration directly. During this study, our results confirmed that BMAL1 regulated osteogenesis around titanium implants. The ability of bone healing of mammals decreased in the aging process with deficiency of BMAL1 function (11, 13). Thus, the bone-to-implant contact was impaired in aged mice and the overexpression of BMAL1 reversed the osteogenesis ability to facilitate the fixation of implants.

Although we have found that the circadian clock component BMAL1 indeed facilitates osseointegration through a mouse model, there are several limitations. First of all, transfection efficiency of BMAL1 vector should be precisely calculated after applied in BMSCs of femur. Moreover, femurs arise from mesoderm embryologically, while alveolar bones where dental implants are placed in reality are from neural crest cells. Differences in the developmental origins lead to discrepancy in bone healing (33). Due to the difficulty in lentiviral vector injection in alveolar bones, implant models are merely conducted in femurs. Otherwise, osseointegration is regulated by a complex molecular network related to bone quality, the transient chondrogenic phase, the vitamin D axis, and the circadian rhythm (34). The molecular mechanism and whether the circadian clock component can influence the other aspects of osseointegration, such as angiogenesis, remain uncertain. As He et al. once proved that Wnt/β-catenin pathway was involved in the regulation of BMAL1 in bone marrow stromal cells (18), it should be considered in further studies. In this study, we use lentiviral vector to accomplish sustained BMAL1 overexpression around implants as it has been considered an effective transgene expression approach (35), while gene knockout mice can achieve more stable gene scavenging models. Thus, further studies with improved models may contribute to a deeper understanding about the effect of BMAL1 on titanium implants osseointegration.

To conclude, this study revealed that the circadian clock component BMAL1 might regulate aging-related impaired osteogenesis around titanium implants *in vivo*, which may be a result of reversing the senescence of BMSCs, and facilitate their osteogenesis ability. The BIC and relevant bone mass parameters are rescued through lentivirus transfection of BMAL1. The regulatory molecule network of osseointegration remains an attractive topic and the circadian clock system may play an essential role. Our results provide a specific sight of peri-implant osteogenesis regulation and further studies are needed.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

The animal study was reviewed and approved by the Ethics Committee of the West China Hospital of Stomatology.

Author contributions

SD and MQ contributed equally to the conception and design of the study and wrote the first draft of the manuscript. SD performed *in vivo* experiments, while MQ finished the *in vitro* part. PG organized the database. SD performed the statistical analysis. SD, MQ, PG, and ZT revised sections of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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Publisher's note

References

1. Savoldelli C, Bailleux S, Chamorey E, Vandersteen C, Lerhe B, Afota F. Impact of a new combined preoperative cleft assessment on dental implant success in patients with cleft and palate: a retrospective study. *BMC Oral Health*. (2022) 22(1):73. doi: 10.1186/s12903-022-02040-5

2. Mossey PA, Little J, Munger RG, Dixon MJ, Shaw WC. Cleft lip and palate. *Lancet*. (2009) 374(9703):1773–85. doi: 10.1016/S0140-6736(09)60695-4

3. Chen B, Zhang H. The study on the morphological changes of oropharynx in patients with complete unilateral cleft lip and palate after palatopharyngeal closure. *Front Neurosci*. (2022) 16:997057. doi: 10.3389/fnins.2022.997057

4. Perillo L, Vitale M, d'Apuzzo F, Isola G, Nucera R, Matarese G. Interdisciplinary approach for a patient with unilateral cleft lip and palate. *Am J Orthod Dentofacial Orthop*. (2018) 153(6):883–94. doi: 10.1016/j.ajodo.2016.12.035

5. Verdi Jr. FJ, Lanzi GL, Cohen SR, Powell R. Use of the Branemark implant in the cleft palate patient. *Cleft Palate Craniofac J*. (1991) 28(3):301–3, discussion 304. doi: 10.1597/1545-1569_1991_028_0301_cotspf_2.3.co_2

6. Cune MS, Meijer GJ, Koole R. Anterior tooth replacement with implants in grafted alveolar cleft sites: a case series. *Clin Oral Implants Res*. (2004) 15 (5):616–24. doi: 10.1111/j.1600-0501.2004.01052.x

7. de Barros Ferreira Jr. S, Esper LA, Sbrana MC, Ribeiro IW, de Almeida AL. Survival of dental implants in the cleft area—a retrospective study. *Cleft Palate Craniofac J*. (2010) 47(6):586–90. doi: 10.1597/08-155

8. Härtel J, Pögl C, Henkel KO, Gundlach KK. Dental implants in alveolar cleft patients: a retrospective study. *J Craniomaxillofac Surg*. (1999) 27(6):354–7. doi: 10.1054/jcms.2000.0096

9. Brånemark PI. Osseointegration and its experimental background. *J Prosthet Dent*. (1983) 50(3):399–410. doi: 10.1016/s0022-3913(83)80101-2

10. Terheyden H, Lang NP, Bierbaum S, Stadlinger B. Osseointegration—communication of cells. *Clin Oral Implants Res*. (2012) 23(10):1127–35. doi: 10.11/j.600-0501.2011.02327.x

11. Infante A, Rodríguez CI. Osteogenesis and aging: lessons from mesenchymal stem cells. *Stem Cell Res Ther*. (2018) 9(1):244. doi: 10.1186/s13287-018-0995-x

12. Singh L, Brennan TA, Russell E, Kim JH, Chen Q, Brad Johnson F, et al. Aging alters bone-fat reciprocity by shifting in vivo mesenchymal precursor cell fate towards an adipogenic lineage. *Bone*. (2016) 85:29–36. doi: 10.1016/j.bone.2016.01.014

13. Chen Y, Xu X, Tan Z, Ye C, Zhao Q, Chen Y. Age-related BMAL1 change affects mouse bone marrow stromal cell proliferation and osteo-differentiation potential. *Arch Med Sci*. (2012) 8(1):30–8. doi: 10.5114/aoms.2012.27277

14. Samsa WE, Vasanji A, Midura RJ, Kondratov RV. Deficiency of circadian clock protein BMAL1 in mice results in a low bone mass phenotype. *Bone*. (2016) 84:194–203. doi: 10.1016/j.bone.2016.01.006

15. Tsang K, Liu H, Yang Y, Charles JF, Ermann J. Defective circadian control in mesenchymal cells reduces adult bone mass in mice by promoting osteoclast function. *Bone*. (2019) 121:172–80. doi: 10.1016/j.bone.2019.01.016

16. Shearman LP, Sriram S, Weaver DR, Maywood ES, Chaves I, Zheng B, et al. Interacting molecular loops in the mammalian circadian clock. *Science*. (2000) 288 (5468):1013–9. doi: 10.126/science.288.5468.1013

17. Yang G, Chen L, Grant GR, Paschos G, Song WL, Musiek ES, et al. Timing of expression of the core clock gene Bmal1 influences its effects on aging and survival. *Sci Transl Med*. (2016) 8(324):324ra16. doi: 10.1126/scitranslmed.aad3305

18. He Y, Chen Y, Zhao Q, Tan Z. Roles of brain and muscle ARNT-like 1 and Wnt antagonist Dkk1 during osteogenesis of bone marrow stromal cells. *Cell Prolif*. (2013) 46(6):644–53. doi: 10.1111/cpr.12075

19. Li X, Liu N, Wang Y, Liu J, Shi H, Qu Z, et al. Brain and muscle aryl hydrocarbon receptor nuclear translocator-like protein-1 cooperates with glycogen synthase kinase-3β to regulate osteogenesis of bone-marrow mesenchymal stem cells in type 2 diabetes. *Mol Cell Endocrinol*. (2017) 440:93–105. doi: 10.1016/j.mce.2016.10.001

20. Xiang L, Ma L, Wei N, Wang T, Yao Q, Yang B, et al. Effect of lentiviral vector overexpression α-calcitonin gene-related peptide on titanium implant osseointegration in α-CGRP-deficient mice. *Bone*. (2017) 94:135–40. doi: 10.1016/j.bone.2015.08.009

21. Xue H, Guo Y, Zhang S, Xu T, Wen J, Kang N, et al. The role of USP34 in the fixation of titanium implants in murine models. *Eur J Oral Sci*. (2020) 128 (3):211–7. doi: 10.1111/eos.12696

22. Zhou C, Chen YQ, Zhu YH, Lin GF, Zhang LF, Liu XC, et al. Antiadipogenesis and osseointegration of strontium-doped implant surfaces. *J Dent Res*. (2019) 98(7):795–802. doi: 10.1177/0022034519850574

23. Howe MS, Keys W, Richards D. Long-term (10-year) dental implant survival: a systematic review and sensitivity meta-analysis. *J Dent*. (2019) 84:9–21. doi: 10.1016/j.jdent.2019.03.008

24. Marcheva B, Ramsey KM, Buhr ED, Kobayashi Y, Su H, Ko CH, et al. Disruption of the clock components CLOCK and BMAL1 leads to hypoinsulinaemia and diabetes. *Nature*. (2010) 466(7306):627–31. doi: 10.1038/nature09253

25. Janich P, Pascual G, Merlos-Suárez A, Batlle E, Ripperger J, Albrecht U, et al. The circadian molecular clock creates epidermal stem cell heterogeneity. *Nature*. (2011) 480(7376):209–14. doi: 10.1038/nature10649

26. Patel SA, Chaudhari A, Gupta R, Velingkaar N, Kondratov RV. Circadian clocks govern calorie restriction-mediated life span extension through BMAL1- and IGF-1-dependent mechanisms. *FASEB J*. (2016) 30(4):1634–42. doi: 10.096/fj.15-282475

27. Takarada T, Xu C, Ochi H, Nakazato R, Yamada D, Nakamura S, et al. Bone resorption is regulated by circadian clock in osteoblasts. *J Bone Miner Res*. (2017) 32(4):872–81. doi: 10.1002/jbmr.3053

28. Xu C, Ochi H, Fukuda T, Sato S, Sunamura S, Takarada T, et al. Circadian clock regulates bone resorption in mice. *J Bone Miner Res*. (2016) 31(7):1344–55. doi: 10.002/jbmr.2803

29. Zhuo H, Wang Y, Zhao Q. The interaction between Bmal1 and Per2 in mouse BMSC osteogenic differentiation. *Stem Cells Int*. (2018) 2018:3407821, eCollection 2018. doi: 10.1155/2018/3407821

30. Qian Z, Zhang Y, Kang X, Li H, Zhang Y, Jin X, et al. Postnatal conditional deletion of Bmal1 in osteoblasts enhances trabecular bone formation via increased BMP2 signals. *J Bone Miner Res*. (2020) 35(8):1481–93. doi: 10.002/jbmr.4017

31. Mengatto CM, Mussano F, Honda Y, Colwell CS, Nishimura I. Circadian rhythm and cartilage extracellular matrix genes in osseointegration: a genome-wide screening of implant failure by vitamin D deficiency. *PLoS One*. (2011) 6 (1):e15848. doi: 10.1371/journal.pone.0015848

32. Morinaga K, Sasaki H, Park S, Hokugo A, Okawa H, Tahara Y, et al. Neuronal PAS domain 2 (Npas2) facilitated osseointegration of titanium implant with rough surface through a neuroskeletal mechanism. *Biomaterials*. (2019) 192:62–74. doi: 10.1016/j.biomaterials.2018.11.003

33. Ichikawa Y, Watahiki J, Nampo T, Nose K, Yamamoto G, Irie T, et al. Differences in the developmental origins of the periosteum may influence bone healing. *J Periodontal Res*. (2015) 50(4):468–78. doi: 10.1111/jre.12229

34. Nishimura I. Genetic networks in osseointegration. *J Dent Res*. (2013) 92(12 Suppl):109S–18S. doi: 10.1177/0022034513504928

35. Perry C, Rayat A. Lentiviral vector bioprocessing. *Viruses*. (2021) 13(2):268. doi: 10.3390/v13020268

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Short-term surgical outcomes in patients with unilateral complete cleft lip and palate after presurgical nasoalveolar molding therapy: A three-dimensional anthropometric study

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Objective: This brief research report aimed to evaluate the short-term efficacy of presurgical nasoalveolar molding (PNAM) therapy on the nasolabial morphology three dimensionally in patients with non-syndromic complete unilateral cleft lip and palate (UCLP).
Methods: Thirty-six patients with non-syndromic complete unilateral complete cleft lip and palate were enrolled retrospectively and categorized into 2 groups: 18 patients who had received PNAM treatment (PNAM group) and 18 age-matched patients who have not receive PNAM treatment (no PNAM group) from 2017 to 2021. The average starting age for PNAM therapy was 18.33 days, and the average PNAM treatment duration was 99.08 days. Twelve nasolabial parameters were measured to compare the postsurgical outcomes of two groups.
Results: In PNAM groups, cleft width, vertical distance between double Crista philtri and columellar deviation were reduced compared to that in no PNAM group. And nostril height was larger than that in no PNAM group. The differences between two groups were statistically significant ($p < .05$). There were no statistical differences in columellar length, nostril width and bi-alar width between two groups. However, the nostril width on cleft side in PNAM group was decreased by an average of 1.1 mm.
Conclusion: Our result indicated that PNAM therapy decreased cleft width and vertical distance between Crista philtri. It also increased nasal symmetry by decreasing columellar deviation, increasing nostril height.

KEYWORDS
nasoalveolar molding (NAM), cleft lip and palate, anthropometry, nasal deformity, short time observation

Introduction

The difficulties of primary surgical treatment for unilateral complete cleft lip (UCLP) are the discrepancies and displacement of the nasomaxillary morphology, such as wide cleft gap and the displacement of alveolar segments. Presurgical nasoalveolar molding (PNAM), established by Grayson et al. (1), is a non-surgical method of reducing cleft width, aligning the alveolar segments and deforming nasal lower lateral cartilages to minimize the severity of cleft deformity before primary unilateral cleft lip repair and palatoplasty and consequently improving surgical outcomes. In the past few decades, there have been many reports documented favorable efficacy of PNAM in decreasing cleft avelo (2–5).

Precise imaging of craniofacial malformation is a crucial precondition for UCLP patients' treatment. The introduction of three-dimensional (3D) measurements such as stereophotogrammetry (6–9) and 3D laser scanning (10–13), facilitates the recording and assessment of CLP patients' dento-maxillofacial morphology compared to traditional direct anthropometric and two-dimensional measurement based on photographs. However, the 3D reconstruction of dento-maxillofacial profile might have distortion due to insufficient instrument precision, change in patient's facial expression and head movement etc. The profile deviation, stringent specification of the measuring device and high expense limit the promotion in clinical application. Another frequently used method is facial plaster casts. It is economic, accessible and guarantees the verisimilitude and accuracy of facial details. Therefore, the present study used dental plaster casts to quantify facial landmarks of infants with complete UCLP and retrospectively evaluate the short-term effect of PNAM therapy on nasolabial symmetry.

Materials and methods

Patients

Patient data were retrieved from the electronic records of the department of cleft lip and palate at West China Hospital of Stomatology, Sichuan University. 18 complete UCLP patients (11 boys, 7 girls) aged 3 to 6 months who received PNAM from November 2017 to November 2021 were extracted for the study. Besides, 18 age-matched complete UCLP patients (10 boys, 8 girls) who didn't undergo any non-surgical treatment were enrolled as control group. The participants were selected for inclusion in the present study based on the following criteria: (1) infants with non-syndromic complete UCLP; (2) no other co-existing craniofacial malformations; (3) first consultation during the neonatal period, (4) written consent of one or both parents for any clinical-surgical practice.

The average age of the patients upon commencing PNAM therapy was 18.33 days (range 2 to 32 days), and the average therapy duration was 99.08 days (range 65 to 126 days). The procedure of PNAM therapy was basically in accordance with the Grayson's technique (1). There were two main differences: first, nasal stent was added to the dental plate when the patients adapted to it (The infant only spent 7–14 days to completely adapt to the nasal stent) and then the nasal stent was adjusted weekly; second, the PNAM appliance was fixed in position with denture adhesive. A horizontal tape (3M Steri strips-1/4 Inch) was placed at the base of nose, stretching the lip segments toward each other. Artificial skin was applied to each cheek to avoid skin irritation created by adhesive tape (**Figure 1**).

All impressions were taken from participated infants under general anesthesia and the casts were fabricated with dental plaster. The bases of the facial casts were trimmed and adjusted to make the planes of all casts identical. All casts were marked with computerized random numbers for the subsequent blinded measurement. All PNAM therapy and casts were accomplished by the same author (C.Y). The protocol for the current study was reviewed and approved by the Institutional Review Board of West China Hospital of Stomatology, Sichuan University (No. WCHSIRB-D-2016–084R1).

Landmarks and measurement

The facial anatomical landmarks were identified on each cast (**Table 1**). The horizontal reference line was constructed

FIGURE 1
A study patient wearing the presurgical nasoalveolar molding (PNAM) appliance.

TABLE 1 The facial landmarks and descriptions.

Landmark	Description
Endocanthion right and left (Enr and Enl)	The inner commissure of palpebral fissures on right and left side
Alare right and left (Alr and All)	The lateral insertion of the nasal rim near the upper lip.
Subalare right and left (Sar and Sal)	The medial insertion of the nasal rim near the upper lip; the most caudal end of the nasolabial crease
Columella (C)	Most superior point on the midline of columella
Subnasale (Sn)	The Midpoint of columella base where borders of nasal septum and upper lip meet
Crista philtri right and left (Cphr and Cphl)	The top points of Cupid's bow on right and left side
Cheilion right and left (Chr and Chl)	The most lateral labial commissure point on the right and left
Labrale superius (Ls)	The midpoint of Cupid's bow

by connecting the endocanthion points (Enr-Enl). Clefts were standardized to the right side by "mirroring" the facial measurements of patients with left-sided clefts.

Twelve parameters were assessed to evaluate nasolabial symmetry: non-cleft/cleft lip height (Sal-Cphl; Sar-Cphr), non-cleft/cleft lip length (Cphl-Chl; Cphr-Chr), cleft width (Cphr-Cphr'), vertical distance between Crista philtri left and right (h), columellar deviation (CD), columellar length (Sn-C), non-cleft/cleft nostril width (Sn-sar;Sn-sal), cleft nostril height(H); bi-alar width(all-alr) (**Figure 2**).

The casts were measured directly using the electronic vernier caliper and protractor. The measurements were completed and repeated the three times by a single operator (S.L) on three different occasions.

Numerical data are presented as means ± SDs. Paired t-test was performed to compare the outcomes of PNAM group and no PNAM group. The statistical analyse was performed using IBM SPSS Statistics 20.0 (IBM Corp., Armonk, NY, USA). The p value <0.05 was considered as statistical significance.

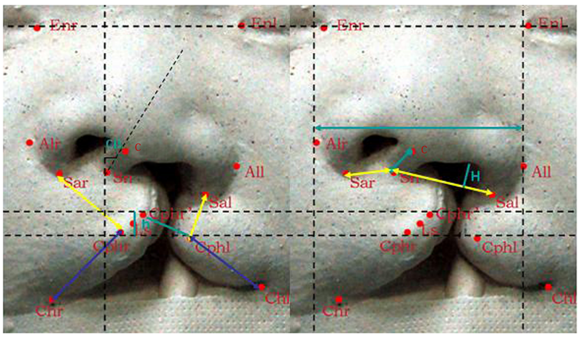

FIGURE 2
The horizontal reference line and facial anthropometric parameters. The horizontal reference line(Enr-Enl), non-cleft/cleft lip height (Sal-Cphl;Sar-Cphr),non-cleft/cleft lip length (Cphl-Chl;Cphr-Chr), cleft width (Cphr-Cphr'), vertical distance between double Crista philtri (h), columellar deviation (CD), columellar length (Sn-C), non-cleft/cleft nostril width (Sn-sar;Sn-sal), cleft nostril height(H); bi-alar width(All-Alr).

Results

All results are shown in **Table 2**. The cleft width reduced significantly ($p < 0.001$), resulting in better approximated lips. The vertical distance between Crista philtri demonstrated significant decrease in PNAM group ($p < 0.001$). However, lip height and lip length on both sides were not significantly different. In the assessment of nasal morphology, the PNAM group showed significant improvement in columellar deviation ($p < 0.001$). Columellar length and nostril width on cleft and non-cleft side did not show significant difference between two groups ($p = 0.167$, $p = 0.847$ and $p = 0.628$ respectively). The mean value of columellar length of PNAM group was higher compared to no PNAM group. The mean value of nostril width on non-cleft side was almost identical between the two groups while the mean value of nostril width on cleft side in the PNAM group was decreased by an average of 1.1 mm compared to no PNAM group. The cleft nostril height was larger in PNAM group, and the difference between two groups was statistically significant ($p < 0.001$). The mean value of bi-alar width exhibited non-statistically significance between two groups.

Discussion

The prime aim of presurgical treatment in patients with UCLP is rehabilitating the deformed dento-maxillofacial

TABLE 2 Comparison of the nasal symmetry between PNMD group and np PNMD group.

Measurements	Mean ± Standard Deviation (mm)		p value
	No PNAM group	PNAM group	
Sal-cphl	8.52 ± 0.96	8.26 ± 2.02	0.694
Sar-cphr	10.92 ± 1.18	10.98 ± 1.02	0.775
Chl-Cphl	13.12 ± 1.44	13.28 ± 1.83.	0.847
Chr-Cphr	16.01 ± 2.14	18.83 ± 2.31	0.628
Cphl-Chpr′	15.73 ± 2.97	11.14 ± 1.53	0.038[a]
h	3.68 ± 1.26	2.58 ± 0.42	<0.001[a]
CD	49.30 ± 10.0	30.73 ± 7.24	<0.001[a]
Sn-C	4.31 ± 0.62	3.92 ± 0.68	0.167
Sn-Sar	10.68 ± 0.37	10.34 ± 1.24	0.715
Sn-Sal	20.35 ± 2.68	18.46 ± 2.69	0.088
H	3.02 ± 1.10	4.80 ± 0.83	<0.001[a]
All-Alr	33.38 ± 2.94	32.40 ± 2.59	0.418

All results based on paired sample t tests.
[a]Measurements with [a] indicate a statistical significance ($p < 0.05$).

components to allow for better surgical outcomes and reduced need for secondary revisions (14, 15). The present study was conducted to assess the efficacy of PNAM on short-term nasolabial symmetry before primary UCLP repair and the results demonstrated improvement in cleft width, vertical distance between double Crista philtri, columellar deviation and nostril height on cleft side in PNAM-treated patients. The lip taping during PNAM therapy approximated the lip reduction cleft width segments, improved lip symmetry and centralized the columella. The nasal stent contributed to the significant increase of nostril height on cleft side by reshaping the collapse alar cartilage. The columellar length, nostril width on both sides and bi-alar width showed no statistical difference in the present study. Though the current study demonstrated that PNAM group had improved nasolabial outcomes after the procedure in comparison with no PNAM group and the short-term effectiveness has been corroborated by numerous studies (16, 17), the post-surgical outcomes and long-term sustenance of facial symmetry have yet to be determined (8, 18, 19).

In previous studies, the most commonly used method for facial morphological analyses is two-dimensional (2D) photography (2, 18, 20, 21). The 2D photography offers the benefits of non-invasive, simple and quick facial morphology capturing. However, the photographs provide limited information about the 3D anatomical structure (22). The technique of plaster cast measurements in the current study is an easily reproducible and safe method for recording and evaluation of CLP patients' 3D facial morphology. This method also has some drawbacks, including errors during manual measurement and needs for storage space. Other 3D measurements such as stereophotogrammetry and laser scanning have been reported to be employed in PNAM therapy to acquire digitalized patients' dento-maxillofacial structures and customize templates (23–25). Nevertheless, the equipment was not available for many CLP centers. To further validate the efficacy of PNAM, studies with large sample size and long-term follow-up with the application of 3D analysis were highly recommended.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board of West China Hospital of Stomatology, Sichuan University (No. WCHSIRBD-2016-084R1). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

JY, SZ, NH and CY designed, wrote, and revised the manuscript. BS and QZ revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Grayson BH, Santiago PE, Brecht LE, Cutting CB. Presurgical nasoalveolar molding in infants with cleft lip and palate. *Cleft Palate Craniofac J*. (1999) 36(6):486–98. doi: 10.1597/1545-1569_1999_036_0486_pnmiiw_2.3.co_2

2. Liang Z, Yao J, Chen PKT, Zheng C, Yang J. Effect of presurgical nasoalveolar molding on nasal symmetry in unilateral complete cleft lip/palate patients after primary cheiloplasty without concomitant nasal cartilage dissection: early childhood evaluation. *Cleft Palate Craniofac J*. (2018) 55(7):935–40. doi: 10.1597/14-296

3. Kinouchi N, Horiuchi S, Yasue A, Kuroda Y, Kawai N, Watanabe K, et al. Effectiveness of presurgical nasoalveolar molding therapy on unilateral cleft lip nasal deformity. *Saudi Med J*. (2018) 39(2):169–78. doi: 10.15537/smj.2018.2.21020

4. Attiguppe PR, Karuna YM, Yavagal C, Naik SV, Deepak BM, Maganti R, et al. Presurgical nasoalveolar molding: a boon to facilitate the surgical repair in infants with cleft lip and palate. *Contemp Clin Dent*. (2016) 7(4):569–73. doi: 10.4103/0976-237X.194104

5. Mandwe RS, Puri S, Shingane S, Pawar G, Kolhe VR, Alsi A. Presurgical nasoalveolar remodeling - an experience in the journey of cleft lip and palate. *Clin Cosmet Investig Dent*. (2015) 7:1–7. doi: 10.2147/CCIDE.S70823

6. Al-Rudainy D, Ju X, Stanton S, Mehendale FV, Ayoub A. Assessment of regional asymmetry of the face before and after surgical correction of unilateral cleft lip. *J Craniomaxillofac Surg*. (2018) 46(6):974–8. doi: 10.1016/j.jcms.2018.03.023

7. Rezende Pucciarelli MG, de Lima Toyoshima GH, Marchini Oliveira T, Marques Honorio H, Sforza C, Soares S. Assessment of dental arch stability after orthodontic treatment and oral rehabilitation in complete unilateral cleft lip and palate and non-clefts patients using 3D stereophotogrammetry. *BMC Oral Health*. (2020) 20(1):154. doi: 10.1186/s12903-020-01143-1

8. Mancini L, Gibson TL, Grayson BH, Flores RL, Staffenberg D, Shetye PR. Three-Dimensional soft tissue nasal changes after nasoalveolar molding and primary cheilorhinoplasty in infants with unilateral cleft lip and palate. *Cleft Palate Craniofac J*. (2019) 56(1):31–8. doi: 10.1177/1055665618771427

9. Kimura N, Nozoe E, Okawachi T, Ishihata K, Fuchigami T, Nakamura N. Three-dimensional analyses of nasolabial forms and upper lip surface symmetry after primary lip repair in patients with complete unilateral cleft lip and palate. *J Cranio-Maxillofac Surg*. (2019) 47(2):245–54. doi: 10.1016/j.jcms.2018.11.035

10. Zheng J, He H, Kuang W, Yuan W. Novel three-dimensional coordinate system to analyze alveolar molding effects of Pre-surgical nasoalveolar molding on infants with non-syndromic unilateral cleft lip and palate. *J Craniofac Surg*. (2020) 31(3):653–7. doi: 10.1097/SCS.0000000000006148

11. Fuchigami T, Kimura N, Kibe T, Tezuka M, Amir MS, Suga H, et al. Effects of pre-surgical nasoalveolar moulding on maxillary arch and nasal form in unilateral cleft lip and palate before lip surgery. *Orthod Craniofac Res*. (2017) 20(4):209–15. doi: 10.1111/ocr.12199

12. Fuchigami T, Kimura N, Tezuka M, Kibe T, Subhan Amir M, Tsujii T, et al. Comparison of short-term effects of presurgical nasoalveolar molding and Hotz's Plate on maxillary arch form in unilateral cleft lip and palate. *J Oral Maxillofac Surg Med Pathol*. (2019) 31(1):25–30. doi: 10.1016/j.ajoms.2018.08.008

13. Zhang M, Hattori M, Akiyama M, Elbashti ME, Liu R, Sumita YI. Three-dimensional evaluation of the dental arch in cleft lip and palate after prosthetic treatment. *J Prosthodont Res*. (2022). doi: 10.2186/jpr.JPR_D_21_00033

14. Rubin MS, Clouston S, Ahmed MM, Lowe KM, Shetye PR, Broder HL, et al. Assessment of presurgical clefts and predicted surgical outcome in patients treated with and without nasoalveolar molding. *J Craniofac Surg*. (2015) 26(1):75–9. doi: 10.1097/SCS.0000000000001233

15. Patel PA, Rubin MS, Clouston S, Lalezaradeh F, Brecht LE, Cutting CB, et al. Comparative study of early secondary nasal revisions and costs in patients with clefts treated with and without nasoalveolar molding. *J Craniofac Surg*. (2015) 26(4):1229–33. doi: 10.1097/SCS.0000000000001729

16. Zuhaib M, Bonanthaya K, Parmar R, Shetty PN, Sharma P. Presurgical nasoalveolar moulding in unilateral cleft lip and palate. *Indian J Plast Surg*. (2016) 49(1):42–52. doi: 10.4103/0970-0358.182235

17. Chou PY, Hallac RR, Ajiwe T, Xie XJ, Liao YF, Kane AA, et al. The role of nasoalveolar molding: a 3D prospective analysis. *Sci Rep*. (2017) 7(1):9901. doi: 10.1038/s41598-017-10435-6

18. Nayak T, Bonanthaya K, Parmar R, Shetty PN. Long-Term comparison of the aesthetic outcomes between nasoalveolar molding- and non-nasoalveolar molding-treated patients with unilateral cleft lip and palate. *Plast Reconstr Surg*. (2021) 148(5):775e–84e. doi: 10.1097/PRS.0000000000008463

19. Bhutiani N, Tripathi T, Verma M, Bhandari PS, Rai P. Assessment of treatment outcome of presurgical nasoalveolar molding in patients with cleft lip and palate and its postsurgical stability. *Cleft Palate Craniofac J*. (2020) 57(6):700–6. doi: 10.1177/1055665620906293

20. Zhang S, Yang C, Wu M, Yin J, Zeng N, Shi B, et al. Application of a novel nasal clip for nostril retention after primary unilateral cleft rhinoplasty. *Cleft Palate Craniofac J*. (2022) 10556656221083812. doi: 10.1177/10556656221083812

21. Zhang S, Wu M, Chen J, Yin J, Sakran KA, Wang Y, et al. The necessity of nostril retention application after secondary unilateral cleft rhinoplasty. *Laryngoscope*. (2022). doi: 10.1002/lary.30451

22. Shi B, Huang H. Computational technology for nasal cartilage-related clinical research and application. *Int J Oral Sci*. (2020) 12(1):21. doi: 10.1038/s41368-020-00089-y

23. Ahsanuddin S, Ahmed M, Slowikowski L, Heitzler J. Recent advances in nasoalveolar molding therapy using 3D technology. *Craniomaxillofac Trauma Reconstr*. (2021) 15(4):387–96. doi: 10.1177/19433875211044622

24. Nur Yilmaz RB, Germec Cakan D. Nasolabial morphology following nasoalveolar molding in infants with unilateral cleft lip and palate. *J Craniofac Surg*. (2018) 29(4):1012–6. doi: 10.1097/SCS.0000000000004427

25. Shen C, Yao CA, Magee 3rd W, Chai G, Zhang Y. Presurgical nasoalveolar molding for cleft lip and palate: the application of digitally designed molds. *Plast Reconstr Surg*. (2015) 135(6):1007e–15e. doi: 10.1097/PRS.0000000000001286

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Dental caries and periodontitis risk factors in cleft lip and palate patients

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Cleft lip and palate (CLP) is the most common congenital facial malformation and has a significant developmental, physical, and psychological impact on those with the deformity and their families. Risk factors contributing to CLP may conclude as genetic factors and environmental factors. The anatomical and morphological abnormalities related to CLP are favorable for dental plaque accumulation on the tooth surface. Therefore, patients with CLP undergo poorer oral hygiene and higher susceptibility to dental caries and periodontitis. In this review, we aim to conclude and update probable causes underlying the association between CLP and poor oral health and provide novel ideas of targeted early prevention for such oral diseases.

KEYWORDS

cleft lip and palate, oral hygiene, dental caries, periodontitis, alveolar bone deformity, tooth deformity, microbial dysbiosis

Introduction

During embryogenesis, oral and maxillofacial areas are developed from frontonasal process, the paired lateral and medial nasal processes, and the paired maxillary processes. Cleft lip (CL) and cleft palate (CP) are two kinds of congenital malformation resulting from unsuccessful embryonic facial fusion processes and usually co-occur in the form of complete unilateral (UCLP) or bilateral (BCLP) cleft lip and palate (1). Based on their association with specific malformative patterns or their presence as isolated defects, CL/P can be classified as syndromic (SCLP) and non-syndromic, respectively (NSCLP) (2). Cleft lip and palate (CLP) affects roughly 10 million people worldwide and reduces quality of life, especially children and adolescents (3). Risk factors for facial cleft can be classified into four categories: genetic factors, pharmaceutical and physical factors, maternal metabolic or nutritional imbalances, maternal infection or injury (4) (**Figure 1**).

Children born with head and jaw deformations that affect the development and function of teeth and jaws are generally more susceptible to poor oral health (5). Dental caries and periodontitis are two most common infection-driven diseases in oral cavity prevalent in individuals with poor oral hygiene habits. Although the etiologies of caries and periodontitis are reported independent, with dental decay induced by supragingival plaque while periodontal infections by subgingival plaque (6), disruption of dynamic ecologic equilibrium in oral microbial biofilms can both lead to

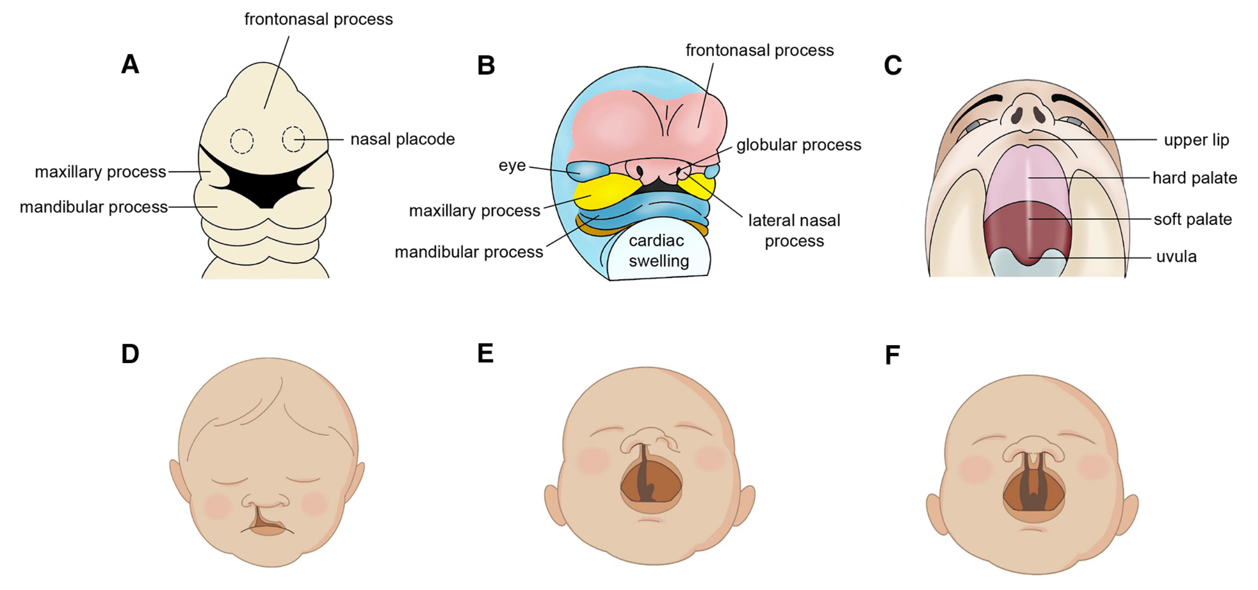

FIGURE 1
Embryonic development in oral and maxillofacial region. (A) embryonic week 4. (B) embryonic week 6. (C) developed lip and palate. Cleft phenotypes (D) Normal cleft lip. (E) unilateral cleft lip and palate (UCLP) and (F) bilateral cleft lip and palate (BCLP).

the onset of these two inflammatory diseases (7). Biofilms on tooth surface will produce acids in the presence of dietary carbohydrates. These acids demineralize the enamel and eventually allow cariogenic bacteria to invade the enamel, dentin and even the pulp (8). Subgingival biofilm destruct the structural integrity of the junctional epithelium, consequently inducing inflammation and thus leading to pocket formation (9).

Cleft lip and palate affect not only patients' appearance, but also disrupts the continuity of maxillary arch, affects tooth structure, shape, number, eruption and maxillofacial growth. Due to the adverse change of the anatomical and morphological alterations, patients with CLP and alveolar cleft are more likely to accumulate dental plaque in oral cavity. Thus, studies have reported that those children presented a higher prevalence of extensive dental caries and periodontitis compared with general population (10–12). The objective of the review is to summarize and update the body of evidence on the causes underlying the association between CLP and poor oral hygiene.

Dental caries and periodontitis prevalence of children with CLP

Various epidemiological studies have demonstrated that there is an association between alveolar cleft and poorer oral health. A recent study found that among the children with cleft the prevalence of dental caries was found to be 71.9% (13). When comparing tooth caries and periodontal status, several studies showed that DMFT (Decayed, Missing, and Filled Teeth) and dmft scores were significantly higher in the control group without CLP, while plaque and gingiva indices such as plaque index and the gingival bleeding index were higher in CLP group than the controls (14–17). Different types of CLP seem to be quite diverged. Hazza'a et al. carried out a study and concluded that bilateral CLP experienced more dental caries than unilateral CLP patients, whereas only plaque accumulation was significantly higher in the BCLP patients (18). Howe et al. conducted a case-control study and recruited 3,326 patients with their relatives and confirmed the genetic factor is highly significant risk factor for children with CLP who are more susceptible to tooth decay (10). Evaluation of oral biofilm in children and adolescent revealed that the level of periodontal pathogens, including the most periodontopathic bacteria *Actinobacillus actinomycetemcomitans*, *Porphyromonas gingivalis*, and *Tannerella forsythia*, were statistically higher in the subgingival biofilms of the CLP group, thereby inducing more severe periodontitis (11, 19). Early-stage intervention such as early surgical repair is frequently performed within the first 1 to 2 years of life, which is of vital importance in team approach to cleft lip and palate (20). While fistulas following cleft palate repair may impair hygiene and occur in up to 35 percent of cases (21). Fritz et al. compared the oral health between patients with or without fistula after surgical correction of cleft palate and demonstrated a significantly lower oral health score in the fistula group, indicating poorer oral hygiene (22). Genes involved in the structure and development of congenital maxillofacial deformity may provide a basis for the link between CLP and dental caries. Mutations in EDARADD (ectodysplasin-A receptor-associated adapter protein) related with ectodermal

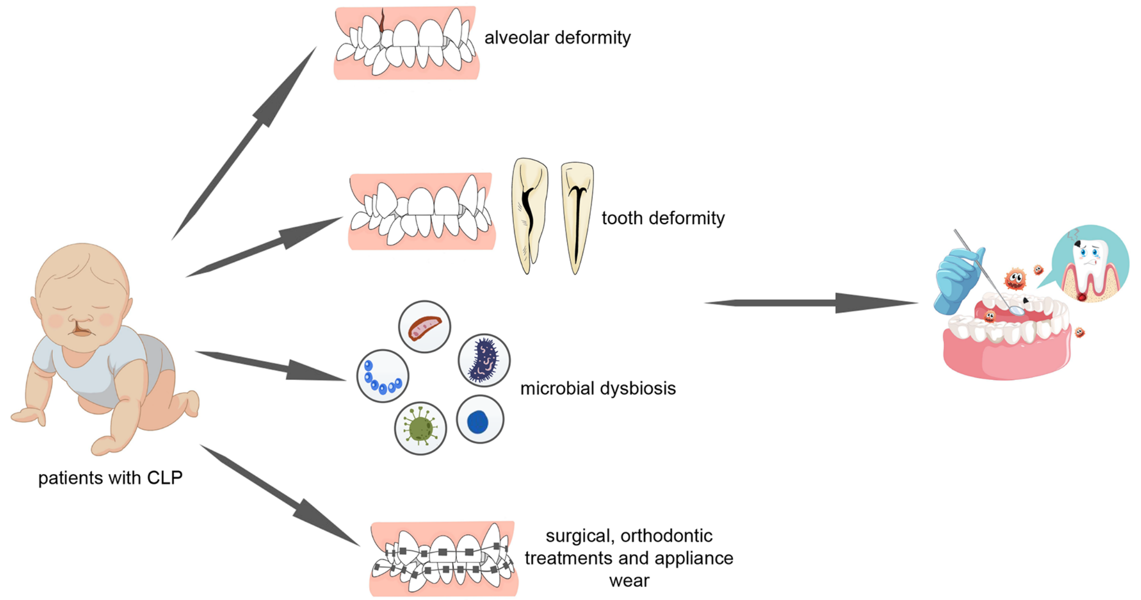

FIGURE 2
Patients with cleft lip and palate undergo poorer oral hygiene as a result of alveolar deformity, tooth deformity, microbial dysbiosis, surgical repair, orthodontic treatment and appliance wear.

dysplasia is likely to cause abnormal development of teeth, skin, hair, nails, and sweat glands (23). Therefore, the prevalence of dental caries was higher in syndromic cleft patients compared with those without a syndrome in northern Finland based on the outcomes of the current study (24).

Collectively, these studies allow us to confirm the hypothesis that children with cleft lip and palate have a significantly increased risk of dental caries and severe periodontal status as compared with the general population. Further in the text, we will explore the mechanisms that may contribute to such phenomenon (**Figure 2**).

Mechanisms linking dental caries and CLP

Tooth deformity

Children with oral clefts have a higher susceptibility for dental anomalies account for genetic and environmental factors. Numerous studies have demonstrated that dental anomalies are seen in a significant percentage of individuals with CLP (25–27). Cleft candidate genes such as MSX1, PAX9, IRF6, ANKS6 were confirmed associated with dental anomalies in individuals with CLP (28, 29). Methionine synthase gene responsible for methionine and homocysteine production may be associated with non-syndromic cleft lip and palate as well as dental caries (30). The structural deficiencies of embryonic development leads to microdontia, multiple missing teeth, ectopic teeth; supernumerary teeth; enamel and dentin malformation (27). Enamel hypoplasia often present with problems of discoloration and aesthetics, tooth sensitivity, reduced acid resistance, wear and erosion (31). Chapple et al. showed that developmental defects of enamel became more prevalent with age, with prevalence of 56% of 4-year-olds and 100% of 12-year-olds in patients with CLP (32). Kulas et al. carried out a case-control study and observed enamel color changes of permanent teeth three times more often in CLP children (33). While another research showed that there was no significant difference ($P > 0.05$) in the prevalence of development defects involving enamel among children with and without cleft (13). The rough surface attenuates acid resistant capacity of tooth and provides a critical niche for cariogenic bacteria to colonize. In addition, maxillary malformation, high incidence of supernumerary teeth and malposition of teeth result in crowding and dental malocclusion (34) which limits the use of toothbrush and antiseptic mouthwash and the natural cleaning of teeth by the tongue and saliva (35). Furthermore, tooth morphologic abnormalities like dens invaginatus also provide a favorable living environment for bacteria and fungi, which might be related to the pathogenesis and progression of dental caries (36, 37).

Cariogenic microbial dysbiosis

Orofacial cleft affects the structures and functions of oral cavities is closely related to potentially harmful changes in the composition and activities of the oral microbiota (referred to as oral microbiota dysbiosis) (38). Some studies have demonstrated the fact that children with cleft may exhibit higher level of *Streptococcus mutans* (*S. mutans*), *Lactobacillus* and *Candida albicans* (*C. albicans*) in their saliva (39–41), which are the most common cariogenic microorganisms (42, 43). In a study determined *S. mutans* and *Lactobacilli* prevalence in children with CLP, *S. mutans* was detected in the saliva of 45% of the children and *Lactobacillus* in 16% with *S. mutans* in 48% of the plaque samples and *Lactobacilli* in 8% (44). A more recent study has collated and analyzed microorganisms in saliva of 80 subjects with CLP and 144 subjects without CLP using checkerboard DNA-DNA hybridisation technique. Although no statistically significance in salivary microbial profile was observed between two groups, low level of species diversity could provide us with microbiota dysbiosis in oral cavities of children with CLP (45). Current mechanistic study in Irf6 cKO animal models confirm that caries incidence/severity and bacterial load was increased in gene knockout mice. They found the number of total bacterial and *S. mutans* colony forming units was significantly higher in Irf6 cKO mice compared with mice of wildtype (46). Lastly, Rawashdeh et al. detected colonization rate of *Candida* was higher in patients with cleft than that in control group (47). However, the high level of *C. albicans* colonization in oral cavities of CLP patients is often related to denture or orthodontic appliance wear, the association between *C. albicans* colonization and CLP itself needs to be further exploration (48).

Orthodontic treatments and appliance wear

Treatment of children and adolescents with CLP needs an organized team approach to provide optimal results. Orthodontic appliances have been linked to a higher caries experience (33). Fixed orthodontic appliances (FOAs) and dental prosthesis wear before or after surgical repair of CLP patients provides blind spots and reduces the effectiveness of saliva self-cleaning function (49). FOAs and denture base increases the area of plaque retention and makes it difficult for patients to maintain proper oral hygiene. The composition of dental plaque would change, leading to an increase in microbial population (50, 51), especially cariogenic bacteria *Streptococcus* and *Lactobacillus* which can lead to dental caries in the already susceptible mouths of individuals with CLP (52). van Loveren et al. carried out showed a comparative study and found that children performing early-stage preoperative orthopedics such as wearing acrylic plate in order to obturate the cleft were colonized earlier with *S. mutans* and *Lactobacillus* compared to non-plate oral cleft children. And the level of *S. mutans* increased with age (53). A meta-analysis that combined 39 studies oral prostheses such as dentures/palatal obturators and FOAs may directly affect the growth of Candida in the oral cavity (48). Additionally, patients wearing such devices are more likely to eat soft food in order not to destroy orthodontic appliances, which may lead to food particles accumulation over tooth surface, and increase the susceptibility of dental caries.

Mechanisms linking periodontitis and CLP

Alveolar bone deformity

Alveolar bone defect, maxillary deformity and deformed dental arch can always be seen in CLP patients (54). CLP defects disrupt the continuity of maxillary dental arch. Study found that poor oral hygiene was found in all CLP patients, while the periodontal disease of patients with cleft lip, palate and alveolar cleft were more severe and might underwent more periodontal tissue destruction compared to patients with cleft palate only (55, 56). Huynh-Ba et al. carried out a 25-year comparative study and concluded that alveolar cleft sites were likely to have more periodontal tissue destruction, patients with orofacial cleft had higher levels of plaque and tended to lose more periodontal attachment at cleft site (57). A related study with 75 complete unilateral CLP patients design showed increased plaque index of teeth in the cleft region compared with teeth on the contralateral non-cleft side (58). Nevertheless, some other studies observed no statistically significance between different type of cleft (11, 47, 59), which need further exploration for lager sample sizes. Additionally, due to vestibule malformation in some CLP patients, the oppression of gingiva near cleft sites may influence oral hygiene, then adversely exacerbate mucogingival and periodontal status at discontinuous dental arches (47).

Tooth deformity

CLP patients are born with a wide variety of dental anomalies, which could not only increase the susceptibility to dental caries, but also adversely affect periodontal status. Hypoplasia teeth were seen in 30.8% CLP subjects in a retrospective review (60). Crowded teeth favor the accumulation of dental plaque and make the removal difficult for CLP patients. In addition, dens invaginatus such as radicular lingual groove always found in maxillary lateral incisor has higher prevalence in patients with CLP (37), it creates a pathological dental pocket. Such a pocket resulted from an infolding of the enamel into dentine destroys the connection between periodontal tissue and cementum and allows bacteria propagate within, which can't be easily removed (26, 61, 62).

Periodontal microbial dysbiosis

Periodontitis is a multifactorial inflammatory disease caused by microorganisms accumulating in dental plaques below the gingiva (63) and the initiation of periodontal diseases can be primarily summed up as commensal oral microbial dysbiosis (64). In the current literature, CLP patients have been reported different in microorganism profile (65). Early studies identified *Porphyromonas gingivalis*, *Actinobacillus actinomycetemcomitans* and *Tannerella forsythia* as causative agents in periodontal disease (66). Passinato et al. sampled dental plaque of individuals with or without CLP for subgingival microbiota analysis, they found higher level of those three periodontal pathogenic bacteria in the subgingival dental plaque of the CLP group, who underwent more severe gingivitis and periodontitis compared with control group (11). While Quirynene et al. did not find any significant differences of bacteria, neither in the proportion of aerobic and anaerobic bacteria among different sites (58). A more recent study described the subgingival microbial profile of children and adolescents with cleft and suggested higher relative proportion of Gram-negative anaerobic bacteria in teeth near the cleft compared with the control group (19). When comparing oral microbiota of infant with CLP and soft cleft palate (CSP), Machorowska et al. detected formation of the microbiota in individuals with CLP differed from that in CSP group, and the bacterial microenvironment was more pathogenic of patients with CLP, which is consistent with another comparative study of Tuna et al. (67). Such phenomenon could be explained by the communication between oral and nasal cavities and the transmission of bacteria from nasal cavity to oral cavity in CLP group (41).

When oral microbial dysbiosis takes place, pathogenic bacteria in oral cavity interacts with host immune system and induces inflammation and thus increases the risk of periodontal diseases. Taken as a whole, compared with individuals without CLP, periodonitits-related bacteria are more likely enriched in patients with CLP, which result in higher level of bacteremia and endotoxemia, consequently aggravating periodontitis.

Surgical and orthodontic treatments

Children affected by CLP need multidisciplinary care from birth to adulthood and treatment of children and adolescents with CLP needs an organized team approach to provide optimal results. The early-stage surgical repair of CLP is central to current CLP team-approached treatment. However, some related technologies are still in their infancy and need further improvement and optimization (68). Some postoperative complications such as hypoplastic maxilla, concaved mid-face, deformed dental arch and oronasal fistula are common and difficult to completely circumvent after surgery (54, 69). Oronasal fistula occurs because of the poor wound healing after surgical repair and the overall incidence varied greatly from 0 to 77.8% (21). Fistula may cause nasal air escape, difficulty with pronunciation, food or liquid regurgitation, all of which may lead to communication between nasal and oral cavities and require repair (70). However, Karim et al. obtained a lower fistula rate using a modified palatoplasty technique (71). Such complications are likely to affect oral hygiene, promote dental plaque adherence to the teeth and influence periodontal health due to the patient's difficulty in tooth brushing around the fistula site. In addition, residual scar tissues after surgical repair constantly pull on their surrounding gingiva and could result in gingival recession along with speaking and swallowing, and thus make it easier for plaque accumulation (72). Notably, besides surgical procedures, combination of preoperative and postoperative orthodontic treatment play an indispensable role in team-approached treatment of CLP (73). Excessive orthodontic force may induce localized inflammatory responses and exacerbate the loss of periodontal attachment (55).

Dental caries and periodontitis treatment effect of patients with CLP

Based on the ideas presented above, we can easily conclude that proper oral hygiene is difficult for many reasons, including anatomic factors, developmental factors, medical interventions, fear of pain, bleeding and soft tissue damage during toothbrushing near cleft site. Therefore, early dental interventions are necessary. Rivkin et al. found and stated that a regular brush may not be effective in the hygiene of the cleft area, the use of a small-sized toothbrush along with an interspace brush is efficient in some situations to improve oral hygiene of the patients with CLP mainly because the special toothbrush made it easier to reach interdental spaces (74).In other cases, selection of toothpastes, mouth rinses and use of fluoride products under the guidance of dentists could be helpful for improving oral hygiene (10, 75, 76). However, some studies found that there was no significant decrease of periodontal-related indices between CLP children with or without preventive dental care, suggesting nothing is more prior and effective than toothbrushing to remove dental plaque (77, 78). Novel biomaterials such as nanoparticulate cfDNA scavenger G3@SeHANs shows the therapeutic potential in periodontitis which is expected to be useful in CLP-related oral diseases and need to be further studied (79, 80).

Summary

Given that the present state of knowledge suggests that children with CLP may have a greater risk factor for poor oral health than the general population. Risk factors include those related to the cleft itself and/or some complications of secondary surgical repair.

In healthy state, there is a well-balanced equilibrium between bacteria and the host. Maxillary bone or tooth malformation, bad dietary habits, incorrected toothbrushing technique of CLP patients may result in destroying the equilibrium (81), thereby increasing the susceptibility to periodontitis and dental caries. Dental caries and periodontitis are driven by a variety of pathogenic microorganism (7). However, much current studies have been limited to several bacteria or fungi detection. Further studies need to be carried out to include more kinds of microbial and compare microbiota profile between patients with or without CLP, even between different types of clefts.

In summary, poor oral hygiene-related dental caries and periodontitis are unfavorable for oral function, aesthetics and self-confidence of CLP patients. Although rehabilitation and some quality of life (QOL) instruments is possible with good quality care (82), orofacial clefts inevitably impose a burden to the individual, the family, and society. Therefore, families with CLP children are likely to participate in and strictly adhere to more health care programs and related services (83). Under such circumstances, parents of children with CLP should raise their awareness of oral health and receive preventive dental care as early as possible, which may reduce the risk of dental caries and periodontitis in the future.

Author contributions

Q.W, Z.L, and Y.Z contributed to the writing of the manuscript. X.P and X.Z contributed to the conceptualization, design, editing of the manuscript and supervised the project. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Kožejová Jaklová L, Hoffmannová E, Dupej J, Borský J, Jurovčík M, Černý M, et al. Palatal growth changes in newborns with unilateral and bilateral cleft lip and palate from birth until 12 months after early neonatal cheiloplasty using morphometric assessment. *Clin Oral Investig.* (2021) 25(6):3809–21. doi: 10.1007/s00784-020-03711-9

2. Mossey PA, Little J, Munger RG, Dixon MJ, Shaw WC. Cleft lip and palate. *Lancet.* (2009) 374(9703):1773–85. doi: 10.1016/S0140-6736(09)60695-4

3. Sandy J, Davies A, Humphries K, Ireland T, Wren Y. Cleft lip and palate: care configuration, national registration, and research strategies. *J World Fed Orthod.* (2020) 9(3s):S40–s4. doi: 10.1016/j.ejwf.2020.09.003

4. Seifeldin SA. Is alveolar cleft reconstruction still controversial? (review of literature). *Saudi Dent J.* (2016) 28(1):3–11. doi: 10.1016/j.sdentj.2015.01.006

5. Cheng LL, Moor SL, Ho CT. Predisposing factors to dental caries in children with cleft lip and palate: a review and strategies for early prevention. *Cleft Palate Craniofac J.* (2007) 44(1):67–72. doi: 10.1597/05-112

6. Loesche W. Dental caries and periodontitis: contrasting two infections that have medical implications. *Infect Dis Clin North Am.* (2007) 21(2):471–502. vii. doi: 10.1016/j.idc.2007.03.006

7. Sanz M, Beighton D, Curtis MA, Cury JA, Dige I, Dommisch H, et al. Role of microbial biofilms in the maintenance of oral health and in the development of dental caries and periodontal diseases. Consensus report of group 1 of the joint EFP/ORCA workshop on the boundaries between caries and periodontal disease. *J Clin Periodontol.* (2017) 44(Suppl 18):S5–s11. doi: 10.1111/jcpe.12682

8. Hujoel PP, Hujoel MLA, Kotsakis GA. Personal oral hygiene and dental caries: a systematic review of randomised controlled trials. *Gerodontology.* (2018) 35(4):282–9. doi: 10.1111/ger.12331

9. Bosshardt DD. The periodontal pocket: pathogenesis, histopathology and consequences. *Periodontol 2000.* (2018) 76(1):43–50. doi: 10.1111/prd.12153

10. Howe BJ, Cooper ME, Wehby GL, Resick JM, Nidey NL, Valencia-Ramirez LC, et al. Dental decay phenotype in nonsyndromic orofacial clefting. *J Dent Res.* (2017) 96(10):1106–14. doi: 10.1177/0022034517709961

11. Passinato Gheller SA, Porto AN, Borba AM, Veiga KA, Aranha AMF. Periodontal findings in children and adolescents with cleft lip and/or palate: a case-control study. *Pediatr Dent.* (2021) 43(2):133–9.

12. Worth V, Perry R, Ireland T, Wills AK, Sandy J, Ness A. Are people with an orofacial cleft at a higher risk of dental caries? A systematic review and meta-analysis. *Br Dent J.* (2017) 223(1):37–47. doi: 10.1038/sj.bdj.2017.581

13. Chopra A, Lakhanpal M, Rao NC, Gupta N, Vashisth S. Oral health in 4-6 years children with cleft lip/palate: a case control study. *N Am J Med Sci.* (2014) 6(6):266–9. doi: 10.4103/1947-2714.134371

14. Rocha MO, Oliveira DD, Costa FO, Pires LR, Diniz AR, Soares RV. Plaque index and gingival index during rapid maxillary expansion of patients with unilateral cleft lip and palate. *Dental Press J Orthod.* (2017) 22(6):43–8. doi: 10.1590/2177-6709.22.6.043-048.oar

15. Sundell AL, Nilsson AK, Ullbro C, Twetman S, Marcusson A. Caries prevalence and enamel defects in 5- and 10-year-old children with cleft lip and/or palate: a case-control study. *Acta Odontol Scand.* (2016) 74(2):90–5. doi: 10.3109/00016357.2015.1044562

16. Veiga KA, Porto AN, Matos FZ, de Brito PC, Borges ÁH, Volpato LE, et al. Caries experience and periodontal status in children and adolescents with cleft lip and palate. *Pediatr Dent.* (2017) 39(2):139–44.

17. Marzouk T, Youssef M, Tsigarida A, McKinney C, Wong C, DeLucia L, et al. Association between oral clefts and periodontal clinical measures: a meta-analysis. *Int J Paediatr Dent.* (2022) 32(4):558–75. doi: 10.1111/ipd.12934

18. Hazza'a AM, Rawashdeh MA, Al-Nimri K, Al Habashneh R. Dental and oral hygiene status in Jordanian children with cleft lip and palate: a comparison

between unilateral and bilateral clefts. *Int J Dent Hyg*. (2011) 9(1):30–6. doi: 10.1111/j.1601-5037.2009.00426.x

19. Perdikogianni H, Papaioannou W, Nakou M, Oulis C, Papagiannoulis L. Periodontal and microbiological parameters in children and adolescents with cleft lip and /or palate. *Int J Paediatr Dent*. (2009) 19(6):455–67. doi: 10.1111/j.1365-263X.2009.01020.x

20. Preidl RHM, Kesting M, Rau A. Perioperative management in patients with cleft lip and palate. *J Craniofac Surg*. (2020) 31(1):95–101. doi: 10.1097/SCS.0000000000005897

21. Hardwicke JT, Landini G, Richard BM. Fistula incidence after primary cleft palate repair: a systematic review of the literature. *Plast Reconstr Surg*. (2014) 134(4):618e–27e. doi: 10.1097/PRS.0000000000000548

22. Fritz A, Jodeh DS, Qamar F, Cray JJ, Rottgers SA. Patients with a history of oronasal Fistula repair exhibit lower oral health measured with patient-centric outcomes measures. *Cleft Palate Craniofac J*. (2021) 58(9):1142–9. doi: 10.1177/1055665620981331

23. Shaffer JR, Wang X, Feingold E, Lee M, Begum F, Weeks DE, et al. Genome-wide association scan for childhood caries implicates novel genes. *J Dent Res*. (2011) 90(12):1457–62. doi: 10.1177/0022034511422910

24. Lehtonen V, Sándor GK, Ylikontiola LP, Koskinen S, Pesonen P, Harila V, et al. Dental treatment need and dental general anesthetics among preschool-age children with cleft lip and palate in northern Finland. *Eur J Oral Sci*. (2015) 123(4):254–9. doi: 10.1111/eos.12195

25. Howe BJ, Cooper ME, Vieira AR, Weinberg SM, Resick JM, Nidey NL, et al. Spectrum of dental phenotypes in nonsyndromic orofacial clefting. *J Dent Res*. (2015) 94(7):905–12. doi: 10.1177/0022034515588281

26. das Neves LT, de Carvalho IMM, Cobourne MT, Gomide MR. Dental anomalies in non-syndromic orofacial clefts: a clinical approach. *Oral Dis*. (2022) 28(5):1351–68. doi: 10.1111/odi.14226

27. Haque S, Alam MK. Common dental anomalies in cleft lip and palate patients. *Malays J Med Sci*. (2015) 22(2):55–60.

28. Vieira AR, Meira R, Modesto A, Murray JC. MSX1, PAX9, and TGFA contribute to tooth agenesis in humans. *J Dent Res*. (2004) 83(9):723–7. doi: 10.1177/154405910408300913

29. Letra A, Fakhouri W, Fonseca RF, Menezes R, Kempa I, Prasad JL, et al. Interaction between IRF6 and TGFA genes contribute to the risk of nonsyndromic cleft lip/palate. *PLoS One*. (2012) 7(9):e45441. doi: 10.1371/journal.pone.0045441

30. Mostowska A, Hozyasz KK, Jagodzinski PP. Maternal MTR genotype contributes to the risk of non-syndromic cleft lip and palate in the Polish population. *Clin Genet*. (2006) 69(6):512–7. doi: 10.1111/j.1399-0004.2006.00618.x

31. Seow WK. Developmental defects of enamel and dentine: challenges for basic science research and clinical management. *Aust Dent J*. (2014) 59(Suppl 1):143–54. doi: 10.1111/adj.12104

32. Chapple JR, Nunn JH. The oral health of children with clefts of the lip, palate, or both. *Cleft Palate Craniofac J*. (2001) 38(5):525–8. doi: 10.1597/1545-1569_2001_038_0525_tohocw_2.0.co_2

33. Kulas A, Illge C, Bekes K, Eckert AW, Fuhrmann RA, Hirsch C. Structural color changes in permanent enamel of patients with cleft lip and palate: a case-control study. *J Orofac Orthop*. (2016) 77(1):45–51. doi: 10.1007/s00056-015-0007-z

34. Suzuki A, Nakano M, Yoshizaki K, Yasunaga A, Haruyama N, Takahashi I. A longitudinal study of the presence of dental anomalies in the primary and permanent dentitions of cleft lip and/or palate patients. *Cleft Palate Craniofac J*. (2017) 54(3):309–20. doi: 10.1597/15-186

35. Zou J, Meng M, Law CS, Rao Y, Zhou X. Common dental diseases in children and malocclusion. *Int J Oral Sci*. (2018) 10(1):7. doi: 10.1038/s41368-018-0012-3

36. Fonseca-Souza G, de Oliveira LB, Wambier LM, Scariot R, Feltrin-Souza J. Tooth abnormalities associated with non-syndromic cleft lip and palate: systematic review and meta-analysis. *Clin Oral Investig*. (2022) 26(8):5089–103. doi: 10.1007/s00784-022-04540-8

37. Ickow IM, Zinn S, Stacy Jr. JM, Martin B, Losee JE, D'Alesio A, et al. Dens invaginatus in patients with cleft lip and palate: a case series. *Cleft Palate Craniofac J*. (2021) 58(11):1452–8. doi: 10.1177/1055665621998534

38. Pitts NB, Zero DT, Marsh PD, Ekstrand K, Weintraub JA, Ramos-Gomez F, et al. Dental caries. *Nat Rev Dis Primers*. (2017) 3:17030. doi: 10.1038/nrdp.2017.30

39. Shashni R, Goyal A, Gauba K, Utreja AK, Ray P, Jena AK. Comparison of risk indicators of dental caries in children with and without cleft lip and palate deformities. *Contemp Clin Dent*. (2015) 6(1):58–62. doi: 10.4103/0976-237X.149293

40. Sundell AL, Ullbro C, Marcusson A, Twetman S. Comparing caries risk profiles between 5- and 10- year-old children with cleft lip and/or palate and non-cleft controls. *BMC Oral Health*. (2015) 15:85. doi: 10.1186/s12903-015-0067-x

41. Machorowska-Pieniążek A, Mertas A, Skucha-Nowak M, Tanasiewicz M, Morawiec T. A comparative study of oral Microbiota in infants with complete cleft lip and palate or cleft soft palate. *Biomed Res Int*. (2017) 2017:1460243. doi: 10.1155/2017/1460243

42. Struzycka I. The oral microbiome in dental caries. *Pol J Microbiol*. (2014) 63(2):127–35. doi: 10.33073/pjm-2014-018

43. Du Q, Ren B, He J, Peng X, Guo Q, Zheng L, et al. Candida albicans promotes tooth decay by inducing oral microbial dysbiosis. *Isme j*. (2021) 15(3):894–908. doi: 10.1038/s41396-020-00823-8

44. Bokhout B, van Loveren C, Hofman FX, Buijs JF, van Limbeek J, Prahl-Andersen B. Prevalence of Streptococcus mutans and lactobacilli in 18-month-old children with cleft lip and/or palate. *Cleft Palate Craniofac J*. (1996) 33(5):424–8. doi: 10.1597/1545-1569_1996_033_0424_posmal_2.3.co_2

45. Sundell AL, Ullbro C, Dahlén G, Marcusson A, Twetman S. Salivary microbial profiles in 5-year old children with oral clefts: a comparative study. *Eur Arch Paediatr Dent*. (2018) 19(1):57–60. doi: 10.1007/s40368-018-0326-z

46. Tamasas B, Cox TC. Massively increased caries susceptibility in an Irf6 cleft lip/palate model. *J Dent Res*. (2017) 96(3):315–22. doi: 10.1177/0022034516679376

47. Rawashdeh MA, Ayesh JA, Darwazeh AM. Oral candidal colonization in cleft patients as a function of age, gender, surgery, type of cleft, and oral health. *J Oral Maxillofac Surg*. (2011) 69(4):1207–13. doi: 10.1016/j.joms.2010.02.044

48. Khan I, Ahmad T, Manzoor N, Rizvi MA, Raza U, Premchandani S. Evaluating the role of local host factors in the candidal colonization of oral cavity: a review update. *Natl J Maxillofac Surg*. (2020) 11(2):169–75. doi: 10.4103/njms.NJMS_161_20

49. Ohyama T. Prosthodontic considerations for patients with cleft lip and palate. *Int Dent J*. (1986) 36(3):140–5.

50. Arikan V, Kizilci E, Ozalp N, Ozcelik B. Effects of fixed and removable space maintainers on plaque accumulation, periodontal health, candidal and Enterococcus Faecalis carriage. *Med Princ Pract*. (2015) 24(4):311–7. doi: 10.1159/000430787

51. Addy M, Shaw WC, Hansford P, Hopkins M. The effect of orthodontic appliances on the distribution of Candida and plaque in adolescents. *Br J Orthod*. (1982) 9(3):158–63. doi: 10.1179/bjo.9.3.158

52. Sukontapatipark W, el-Agroudi MA, Selliseth NJ, Thunold K, Selvig KA. Bacterial colonization associated with fixed orthodontic appliances. A scanning electron microscopy study. *Eur J Orthod*. (2001) 23(5):475–84. doi: 10.1093/ejo/23.5.475

53. van Loveren C, Buijs JF, Bokhout B, Prahl-Andersen B, Ten Cate JM. Incidence of mutans streptococci and lactobacilli in oral cleft children wearing acrylic plates from shortly after birth. *Oral Microbiol Immunol*. (1998) 13(5):286–91. doi: 10.1111/j.1399-302X.1998.tb00709.x

54. Shi B, Losee JE. The impact of cleft lip and palate repair on maxillofacial growth. *Int J Oral Sci*. (2015) 7(1):14–7. doi: 10.1038/ijos.2014.59

55. Schultes G, Gaggl A, Kärcher H. Comparison of periodontal disease in patients with clefts of palate and patients with unilateral clefts of lip, palate, and alveolus. *Cleft Palate Craniofac J*. (1999) 36(4):322–7. doi: 10.1597/1545-1569_1999_036_0322_copdip_2.3.co_2

56. Salvi GE, Brägger U, Lang NP. Periodontal attachment loss over 14 years in cleft lip, alveolus and palate (CLAP, CL, CP) subjects not enrolled in a supportive periodontal therapy program. *J Clin Periodontol*. (2003) 30(9):840–5. doi: 10.1034/j.1600-051X.2003.00390.x

57. Huynh-Ba G, Brägger U, Zwahlen M, Lang NP, Salvi GE. Periodontal disease progression in subjects with orofacial clefts over a 25-year follow-up period. *J Clin Periodontol*. (2009) 36(10):836–42. doi: 10.1111/j.1600-051X.2009.01469.x

58. Quirynen M, Dewinter G, Avontroodt P, Heidbüchel K, Verdonck A, Carels C. A split-mouth study on periodontal and microbial parameters in children with complete unilateral cleft lip and palate. *J Clin Periodontol*. (2003) 30(1):49–56. doi: 10.1034/j.1600-051X.2003.300108.x

59. Al-Wahadni A, Alhaija EA, Al-Omari MA. Oral disease status of a sample of Jordanian people ages 10 to 28 with cleft lip and palate. *Cleft Palate Craniofac J*. (2005) 42(3):304–8. doi: 10.1597/03-161.1

60. Al Jamal GA, Hazza'a AM, Rawashdeh MA. Prevalence of dental anomalies in a population of cleft lip and palate patients. *Cleft Palate Craniofac J*. (2010) 47(4):413–20. doi: 10.1597/08-275.1

61. Chaturvedula BB, Muthukrishnan A, Bhuvaraghan A, Sandler J, Thiruvenkatachari B. Dens invaginatus: a review and orthodontic implications. *Br Dent J*. (2021) 230(6):345–50. doi: 10.1038/s41415-021-2721-9

62. Zhu J, Wang X, Fang Y, Von den Hoff JW, Meng L. An update on the diagnosis and treatment of dens invaginatus. *Aust Dent J*. (2017) 62(3):261–75. doi: 10.1111/adj.12513

63. Curtis MA, Diaz PI, Van Dyke TE. The role of the microbiota in periodontal disease. *Periodontol 2000*. (2020) 83(1):14–25. doi: 10.1111/prd.12296

64. Kinane DF, Stathopoulou PG, Papapanou PN. Periodontal diseases. *Nat Rev Dis Primers*. (2017) 3:17038. doi: 10.1038/nrdp.2017.38

65. Zhou F, Su Z, Li Q, Wang R, Liao Y, Zhang M, et al. Characterization of bacterial differences induced by cleft-palate-related spatial heterogeneity. *Pathogens*. (2022) 11(7). doi: 10.3390/pathogens11070771

66. Zambon JJ. Periodontal diseases: microbial factors. *Ann Periodontol*. (1996) 1(1):879–925. doi: 10.1902/annals.1996.1.1.879

67. Tuna EB, Topçuoglu N, Ilhan B, Gençay K, Kulekçi G. Staphylococcus aureus transmission through oronasal fistula in children with cleft lip and palate. *Cleft Palate Craniofac J*. (2008) 45(5):477–80. doi: 10.1597/06-247.1

68. Campbell A, Costello BJ, Ruiz RL. Cleft lip and palate surgery: an update of clinical outcomes for primary repair. *Oral Maxillofac Surg Clin North Am*. (2010) 22(1):43–58. doi: 10.1016/j.coms.2009.11.003

69. Sakran KA, Wu M, Alkebsi K, Mashrah MA, Al-Rokhami RK, Wang Y, et al. The sommerlad-furlow modified palatoplasty technique: postoperative complications and implicating factors. *Laryngoscope*. (2022). doi: 10.1002/lary.30385. [Epub ahead of print]

70. Mahajan RK, Kaur A, Singh SM, Kumar P. A retrospective analysis of incidence and management of palatal fistula. *Indian J Plast Surg*. (2018) 51 (3):298–305. doi: 10.4103/ijps.IJPS_84_18

71. Sakran KA, Yin J, Yang R, Elayah SA, Alkebsi K, Zhang S, et al. Early cleft palate repair by a modified technique without relaxing incisions. *Cleft Palate Craniofac J*. (2022) 10556656221135288. doi: 10.1177/10556656221135288. [Epub ahead of print]

72. de Almeida AL, Esper LA, Pegoraro TA, do Valle AL. Gingival recession in individuals with cleft lip and palate: prevalence and severity. *Cleft Palate Craniofac J*. (2012) 49(1):92–5. doi: 10.1597/10-052

73. Chen YH, Liao YF, Chang CS, Lu TC, Chen KT. Patient satisfaction and quality of life after orthodontic treatment for cleft lip and palate deformity. *Clin Oral Investig*. (2021) 25(9):5521–9. doi: 10.1007/s00784-021-03861-4

74. Rivkin CJ, Keith O, Crawford PJ, Hathorn IS. Dental care for the patient with a cleft lip and palate. Part 2: the mixed dentition stage through to adolescence and young adulthood. *Br Dent J*. (2000) 188(3):131–4. doi: 10.1038/sj.bdj.4800410

75. Freitas AB, de Barros LM, Fiorini JE, Boriollo MF, Moreira AN, Magalhães CS. Caries experience in a sample of adolescents and young adults with cleft lip and palate in Brazil. *Cleft Palate Craniofac J*. (2013) 50(2):187–91. doi: 10.1597/11-143

76. Parapanisiou V, Gizani S, Makou M, Papagiannoulis L. Oral health status and behaviour of Greek patients with cleft lip and palate. *Eur Arch Paediatr Dent*. (2009) 10(2):85–9. doi: 10.1007/BF03321606

77. Pradhan L, Shakya P, Thapa S, Nakarmi KK, Maharjan A, Sagtani RA, et al. Prevalence of dental anomalies in the patient with cleft lip and palate visiting a tertiary care hospital. *JNMA J Nepal Med Assoc*. (2020) 58(228):591–6. doi: 10.31729/jnma.5149

78. Dogan MC, Serin BA, Uzel A, Seydaoglu G. Dental anxiety in children with cleft lip and palate: a pilot study. *Oral Health Prev Dent*. (2013) 11(2):141–6. doi: 10.3290/j.ohpd.a29364

79. Huang H, Pan W, Wang Y, Kim HS, Shao D, Huang B, et al. Nanoparticulate cell-free DNA scavenger for treating inflammatory bone loss in periodontitis. *Nat Commun*. (2022) 13(1):5925. doi: 10.1038/s41467-022-33492-6

80. Zhu X, Chu C-J, Pan W, Li Y, Huang H, Zhao L. The correlation between periodontal parameters and cell-free DNA in the gingival crevicular fluid, Saliva, and plasma in Chinese patients: a cross-sectional study. *J Clin Med*. (2022) 11 (23):6902. doi: 10.3390/jcm11236902

81. Gürsoy UK, Gürsoy M, Könönen E, Sintim HO. Cyclic dinucleotides in oral Bacteria and in oral biofilms. *Front Cell Infect Microbiol*. (2017) 7:273. doi: 10.3389/fcimb.2017.00273

82. Chen N, Shi B, Huang H. Velopharyngeal inadequacy-related quality of life assessment: the instrument development and application review. *Front Surg*. (2022) 9:796941. doi: 10.3389/fsurg.2022.796941

83. Lewis CW, Jacob LS, Lehmann CU. The primary care pediatrician and the care of children with cleft lip and/or cleft palate. *Pediatrics*. (2017) 139:e20170628. doi: 10.1542/peds.2017-0628

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Clinical study to assess influence of immediate provisionalization and various implant morphologies on implant stability: A prospective clinical study

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Introduction: The aim of this study was to evaluate the influence of different implant morphologies and immediate provisionalization options on the change of implant stability.
Methods: 94 Patients were randomized to receive implants from Straumann® BL/Straumann® BLT/Astra OsseoSpeed® TX, meanwhile having the same opportunity to receive healing abutment or immediate provisionalization. Implant stability quotient (ISQ) and marginal bone loss (MBL) were recorded at following timepoints. Parametric statistic was used for data analysis.
Results: Data showed that ISQ and MBL values of conical/straight/straight with micro-thread neck implants had no significant difference.
Discussion: Immediate provisionalization options could move the dip point of ISQ values ahead or delayed around one week, which were also relevant to implant systems. MBL values were proved to be unaffected by both two factors mentioned above.

KEYWORDS
implant therapy, implant stability quotient, resonance frequency analysis, immediate provisionalization, clinical study

Introduction

Recently, implant-supported maxillofacial prostheses have become one of the most favored methods to cope with congenital craniofacial deformities, chosen by both patients and surgeons. This therapeutic regimen is frequently applied in multiple areas of oral and maxillofacial surgery, including reconstruction of the maxillofacial skeleton, restoration of hemifacial/small mandibular deformity, temporomandibular joint (TMJ) total joint replacement, and orthognathic surgery (1, 2). As a kind of restoration and/or replacement of stomatognathic and associated facial structures by artificial substitutes, implant-supported prostheses not only help disfigured and socially unacceptable people to regain a normal life with normal craniofacial appearance but also help reconstructing their facial esthetics, oral function, socialacceptance, and self-confidence (3). The stability of implants is the guarantee of a long-term successful treatment.

Achieving good primary and secondary stability after implantation is one of the necessary conditions for realizing the functional load of the implant, and it is the decisive factor for whether it can bear the functional load and affect the long-term stability. Therefore, the evaluation of implant stability after implantation is of great significance.

Implant stability testing methods are as follows, including bone-implant-contact (BIC) histomorphological analysis, mechanical test, impact test, implant insertion torque (IT) test, periodic inspection value test, x-ray follow-up, and resonance frequency analysis (RFA) (4, 5). Among them, BIC histomorphological analysis (bone to implant contact analysis) is considered to be the gold standard, but its application conditions are limited. The most commonly used ones clinically are IT and RFA. IT is a measure of the frictional resistance that the implant encounters through the axial rotational movement of the top. RFA records the peak amplitude of the vibration response to small sinusoidal signals through a magnetic device fixed on the implant and encodes it as an implant stability quotient (ISQ). ISQ is an objective index reflecting the stiffness of the bone-implant system. As the stiffness of the bone-implant interface increases, so does the ISQ (5). A series of studies have proved the repeatability and accuracy of the Osstell system in measuring ISQ values (6–8).

ISQ varies with the progression of implant-bone osseointegration. During osseointegration, the initial mechanical stability is gradually replaced by biological stability. It is generally believed that with the decrease of initial stability and the increase of secondary stability, ISQ will experience a process of decrease and then increase. The lowest value of ISQ appears at 4–5 weeks after operation, in general, while it is not fixed among different implant systems and may appear in the third or seventh week (9, 10). The literature suggests that implants with failed osseointegration will have a significantly lower ISQ (4). ISQ < 36 was significantly associated with implant failure, but not with overall implant survival (11, 12). Due to its low predictive sensitivity, ISQ cannot be used as a reference indicator for implant failure (13).

The jaw position of the implant has a significant impact on ISQ. Systematic review shows that the ISQ of mandibular implants was significantly higher than that of maxillary implants, and the difference was statistically significant (4). There are also significant differences in ISQ between different restoration methods. For example, the ISQ of fixed denture restoration is significantly higher than that of overdenture restoration (4) and progressive provisionalization (immediate provisionalization without abutment and occlusal contact, adjacent contact at 1 month after surgery, and occlusal contact at 2 months after surgery). Median occlusal contact increased faster than the delayed load ISQ (14).

The effect of different implant morphologies on ISQ has also been studied. Different implant systems often have different thread spacing, implant morphology, microscopic topography, and surface modification methods, which may affect the mechanical retention force and osseointegration efficiency of the implant. A randomized controlled trial demonstrated that different implant neck designs affected ISQ changes within 6 months after implantation (15). The ISQ value and change in trend of implants of different systems are slightly different (16). Implants with wider thread spacing may have higher initial ISQ than implants with narrow thread spacing, and this difference disappears after 90 days (17). There are also differences in the ISQ curve between bone-level implants and soft-tissue-level implants (9).

The aim of this study was to investigate the difference in the trend of implant stability measured as ISQ among ASTRA TX, Straumann BL, and Straumann BLT systems with various implant morphologies. Another aim of this study was to determine whether a relation exists between the ISQ and provisional options. Further investigation considered the effect of implant morphologies and surface modifications on marginal bone loss (MBL).

Materials and methods

Patient selection

Patients with missing teeth in upper or lower jaw who were allocated for implant placement were recruited at the Department of Implantology, West China School of Stomatology, Sichuan University, between September 2020 and December 2021.

Inclusion criteria were as follows: (a) aged between 18 and 70 years; (b) generally healthy, without systemic diseases; (c) 3 months or more after teeth extraction, requiring implant-support fix restoration,; (d) sound oral hygiene and stable periodontal status; (e) without surgical contraindications or anesthesia contraindications; (f) possibility for a one-stage implant with transmucosal healing, without any need of bone augmentation; (g) the ability and willingness to comply with all study requirements and agree to observation till final restoration; (h) self-signed informed consent.

Exclusion criteria were as follows: (a) moderate or heavy smokers (≥10 cigarettes per day); (b) patients suffering from severe bruxism; (c) history of head and neck radiotherapy, chemotherapy, or bisphosphonate treatment; (d) pregnant or lactating females; (e) poor oral hygiene and unstable periodontal condition; (f) alcoholism; (g) uncontrolled diabetes, osteoporosis, rheumatic arthritis, oral cancer, or neoplasm; (h) a need for bone grafting in the implant site; (i) insertion torque under 20 N cm (due to the need to remove the healing abutment/provisional teeth several time during the healing period).

The study protocol and the consent forms were approved by the Ethics Committee of West China School of Stomatology (WCHSIRB-CT-2022-250), Sichuan University, and the guidelines for Good Clinical Practice were respected. All participating individuals were informed of the risks and benefits as well as the procedures of the study; they all gave written informed consent. The study was investigator-initiated and was supported by an unconditional grant from Sichuan University. The study was in compliance with the EQUATOR guidelines for clinical studies.

Study design

Implants and surgical procedure

All recruited patients should go through preoperation examination, including the following: (1) Basic health data acquisition, preoperative blood test, and blood pressure measurement to exclude contraindications; (2) cone-beam computed tomography (CBCT) examination to obtain hard tissue data; (3) intraoral photographs to obtain soft tissue condition. Then, the principal investigator of the project would make a treatment plan for each patient before surgery, ensuring the patient's oral condition was suitable for implant placement surgery and restoration without necessity of bone augmentation, after which the consent form would be signed by the patient himself/herself.

All patients received a dental implant in the missing site be means of a one-stage transmucosal approach with healing abutment or immediate provisional restoration. Prior to surgery, patients were randomly allocated to Straumann Bone Level, Straumann Bone Level Tapered, and ASTRA OsseoSpeed TX groups, while in each group provisionalization timing were stochastically chosen (immediate provisionalization or nonimmediate provisionalization). All the surgical procedures were performed by one certified surgeon (ZT) using the same surgical technique and protocols. Three different commercially available tapered dental implants were used (**Figure 1**): Straumann Bone Level, Straumann Bone Level Tapered, and ASTRA OsseoSpeed TX. Healing abutments or temporary abutments of the same system as the implants were applied after surgery. Implants from every individual system are manufactured using the same titanium alloy and have identical surface characteristics.

Antibiotics were used prophylactically for 0.5–1 h before surgery. Every patient was asked to do mouth rinsing with 0.2% chlorhexidine solution for 3 min. Surgery was performed under local infiltration anesthesia with articaine and epinephrine. Following local anesthesia, the implant site was exposed *via* a mid-crestal incision and a full-thickness flap was elevated. Positions of the implants were marked with a round bur. The surgical procedure followed the recommendation of the manufacturers. After preparation of the osteotomy site, the clinical records of implant diameter, length and implant torque, and ISQ values were recorded, and a healing abutment or an immediate restoration was randomly placed.

(1) Immediate provisionalization group: The three positions of the implant were obtained by intraoral pick-up to make a temporary restoration. Immediately after the operation, the immediate restoration was inserted and adjusted to make it in the median jaw position, forward extension and lateral movement. There was no contact with the opposite teeth and adjacent teeth, and the wounds were closed tightly with sutures.
(2) Nonimmediate provisionalization group: The wound was closed tightly after the healing abutment was installed.

Immediate treatment after operation included the following: (1) taking CBCT to verify the three-dimensional position of

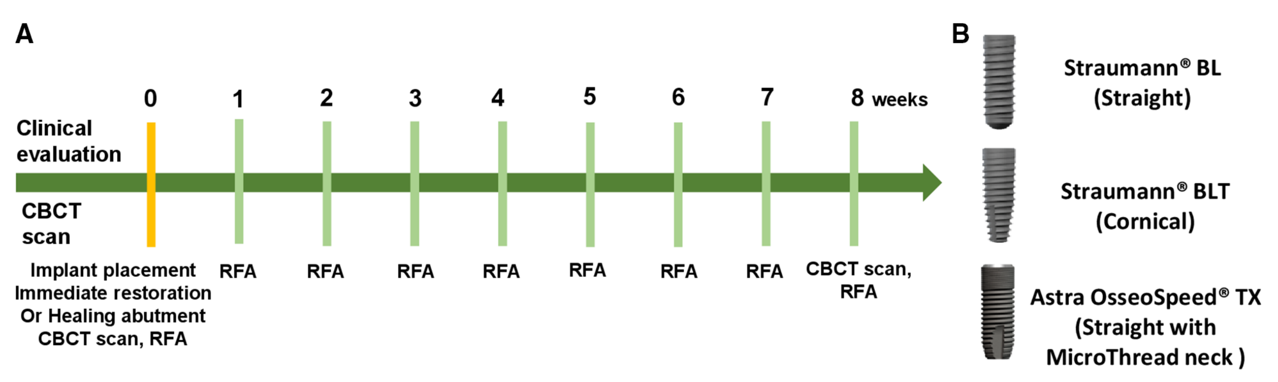

FIGURE 1
(A) Implant stability parameters and data collection time points. (B) Implants with different morphologies used in the study: Straumann® BLT/Straumann® BL/ASTRA OsseoSpeed® TX. All implants are with a tapered design.

implant placement; (2) taking 2 g amoxicillin (600 mg clindamycin for allergic patients) every 8 h, and 600 mg diclofenac sodium twice a day to relieve pain for 7 consecutive days after operation; (3) rinsing with 0.2% chlorhexidine solution daily for 14 days after surgery to prevent infection.

Clinical measurements and follow-up

The maximal insertion torque value of each implant was approximately reported and recorded by the surgery performer. All RFA measurements were carried out using the Osstell resonance frequency analyzer (Integration Diagnostics, Sweden), by connecting directly to the implant. A total of nine ISQ measurements were taken per implant per time point: three from buccal, three from mesial, and three from the proximal side.

From the surgery (0 week), resonance frequency analysis measurements were obtained in the same way at 7, 14, 21, 28, 35, 42, 49, and 56 days (1, 2, 3, 4, 5 ,6, 7, and 8 weeks, respectively) following implant placement; the implant stability quotient was measured at the buccal, lingual, and proximal sides. At each follow-up evaluation, the healing abutment was removed and cleaned. The SmartPeg was inserted into the implant, and the ISQ measurements were taken. The peg was then removed, and the healing abutment or provisional restoration was replaced.

At the final examination day (day 56), a second digitized CBCT examination was taken, prior to implant restoration. MBL around each implant was assessed using the radiograph acquisition program by measuring the distances between the implant platform and the most coronal bone contact with the implant; implant diameter was used for internal calibration. This allowed a millimetric assessment of the actual bone loss. The differences between the baseline CBCT (postoperative) and the final CBCT were used for data analysis.

Statistical analysis

The statistical analyses performed included Student's *t*-test for independent samples and a one-way ANOVA and Tukey's procedure for multiple pairwise comparisons. Mann–Whitney, Wilcoxon, and Friedman tests were used when nonparametric alternatives were required. Statistical correlations were analyzed with Pearson's coefficient and Spearman's rank correlation test.

Multivariate linear regression was used to determine how much of the variation in each outcome variable was accounted for by each predictor variable. The categorical predictor variable (bone type; more than two categories) was converted into two binary dummy variables, one for each original predictor variable category. This procedure was unnecessary for regression analysis with the two binary independent variables diameter and length. All statistical analyses were performed by an experienced dental statistician using IBM SPSS Statistics v. 22.0 software.

Results

Patients who arrived at the hospital dental clinic seeking restoration of missing tooth and have the right dimensions of the implant site in their CT imaging were offered to participate in the study. A total of 94 patients (46 females, 48 males) received dental implant-supported restoration. Seventeen patients received Straumann® BL implants (Straumann® BL group), 15 patients received Straumann® BL implants with immediate temporary restoration (Straumann® BL immediate provisionalization group), 15 patients received Straumann® BLT implants (Straumann® BLT group), 15 patients received Straumann® BLT implants with immediate temporary restoration (Straumann® BLT immediate provisionalization group), 15 patients received ASTRA OsseoSpeed® TX (OsseoSpeed® TX group), and 17 patients received ASTRA OsseoSpeed® TX implants with immediate temporary restoration (ASTRA® TX immediate provisionalization group). Most implant placement procedures were completed, except for one adverse event [one patient in the ASTRA TX immediate provisional group presented low insertion torque value (lower than 20 N cm) and was excluded from the longitudinal RFA analysis, due to the exclusion criteria]. Implant stability parameters and data collection time points are shown in **Figure 1A**, with the three different implant morphologies pictured in **Figure 1B**. All implants achieved a sufficient insertion torque. **Figure 2** exhibited the whole treatment sequences of one patient in the immediate provisionalization group, including receiving surgery, doing RFA measurements, receiving immediate provisionalization, and final restoration.

The demographic characteristics of the patients were comparable between groups, and they are presented in **Table 1**. Of the 94 implants studied, 47 (50%) were inserted in women and the remaining 47 (50%) were in men. Patients' age ranged between 19 and 68 years with a mean of 49 years.

With respect to implants position and numbers (**Table 2**), 34 (36%) implants were put in the maxilla, while the rest 60 (64%) were inserted in the mandible. Implants put in the site of central/lateral incisors, canines, premolars, and molars were 5 (5%), 5 (5%), 22 (23%), and 62 (66%), respectively.

RFA measurements—ISQ analysis

On surgery (day 0), according to **Table 3**, the mean ISQ of three implant systems (immediate provisionalization or nonimmediate provisionalization) were 78.24/81.65 (Straumann® BL, SD = 4.83/4.23), 77.86/81.29 (Straumann®

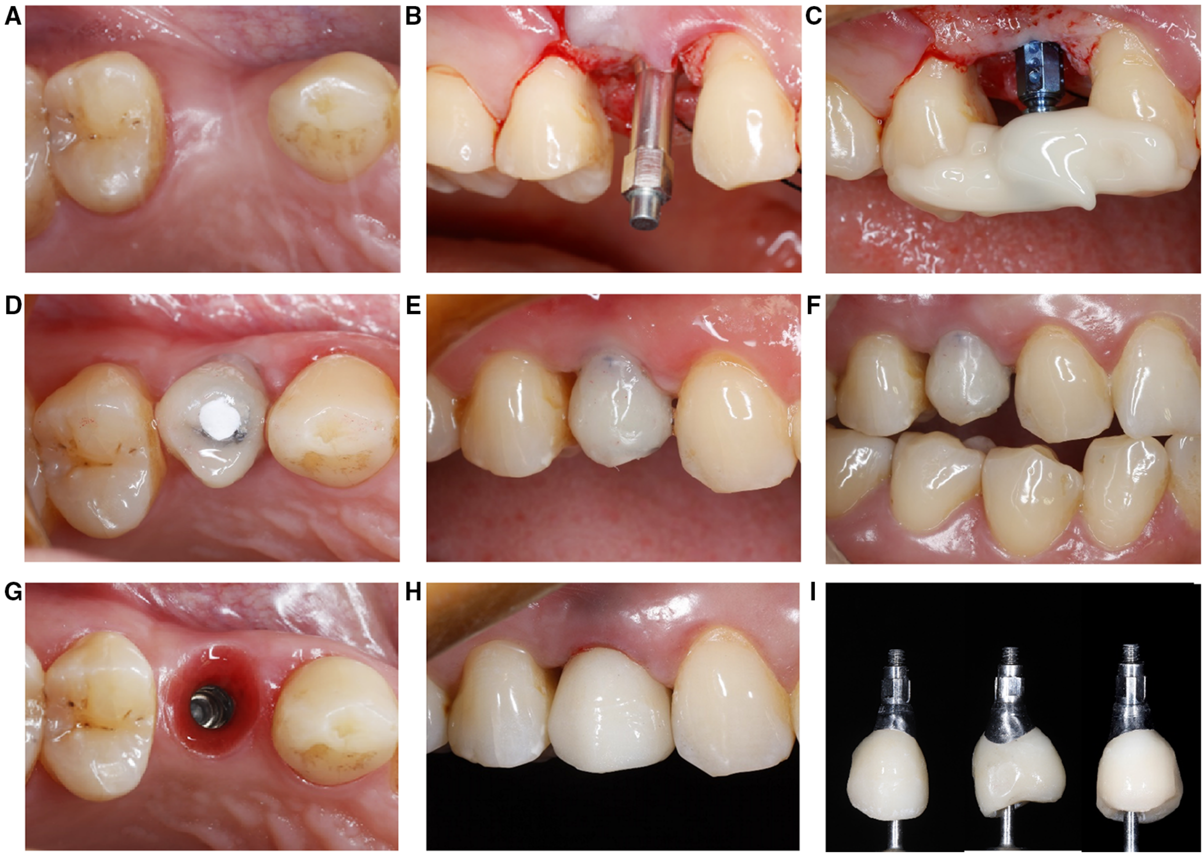

FIGURE 2
Clinical images of experimental sequences (immediate provisionalization group). (A) Implant recipient site. (B) An RFA transducer attached to the implant body to measure ISQ value. (C) On-site pick-up to make chair side immediate provisionalization. (D–F) Immediate provisionalization restored. (G–I) Final restoration marked the end of the study period. RFA, resonance frequency analysis; ISQ, implant stability quotient.

TABLE 1 Patient and implant demographic characteristics.

	Straumann® BL	Straumann® BL immediate provisionalization	Straumann® BLT	Straumann® BLT immediate provisionalization	ASTRA® TX	ASTRA OsseoSpeed® TX immediate provisionalization
Patient gender (M/F)	9/8	6/9	8/7	7/8	7/8	10/7
Patient age (years)	47 ± 23 (range: 19–63)	38 ± 31 (range: 22–63)	46 ± 22 (range: 21–68)	46 ± 24 (range: 22–70)	45 ± 21 (range: 24–67)	39 ± 29 (range: 20–68)

BLT, SD = 5.20/6.05), and 79.30/82.48 (ASTRA OsseoSpeed® TX, SD = 5.27/4.87), exhibiting no significant difference. In general, ISQ of day 56 (secondary ISQ) postop was statistically significantly higher than the measurements recorded for days 0 (primary ISQ). Little variation of ISQ values, among the three different-morphology implant groups, were observed, indicating that ISQ values mainly change accordingly to healing status (primary and secondary). Therefore, conclusions can be reached that under the same surgical procedure, implant morphologies did not seem to affect ISQ value much.

In terms of immediate provisionalization choice, ISQ value at day 14 exhibited significant difference between the immediate provisionalization group and the nonimmediate provisionalization group (mean ISQ values 76.69/79.27, SD = 5.32/4.78), which reminded us that at the early stage (14

TABLE 2 Implants position and numbers.

	Implant position and numbers (BL + BLT + TX = 94)		
	Straumann® BL	Straumann® BLT	ASTRA OsseoSpeed® TX
Upper/lower	14/18	10/20	10/22
Central incisor	0	2	0
Lateral incisor	1	0	2
Canine	0	4	1
Premolar	11	4	7
Molar	20	20	22

TABLE 3 Mean and SDs of three implant systems in terms of maximum insertion torque and RFA ($p < 0.05$, one-way ANOVA).

	Implant System	*n*	Mean	SD	Significance (*p*)
RFA (ISQ) (immediately postop)	Straumann® BL	32	78.24	4.83	0.511
	Straumann® BLT	30	77.86	5.20	
	ASTRA OsseoSpeed® TX	32	79.30	5.27	
RFA (ISQ) (56 days postop)	Straumann® BL	32	81.65	4.23	0.638
	Straumann® BLT	30	81.29	6.05	
	ASTRA OsseoSpeed® TX	32	82.48	4.87	

SD, standard deviation; RFA, resonance frequency analysis; ISQ, implant stability quotient.

postop), a more careful attitude should be taken facing implants with immediate provisionalization. Unnecessary operation should be avoided at the first 2–3 weeks after implantation (Table 4). During the whole healing period, the RFA values fluctuated and showed an overall trend of declining first and then rising later. It was worth noting that, at the time point of 7, 14, and 28 days (1, 2, and 3 weeks after implantation, respectively), ISQ values fell to the bottom of the whole period, though without statistical significance (Figure 3). An interesting finding was that all three implant groups showed a similar pattern of stability change over time; there was a drop in ISQ among the first 1–3 weeks, and then, the ISQ gradually increased back until reaching the top at the end of the study (day 56, week 8). /the Straumann® BLT group exhibited the earliest bottom ISQ time point at week 1, while the other five groups varied little, indicating us that during 1–3 weeks, implants should be handled with extra caution.

In order to cast light on the variation of ISQ values at the first and last time points, the Pearson correlation coefficient

TABLE 4 Mean and SD of immediate provisionalization group and nonimmediate provisionalization group in terms of maximum insertion torque and RFA ($p < 0.05$, Student's *t*-test for independent samples).

	Immediate provisionalization	*n*	Mean	SD	Significance (*p*)
RFA (ISQ) (14 days postop)	Yes	47	76.69	5.31	0.047
	No	47	79.27	4.78	
RFA (ISQ) (56 days postop)	Yes	47	81.01	4.80	0.124
	No	47	82.62	5.22	

SD, standard deviation; RFA, resonance frequency analysis; ISQ, implant stability quotient.

(PCC) was analyzed. However, results showed that the two factors that we were interested in (different implant morphologies and immediate provisionalization choice) exhibited minor influence on the ISQ values at days 0 and 56 (Tables 5, 6). Intuitive differences between groups are shown in Figures 4A,B.

Radiographic measurements—MBL analysis

The average radiographic MBL was measured at the final CBCT taken on day 56 compared with day 0; the mean bone loss for the Straumann® BL/Straumann® BLT/ASTRA OsseoSpeed® TX group was 0.08/0.19/0.16 mm (SD = 0.26/0.24/0.16). There was no statistical significance ($p = 0.1114$) among the different implant design groups, from which we could speculate that implant morphologies did not affect MBL much (Table 7). As for immediate provisional and nonimmediate provisional groups, average MBL was 0.16/0.12 mm (SD = 0.18/0.27). MBL amount was slightly higher in the immediate provisionalization group (Table 8), still without statistical significance ($p = 0.459$). Intuitive differences between groups are shown in Figure 4C.

Discussion

Nowadays, congenital craniofacial deformities, causing bone defects, misalignment, and soft tissue asymmetry, often lead to severe defects of related soft and hard tissues, which cause serious obstacles to patients' speech, swallowing, chewing, breathing, and other functions, and severely affect patients' physiology and psychology. Commonly used methods for craniofacial defect repair include prosthesis repair, bone graft repair, and individualized implant repair, among which the dental-supported prosthesis repair has been widely used, while

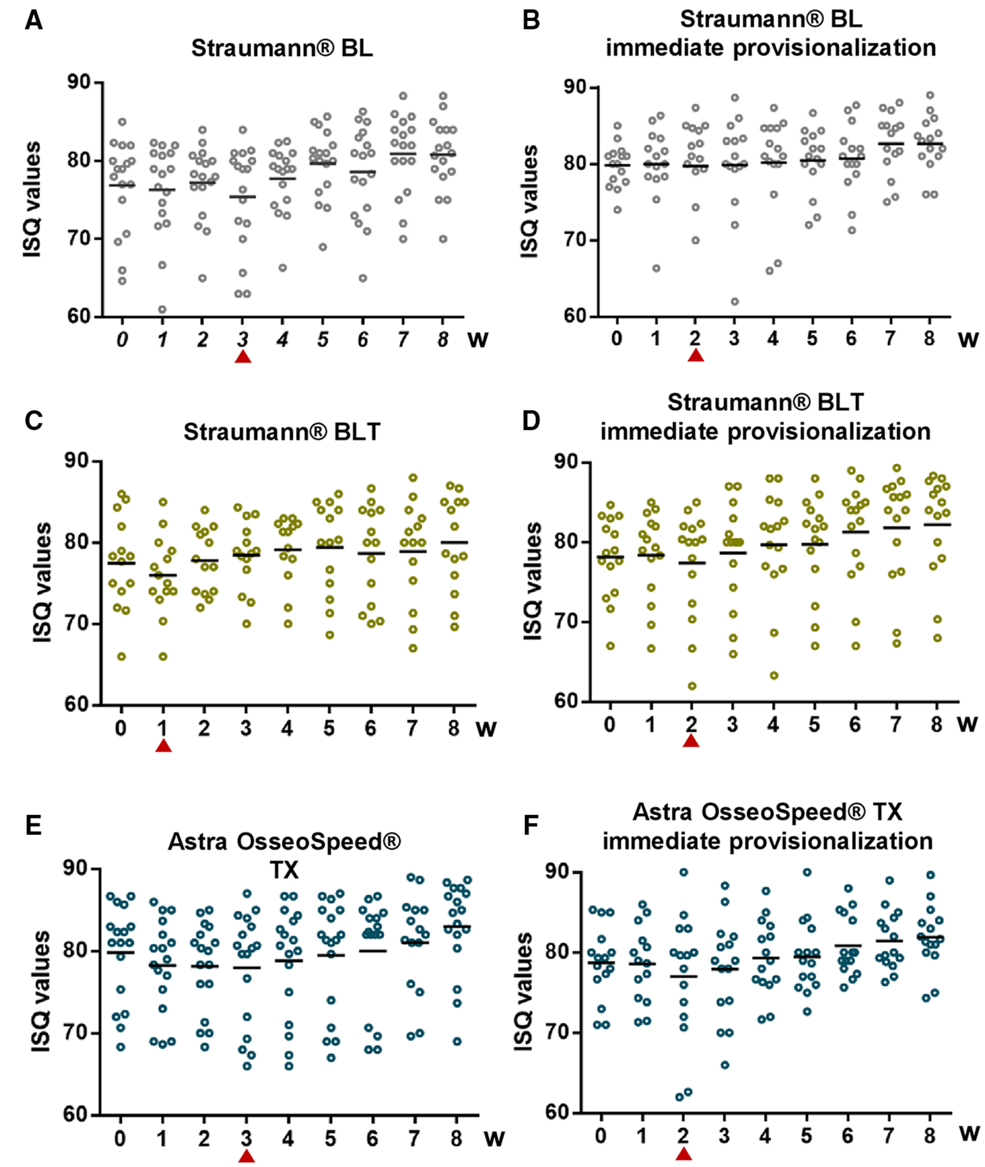

FIGURE 3
Mean ISQ values of each time point during examination period, lowest implant stability quotient (ISQ) points marked by red triangles. (A-F) All six groups of different implant morphologies and immediate provisionalization options.

its postoperative functional recovery is proved to be more than acceptable. Implant-supported prostheses with different structural designs have been gradually applied in clinical practice.

Implant stability is considered one of the most essential factors that affect the long-term survival rate. In this study, ISQ values and trend of change were similar to previous clinical reports (18, 19). Thickness of the cortical bone, cortical-and-cancellous ratios, implant morphologies, and immediate/late provisionalization options all proved to play a role in regulating implant stability (20). The changing trend of ISQ values were mainly reported to have a bottom period around week 2–4 after implant insertion, which were quite similar to the results in this study (week 1–3) (4).

As for different implant morphologies, previous studies proved that both straight and conical implants had approximately the same lowest ISQ values period, which was around 1–3 weeks after surgery. In our study, the same results were reached by parameter analysis. Rotation force should not be applied onto the implants, or unexpected situation might happen. With respect to three implant morphologies (straight/conical/straight with a microthread neck), the bottom point of ISQ value curve came 1 week later (2–3 weeks) in the group of straight and straight with microthread neck implants, while

TABLE 5 Mean of the RFA immediately after insertion and after 3 months and the PCC (*r*).

Implant system	*n*	Mean RFA (ISQ) (immediately postop)	Mean RFA (ISQ) (3 months postop)	PCC (*r*)
Total	94	78.48	81.82	0.524
Straumann® BL	32	78.24	81.65	0.639
Straumann® BLT	30	77.86	81.29	0.520
ASTRA OsseoSpeed® TX	32	79.30	82.48	0.432

PCC, Pearson correlation coefficient; RFA, resonance frequency analysis; ISQ, implant stability quotient.

TABLE 6 Mean and the PCC (*r*) of the RFA of immediate provisionalization group and nonimmediate provisionalization group.

Immediate provisionalization	*N*	Mean RFA (ISQ) (immediately postop)	Mean RFA (ISQ) (3 months postop)	PCC (*r*)
Total	94	78.48	81.82	0.524
Yes	47	77.69	81.01	0.421
No	47	79.27	82.62	0.610

PCC, Pearson correlation coefficient; RFA, resonance frequency analysis; ISQ, implant stability quotient.

the conical implant groups had their dip point 1 week earlier (1–2 weeks). This characteristic difference can be owned mainly to the conical shape and narrowed root diameter and, probably, the unique surface modification (21–23).

In recent decades, on behalf of higher esthetic requirements and improvements in chair-side restoration techniques, immediate provisionalization, from single-tooth implant restorations and full-arch restorations, have gained intense attention and popularity (24). Studies have been made to investigate different patterns of osseointegration in the immediate and nonimmediate provisionalization group, which mainly laid in the pattern of dynamic or static interfacial activities (25). Implant stability has long been identified as a prerequisite for osseointegration (26). Therefore, losing stability would be disastrous for restoration effect, leading to early failure and unsatisfied doctor–patient relationship. As one of the most important prerequisites in immediate provisionalization, achieving high primary implant stability among groups should not be neglected.

As for the influence of the immediate provisionalization on the ISQ values, it still remained unclear (27, 28). From our findings in this study, in the straight implant groups (Straumann BL and ASTRA TX, with or without immediate provisionalization), ISQ value dip points intended to occur 1 week earlier among the immediate provisionalization group, indicating that the most hazard period of implant survival had been brought 1 week forward by the immediate provisionalization process. However, things turned out slightly different among the conical implant groups (Straumann BLT, with or without immediate provisionalization). The dip points of ISQ values tended to delay approximately 1 week in the immediate provisionalization group. So far, there have been no literature studies focusing on the influence of immediate provisionalization on the change of ISQ values. We boldly speculated from our previous results that the immediate provisionalization process played a crucial role in affecting the change, while the dip points of ISQ moving beforehand or afterward were majorly decided by the morphology of implants. The stability of straight or columnized implants with immediate provisionalization was achieved 1 week later. Nevertheless, it seemed that the stability of conical implants with immediate provisionalization was obtained 1 week earlier than the group without immediate provisionalization. To conclude, it could enlighten implant practitioners that when using conical implants, designing immediate provisionalization should be a way to obtain acceptable ISQ values earlier than usual, even though the mechanism behind this remained undiscovered.

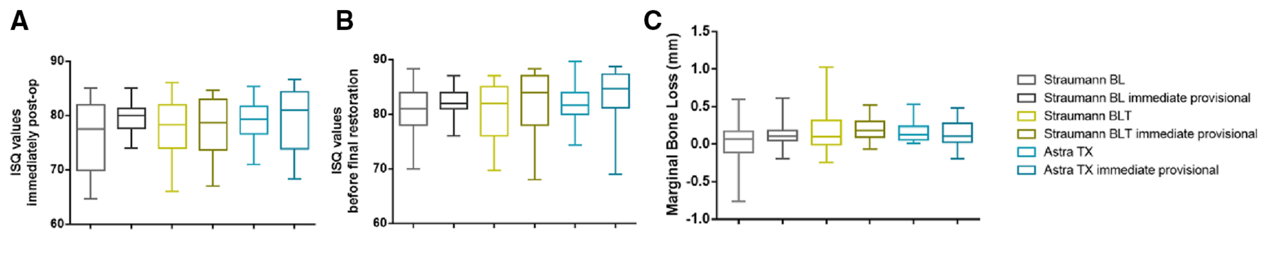

FIGURE 4
(A,B) ISQ measurements at immediately post-surgery (day 0) and before final restoration (day 56) in the six groups. Boxes denote quartile range of measurements. (C) Mean MBL values of the six groups (whiskers—95% confidence intervals). MBL, marginal bone loss.

TABLE 7 Mean and SD of three implant systems in terms of MBL ($p < 0.05$, one-way ANOVA).

	Implant system	*N*	Mean	SD	Significance (*p*)
MBL	Straumann® BL	32	0.08	0.26	0.114
	Straumann® BLT	30	0.19	0.24	
	ASTRA OsseoSpeed® TX	32	0.16	0.16	

SD, standard deviation; MBL, marginal bone loss.

TABLE 8 Mean and SD of immediate provisionalization group and nonimmediate provisionalization group in terms of MBL ($p < 0.05$, Student's *t*-test for independent samples).

	Immediate provisionalization	*N*	Mean	SD	Significance (*p*)
MBL	Yes	47	0.16	0.18	0.459
	No	47	0.12	0.27	

SD, standard deviation; MBL, marginal bone loss.

Marginal bone loss has been proved to be associated with loads of factors (25, 29). According to Simmons et al., surgical techniques, insertion torques, provisionalization options, and implant designs all contribute to the variation (19). In this study, factors such as surgical procedures and insertion torques had already been constricted; implant morphologies and provisionalization options were the major influencers (30). The amount of marginal bone loss for implants with three different morphologies all fell within the acceptable range. We observed the highest MBL in conical implants (0.19 mm) after 9 weeks, and then came the straight implants (0.16 and 0.08 mm). However, there were no statistically significant differences between these groups. This indistinctive difference in MBL could possibly be owned to the unique structure of conical implants, whose necks were supposed to yield more compressive force than the straight ones (31, 32), and then accelerating bone loss around implant marginal areas. This conclusion also clicked with findings published by Atieh et al. that parallel-walled dental implants appeared to slow down marginal bone loss (33).

This study proved that the difference of ISQ values and MBL among implant groups with differed morphologies is minor. Ensuring the premise of implantation torque, straight implants (with or without microthread neck design), and conical implants were all suitable for immediate provisionalization with a relatively high success rate. However, during the dip periods of ISQ values, which varied among groups, more care should be taken into our treatment procedure. Limitation of this study was that longer term of observation should be performed. Further studies are required to make certain the mechanism behind the different ISQ trend of dental implants with varied morphologies.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Written informed consent was obtained from the individual (s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

MQ, SD, and ZT all contributed to conception and design of the study. ZT performed implant operation, while MQ recorded patients' data during the therapy session. MQ and SD organized the database and finished the statistical analysis. MQ wrote the first draft of the manuscript. MQ, SD, and ZT revised sections of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Laino L, Cicciù M, Russo D, Cervino G. Surgical strategies for multicystic ameloblastoma. *J Craniofac Surg.* (2020) 31(2):e116–9. doi: 10.1097/SCS.0000000000005903

2. Huang MF, Alfi D, Alfi J, Huang AT. The use of patient-specific implants in oral and maxillofacial surgery. *Oral Maxillofac Surg Clin North Am.* (2019) 31 (4):593–600. doi: 10.1016/j.coms.2019.07.010

3. Hooper SM, Westcott T, Evans PL, Bocca AP, Jagger DC. Implant-supported facial prostheses provided by a maxillofacial unit in a U.K. regional hospital: longevity and patient opinions. *J Prosthodont.* (2005) 14(1):32–8. doi: 10.1111/j.532-849X.2005.00004.x

4. Chen MH, Lyons K, Tawse-Smith A, Ma S. Resonance frequency analysis in assessing implant stability: a retrospective analysis. *Int J Prosthodont.* (2019) 32 (4):317–26. doi: 10.11607/ijp.6057

5. Hsu JT, Shen YW, Kuo CW, Wang RT, Fuh LJ, Huang HL. Impacts of 3D bone-to-implant contact and implant diameter on primary stability of dental implant. *J Formos Med Assoc.* (2017) 116(8):582–90. doi: 10.1016/j.jfma.2017.05.005

6. Norton MR. Resonance frequency analysis: agreement and correlation of implant stability quotients between three commercially available instruments. *Int J Oral Maxillofac Implants.* (2018) 3(10). doi: 10.11607/jomi.6964. [Epub ahead of print]

7. Herrero-Climent M, Santos-García R, Jaramillo-Santos R, Romero-Ruiz MM, Fernández-Palacin A, Lázaro-Calvo P, et al. Assessment of Osstell ISQ's reliability for implant stability measurement: a cross-sectional clinical study. *Med Oral Patol Oral Cir Bucal.* (2013) 18(6):e877–82. doi: 10.4317/medoral.19120

8. Jaramillo R, Santos R, Lázaro P, Romero M, Rios-Santos JV, Bullón P, et al. Comparative analysis of 2 resonance frequency measurement devices: Osstell Mentor and Osstell ISQ. *Implant Dent.* (2014) 23(3):351–6. doi: 10.1097/ID.0000000000000072

9. Sarfaraz H, Johri S, Sucheta P, Rao S. Study to assess the relationship between insertion torque value and implant stability quotient and its influence on timing of functional implant loading. *J Indian Prosthodont Soc.* (2018) 18(2):139–46. doi: 10.4103/jips.jips_203_17

10. Bavetta G, Bavetta G, Randazzo V, Cavataio A, Paderni C, Grassia V, et al. A retrospective study on insertion torque and implant stability quotient (ISQ) as stability parameters for immediate loading of implants in fresh extraction sockets. *Biomed Res Int.* (2019) 2019:9720419. doi: 10.1155/2019/9720419

11. Scarano A, Carinci F, Quaranta A, Iezzi G, Piattelli M, Piattelli A. Correlation between implant stability quotient (ISQ) with clinical and histological aspects of dental implants removed for mobility. *Int J Immunopathol Pharmacol.* (2007) 20(S1):33–6. doi: 10.1177/039463200702001s08

12. Yoon HG, Heo SJ, Koak JY, Kim SK, Lee SY. Effect of bone quality and implant surgical technique on implant stability quotient (ISQ) value. *J Adv Prosthodont.* (2011) 3(1):10–5. doi: .4047/jap.2011.3.1.10

13. Monje A, Ortega-Oller I, Galindo-Moreno P, Catena A, Monje F, O'Valle F, et al. Sensitivity of resonance frequency analysis for detecting early implant failure: a case-control study. *Int J Oral Maxillofac Implants.* (2014) 29(2):456–61. doi: 10.11607/jomi.3357

14. Juboori MJA, Attas MAA, Gomes RZ, Alanbari BF. Using resonance frequency analysis to compare delayed and immediate progressive loading for implants placed in the posterior maxilla: a pilot study. *Open Dent J.* (2018) 12:801–10. doi: 10.2174/1745017901814010801

15. Eshkol-Yogev I, Tandlich M, Shapira L. Effect of implant neck design on primary and secondary implant stability in the posterior maxilla: a prospective randomized controlled study. *Clin Oral Implants Res.* (2019) 30(12):1220–8. doi: 10.111/clr.13535

16. Carmo Filho LCD, Marcello-Machado RM, Castilhos EDD, Del Bel Cury AA, Faot F. Can implant surfaces affect implant stability during osseointegration? A randomized clinical trial. *Braz Oral Res.* (2018) 32:e110. doi: 10.1590/807-3107bor-2018.vol32.0110

17. Gehrke SA, da Silva UT, Del Fabbro M. Does implant design affect implant primary stability? A resonance frequency analysis-based randomized split-mouth clinical trial. *J Oral Implantol.* (2015) 41(6):e281–6. doi: 10.1563/aaid-joi-D-13-00294

18. Su YH, Peng BY, Wang PD, Feng SW. Evaluation of the implant stability and the marginal bone level changes during the first three months of dental implant healing process: a prospective clinical study. *J Mech Behav Biomed Mater.* (2020) 110:103899. doi: 10.1016/j.jmbbm.2020.103899

19. Simmons DE, Maney P, Teitelbaum AG, Billiot S, Popat LJ, Palaiologou AA. Comparative evaluation of the stability of two different dental implant designs and surgical protocols—a pilot study. *Int J Implant Dent.* (2017) 3(1):16. doi: 0.1186/s40729-017-0078-2

20. Liaje A, Ozkan YK, Ozkan Y, Vanlioğlu B. Stability and marginal bone loss with three types of early loaded implants during the first year after loading. *Int J Oral Maxillofac Implants.* (2012) 27(1):162–72. PMID: 22299093.

21. Abtahi J, Henefalk G, Aspenberg P. Impact of a zoledronate coating on early post-surgical implant stability and marginal bone resorption in the maxilla—a split-mouth randomized clinical trial. *Clin Oral Implants Res.* (2019) 30 (1):49–58. doi: 10.1111/clr.13391

22. Fiorillo L, Cicciù M, Tözüm TF, D'Amico C, Oteri G, Cervino G. Impact of bisphosphonate drugs on dental implant healing and peri-implant hard and soft tissues: a systematic review. *BMC Oral Health.* (2022) 22(1):291. doi: 10.1186/s12903-022-02330-y

23. Faria PE, Masalskas B, Heyden A, Rasmusson L, Salata LA. Immediate loading of implants in the edentulous mandible: a multicentre study. *Oral Maxillofac Surg.* (2016) 20(4):385–90. doi: 10.1007/s10006-016-0577-y

24. Collaert B, De Bruyn H. Immediate functional loading of TiOblast dental implants in full-arch edentulous maxillae: a 3-year prospective study. *Clin Oral Implants Res.* (2008) 19(12):1254–60. doi: 10.1111/j.1600-0501.2008.01586.x

25. Nkenke E, Fenner M, Vairaktaris EG, Neukam FW, Radespiel-Tröger M. Immediate versus delayed loading of dental implants in the maxillae of minipigs. Part II: histomorphometric analysis. *Int J Oral Maxillofac Implants.* (2005) 20(4):540–6. PMID: 16161738.

26. Danza M, Tortora P, Quaranta A, Perrotti V, Vozza I, Piattelli A. Randomised study for the 1-year crestal bone maintenance around modified diameter implants with different loading protocols: a radiographic evaluation. *Clin Oral Investig.* (2010) 14(4):417–26. doi: 10.1007/s00784-009-0314-0

27. Kim YK, Yun PY, Kim SB, Ahn KJ, Lee HJ, Yi YJ, et al. Prospective observational study of the early loading of nanostructured calcium phosphate-coated tapered implants in the mandible and maxilla. *Int J Periodontics Restorative Dent.* (2014) 34(5):695–703. doi: 10.11607/prd.1637

28. Mura P. Immediate loading of tapered implants placed in postextraction sockets: retrospective analysis of the 5-year clinical outcome. *Clin Implant Dent Relat Res.* (2012) 14(4):565–74. doi: 10.1111/j.708-8208.2010.00297.x

29. Lombardi T, Berton F, Salgarello S, Barbalonga E, Rapani A, Piovesana F, et al. Factors influencing early marginal bone loss around dental implants positioned subcrestally: a multicenter prospective clinical study. *J Clin Med.* (2019) 8(8):1168. doi: 10.3390/jcm8081168

30. Ajanović M, Hamzić A, Redžepagić S, Kamber-Ćesir A, Kazazić L, Tosum S. Radiographic evaluation of crestal bone loss around dental implants in maxilla and mandible: one year prospective clinical study. *Acta Stomatol Croat.* (2015) 49(2):128–36. doi: 10.15644/asc49/2/6

31. Galindo-Moreno P, Concha-Jeronimo A, Lopez-Chaichio L, Rodriguez-Alvarez R, Sanchez-Fernandez E, Padial-Molina M. Marginal bone loss around implants with internal hexagonal and internal conical connections: a 12-month randomized pilot study. *J Clin Med.* (2021) 10(22):5427. doi: 10.3390/jcm10225427

32. Comuzzi L, Tumedei M, D'Arcangelo C, Piattelli A, Iezzi G. An in vitro analysis on polyurethane foam blocks of the insertion torque (IT) values, removal torque values (RTVs), and resonance frequency analysis (RFA) values in tapered and cylindrical implants. *Int J Environ Res Public Health.* (2021) 18 (17):9238. doi: 10.3390/ijerph18179238

33. Atieh MA, Alsabeeha N, Duncan WJ. Stability of tapered and parallel-walled dental implants: a systematic review and meta-analysis. *Clin Implant Dent Relat Res.* (2018) 20(4):634–45. doi: 10.1111/cid.12623

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Comparison of velopharyngeal morphology of two palatoplasty techniques in patients with hard and soft cleft palate

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Purpose: The study aims to compare the velopharyngeal morphology of hard and soft cleft palate (HSCP) patients after Furlow and Sommerlad palatoplasty.
Patients and methods: A total of 51 patients (20 cases in Furlow palatoplasty group, 16 cases in Sommerlad palatoplasty group and 15 normal children in the control group) were included in our study. Velopharyngeal function and speech outcomes of patients with HSCP who had either Furlow palatoplasty or Sommerlad palatoplasty for cleft palate repair were evaluated by perceptual speech assessment (PSA), lateral cephalometric radiographs and nasopharyngoscopy. To assess velopharyngeal morphology of patients treated with two techqiques, we analyzed measurements such as velar length, pharyngeal depth, and the Adequate ratio (the ratio of velar length to pharyngeal depth). Furthermore, skeletal landmarks including cranial base, cervical vertebrae, posterior nasal spine which were defined as the pharyngeal triangle were measured. Finally, the position of the point U relative to the pharyngeal triangle were compared.
Results: Velopharyngeal closure (VPC) rate in Furlow palatoplasty group accounted for 90%, while that in Sommerlad palatoplasty group was 81.3%. PSA of the former group was significantly better than that of the latter group ($P < 0.05$). Velar length, pharyngeal depth and the Adequate ratio (1.37 ± 0.14 vs. 1.41 ± 0.15) were comparable between the Furlow group and control group ($P > 0.05$), while Sommerlad group had a shorter velar length, deeper pharyngeal depth and a smaller Adequate ratio (1.20 ± 0.18) compared to the above two groups ($P < 0.05$). Furhermore, the point U of Sommerlad group in the pharyngeal triangle was higher than that of the other two groups.
Conclusions: In the treatment modality of patients with HSCP, both Furlow palatoplasty and Sommerlad palatoplasty seem to be effective. Furlow palatoplasty appears to have velopharyngeal morphology similar to normal control group., while Sommerlad group shows a shorter velar length, deeper pharyngeal depth and a smaller Adequate ratio

KEYWORDS

cleft palate, velopharyngeal function, speech outcome, furlow, sommerlad

Introduction

Cleft palate is the most common congenital developmental deformity of the maxillofacial region, the incidence of it lies on top of congenital birth defect diseases (1–3). It exerts a serious socio-economic and psychosocial burden on patients and their families (4–6). Currently, surgical intervention has still emerged as the first treatment choice. Although various techniques have been described for cleft palate repair, however, there is no consensus on the ideal palatal repair technique applicable to all cleft palate types (7–10). The primary goal of cleft palate repair is the achievement of optimal speech outcomes (11, 12). To accomplish this goal, anatomical separation between the oral and nasal cavities and restoration of the muscular sling in the soft palate is pivotal (13). Furlow palatoplasty proposed by Furlow in 1986, and Sommerlad palatoplasty described by Sommerlad in 2002 were currently two popular methods to achieve VPC and yield intelligible speech by means of anatomical reconstruction of the levator palatine muscle (14, 15). Whereas the way restoring abnormally attached muscles was different. The former was by means of dissection and reposition of the levator veli palatini, while the latter was achieved with the help of the double-opposing Z-plasty. Previously, several studies had evaluated the clinical outcomes of these two surgical procedures (16–20). Khosla et al. reported Furlow Z-plasty yielded excellent speech results for primary cleft palate repair, and the rate of VPC reached 84% (16). According to Wang et al., 80% patients with Sommerlad palatoplasty had no evidence of velopharyngeal insufficiency (18). In addition, Li et al. compared the incidence of postoperative fistula formation of the above two techniques and found that the fistula rate of Furlow palatoplasty is lower than that of Sommerlad palatoplasty (19). However, few research have been conducted to compare the velopharyngeal morphology between Furlow and Sommerlad techniques. If any, they were assessed only using subjective evaluation methods (18). Thus, the current study aims to compare velopharyngeal morphology and speech outcomes using subjective and objective parameters after cleft palate repair with Furlow or Sommerlad palatoplasty, to provide clinical evidence for a better choice of surgical methods to reconstruct a functional velopharyngeal unit and restore optimal speech in patients with HSCP.

Materials and methods

Subjects

Medical records of patients with HSCP who underwent primary cleft palate repair in Nanjing Stomatological Hospital, Medical School of Nanjing University between 2012 and 2018 were reviewed retrospectively. All patients enrolled in the study met the following inclusion criteria: patients with HSCP; non-syndromic patients; and primary cleft palate repair using Furlow or Sommerlad palatoplasty. Patients were excluded for syndromic diseases, and for a history of delayed language development and dysacusia.

This study was approved by the Ethics Committee, Nanjing Stomatological Hospital, Medical School of Nanjing University.

Patients with HSCP underwent surgical repair by Furlow or Sommerlad palatoplasty. Their ages performing surgical procedures ranged from 9 months to 12 months. The mean age at follow-up was similar between groups. Patients were randomly assigned to Furlow palatoplasty group ($n = 20$, 9 males and 11females) and Sommerlad palatoplasty group ($n = 16$, 7 males and 9 females). Surgical procedures were performed by two senior surgeons, respectively (14, 15). Fifteen healthy children (good articulation, no hearing handicap, no cleft lip or cleft palate, no congenital maxillofacial developmental malformations, no orthodontic treatment history) were selected as the control group. Details were provided in **Table 1**.

Perceptual speech assessment

Speech evaluation was evaluated by two experienced speech pathologists using a speech articulation test table (21). Patients were asked to read a standard list of 63 phrases that cover all phonemes and most common phonetic combinations in Mandarin Chinese, and 20 short sentences containing voiced and unvoiced pressure consonants, no-pressure consonants, and a mixture of nasal consonants. The next part of the test was a casual conversation between the participants and the speech pathologist, in which speech intelligibility, hypernasality and nasal emission were measured. These parameters were evaluated following the scoring guidelines and definitions of the CAPS-A protocol (22). Intelligibility and hypernasality were evaluated using a five-point scale, whereas for the evaluation of nasal emission a three-point scale was used. Interrater and intrarater reliabilities were investigated using weighted kappa statistics to assess observer variability. Each speech language pathologist rated speech after

TABLE 1 Age and gender distribution of the subjects.

		Surgical age (month)			
	n	Mean	Range	Male	Female
T1 group	20	10.5 months	9–12 months	9	11
T2 group	16	11 months	9–12 months	7	9

T1 group, furlow palatoplasty; T2 group, sommerlad palatoplasty.

listening to 20 recorded speech samples and the ratings were compared to determine agreement between the two raters. The ratings were made twice with an interval of one week by each rater and two ratings by the same rater were compared.

Nasoendoscopy

Nasoendoscopy was performed for patients diagnosed with hypernasality or nasal emission that were cooperative, usually over the age of 4 years. Nasoendoscopy was used to observe the motility of the velum and posterior pharyngeal wall and lateral pharyngeal wall of patients with VPI. The results were diagnosed as VPC and VPI.

Lateral cephalometric assessments

Set points (**Figure 1**): ANS, anterior nasal spine; PNS, posterior nasal spine; PPW, posterior pharyngeal wall; N, nasion; S, center of the sella turcica; PCB, pterygoid cranial base; AA, atlas; U, uvula, tip of the uvula when at rest.

Measurement methods: To eliminate the interference of age and sex among the 3 groups, all craniopharyngeal dimensions were standardized according to the anterior cranial base length (S–N) with a given value of 100 (S–N revision). Measurements derived from tracing of lateral cephalograms by drawing the sella nasion (S–N) plane as the x-axis and projecting a perpendicular line to this plane through the point S as the y-axis. The length of the velar PNS-U, the depth of the nasopharynx PNS-PPW and the length of the hard palate ANS-PNX (**Figure 1**) were measured, and the adequate ratio (velar length to pharyngeal depth ratio) was calculated. For the three groups, ANS, PNS, PCB, AA, U, PPW were marked in the coordinates according to their (x, y) values. To facilitate the comparison of velopharyngeal morphology among the 3 groups, the triangle connecting PNS, PCB, and AA was defined as the pharyngeal triangle (**Figure 2**). Each measurement was performed twice by the first author, and the mean value was recorded.

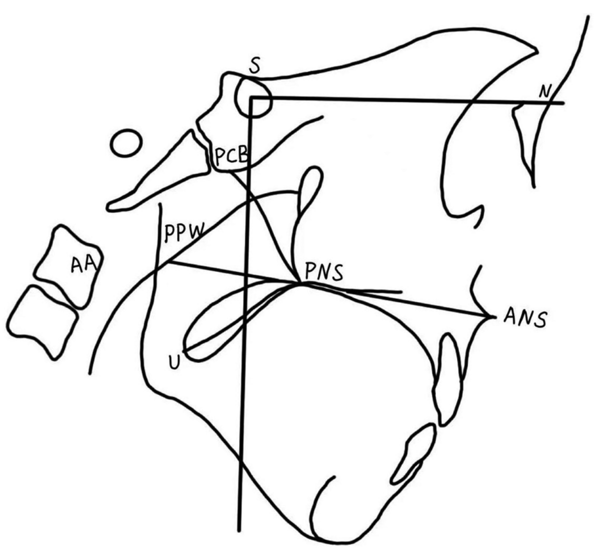

FIGURE 1
Cephalometric landmarks and velopharyngeal measures. ANS, anterior nasal spine; PNS, posterior nasal spine; PPW, posterior pharyngeal wall; N, nasion; S, center of the sella turcica; PCB, pterygoid cranial base; AA, atlas; U, uvula, tip of the uvula when at rest.

Statistical analysis

The Wilcoxon rank sum test was used to compare the speech outcomes. The results of cephalometric measurements of the three groups were subscribed to one-way ANOVA using IBM SPSS (version 26.0). Differences with $P < 0.05$ were considered statistically significant.

Results

Speech outcomes

The kappa values for interrater reliability were 0.67, and for intrarater reliability were 0.72 and 0.68, indicating substantial agreement. The results of PSA were shown in **Table 3**. The speech intelligibility in Furlow group was significantly better than that in Sommerlad palatoplasty ($P = 0.023$). Furlow palatoplasty's hypernasality improved better than Sommerlad palatoplasty ($P = 0.009$). Postoperative nasal emissions differed significantly between the two groups ($P = 0.016$) (**Table 2**).

Nasoendoscopy

3 patients of T1 group and 4 patients of T2 group were recommended to perform nasoendoscopy. There were 2(20) and 3(16) patients who were diagnosed with having VPI, respectively. Eventually, the rate of VPC in T1 group (90%) was higher than that in T2 group (81.3%).

Lateral cephalogram evaluation

The interclass correlation coefficient results for the test-retest reliability ranged between 0.72 and 0.83 ($P < 0.05$), suggesting dependable reliability and reproducibility of the adopted measuring strategy. The results of cephalometric measurements for the velopharyngeal structure of the three groups were presented in **Table 3**. There was no significant

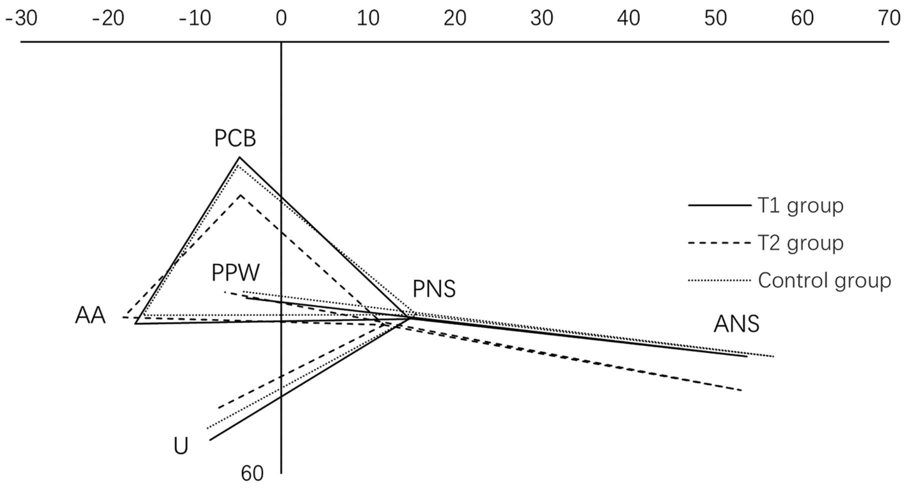

FIGURE 2
Velopharyngeal morphology of three groups. ANS, anterior nasal spine; PNS, posterior nasal spine; PPW, posterior pharyngeal wall; N, nasion; S, center of the sella turcica; PCB, pterygoid cranial base; AA, atlas; U, uvula, tip of the uvula when at rest.

TABLE 2 Comparative analysis of speech intelligibility, hypernasality and nasal emission in furlow and sommerlad palatoplasty groups.

	T1 group ($n = 20$)	T2 group ($n = 16$)	*P*
Speech intelligibility			
0: normal	13	4	0.023
1: different, not enough to cause comment	4	6	
2: different enough to cause comment, but intelligible t	1	3	
3: just intelligible to strangers	2	2	
4: impossible to understand	0	1	
Hypernasality			
0: absent	14	4	0.009
1: borderline	3	6	
2: mild	2	2	
3: moderate	1	3	
4: severe	0	1	
Nasal emission			
0: absent	14	5	0.016
1: occasionally heard	5	7	
2: Nasal emission	1	4	

T1 group, furlow palatoplasty; T2 group, sommerlad palatoplasty.

TABLE 3 Comparison of cephalometric landmarks among three groups.

Item	T1 Group	T2 Group	Control
ANS (*x*)	53.6 ± 2.7	52.9 ± 4.2	57.2 ± 3.7
(*y*)	43.6 ± 4.3	48.4 ± 4.3	43.7 ± 4.5
PNS (*x*)	14.8 ± 3.1	11.8 ± 4.3	15.6 ± 3.9
(*y*)	38.5 ± 3.6	39.3 ± 4.3	37.9 ± 3.6
PCB (*x*)	−4.6 ± 0.4	−4.8 ± 0.8	−5.1 ± 0.8
(*y*)	16.0 ± 2.1	21.3 ± 3.2	17.2 ± 2.6
PPW (*x*)	−4.0 ± 2.6	−6.5 ± 3.4	−4.3 ± 4.0
(*y*)	35.9 ± 3.6	34.8 ± 7.9	34.7 ± 5.0
AA (*x*)	−16.8 ± 4.1	−18.2 ± 4.8	−15.9 ± 5.9
(*y*)	39.5 ± 5.0	38.3 ± 4.6	38.0 ± 5.7
U (*x*)	−8.2 ± 3.6	−7.6 ± 3.2	−8.5 ± 4.5
(*y*)	55.3 ± 5.5	51.1 ± 6.1	53.7 ± 5.8
Velar length/mm	28.2 ± 3.2	25.0 ± 3.8	29.2 ± 3.6
Pharyngeal depth/mm	20.4 ± 2.5	21.1 ± 3.6	20.7 ± 3.3
Adequate ratio	1.37 ± 0.14	1.20 ± 0.18	1.41 ± 0.15

T1 group, furlow palatoplasty; T2 group, sommerlad palatoplasty.
ANS, anterior nasal spine; PNS, posterior nasal spine; PPW, posterior pharyngeal wall; N, nasion; S, center of the sella turcica; PCB, pterygoid cranial base; AA, atlas; U, uvula, tip of the uvula when at rest.

difference in the coordinates of points PNS, PCB, and AA on either axis among the 3 groups ($P > 0.05$). The velar length and Adequate ratio of T1 group was similar to that of the normal group ($P > 0.05$). The velopharyngeal structure was also similar to that of the control group. The velopharyngeal depths of the three groups were similar ($P > 0.05$). Velar length and adequate ratio were significantly smaller in T2 group than in the other two groups ($P < 0.05$). Adequate ratio averaged more than 1.3 in T1 group and control group. The point U of T2 group in the pharyngeal triangle was above that of the other two groups. The coordinate of point ANS on the x-axis in the T1 and T2 group was inferior to that in the control group ($P < 0.05$).

Discussion

The main objective of cleft palate repair is to reconstruct proper velopharyngeal function for normal speech intelligibility (19), which requires restoration of an anatomically well-integrated dynamic and functional soft palate. Furlow and Sommerlad methods are two well-established methods to optimize velopharyngeal function by restoring the velar muscular sling (14, 15). Numerous studies applied these two techniques to cleft repair and evaluated the postoperative outcomes respectively. However, limited studies performed a definitive comparison of velopharyngeal morphology between them. Herein, the comparisons were made between the two techniques in several methods, revealing that better speech outcome was produced in Furlow palatoplasty as opposed to Sommerlad palatoplasty.

VPC is the premise to yield adequate speech intelligibility. It was reported that 5% to 30% of patients have unsatisfactory speech outcomes and require secondary treatment because of velopharyngeal insufficiency (VPI) after primary palatoplasty (23–34), which may be related to several risk factors, including short velar length, insufficient velopharyngeal motility and deep palatopharyngeal cavity (26). Consistent with previous studies, our data suggested that the VPC rate was 90% in Furlow palatoplasty group vs. 81.3% in Sommerlad palatoplasty group. Furthermore, poorer speech intelligibility, higher hypernasality and nasal emissions were displayed in our study. This difference between these two methods is possibly due to the surgical characteristics that exert influence on the outcome of the operation. Both the Sommerlad and Furlow techniques repositioned the displaced levator veli palatini, contributing to develop a functional velum. Sommerlad palatoplasty focused more on anatomical reconstruction of the abnormal levater veli palatine and enhancement of muscular function, while the extension of the soft palate length is limited, which influences the outcome of palatopharynx closure. Nevertheless, Furlow palatoplasty not only restored the velar muscular sling to proper orientation but also elongated the velar length reducing the risk of longitudinal scar contracture. Consequently, the Furlow repair has a stronger ability to extend the soft palate length than sommerlad palatoplasty (18). After 289 patients with cleft palate repaired by Furlow palatoplasty, Chorney et al. (27) found only 5% of the patients needed secondary surgery as a result of VPI. And Wang et al. reported the length of soft palate increased by 13.23%, 10.10% after Furlow and Sommerlad palatoplasty, respectively (18). In line with these results, lateral cephalogram evaluation revealed a significantly increased soft palate length and higher adequate ratio after Furlow palatoplasty compared with Sommerlad palatoplasty, while there were no significantly differences in velopharyngeal depth between them.

Vlopharyngeal function assessment in previous studies depended largely on perceptual examination (8, 28, 29), which existed with the defect of significant heterogeneity and prevented comparison of results from different centers. Several methods have been developed to assess and describe velopharyngeal function and speech outcome, including electromyogram and nasopharyngeal endoscopy, but none of the existing methods can assess all indexes independently (30–34). To ensure a more reliable and accurate evaluation of velopharyngeal function and speech results in cleft patients, various evaluation methods were applied simultaneously in our study. Apart from perceptual assessment, 2-dimensional cephalometric studies provide a static evaluation of the velopharynx, while nasopharyngeal endoscopy can record and immediately replay velopharyngeal closure. Nasoendoscopy played a critical role in determining VPI, especially marginal VPI, which perceptual speech evaluation was in doubt. Therefore, jointly applying these methods can provide compelling data that can be made through comparison and analysis between different centers.

Of course, this present study exists certain limitations that should be acknowledged.

A notable shortcoming of our research is the insufficient sample size. Further data collection is required. Besides the surgical technique, for the lack of standardization of variables such as cleft width and hard palate repair technique, further analyses based on the above variables will be conducted in future research. The present study revealed that Sommerlad technique yielded worse velopharyngeal function and speech outcomes compared to Furlow technique. For HSCP patients, relative to Sommerlad palatoplasty, Furlow palatoplasty may be a more suitable surgical option. Of note, the opposing Z-plasty sacrificed velar width to gain length, which is not applicable to all types of clefts, particularly wide clefts due to excessive tension.

Conclusion

Furlow technique was proven to be superior compared to Sommerlad palatoplasty in terms of velopharyngeal function and morphology following primary cleft palate repair, which showed better speech intelligibility, higher VPC rate, longer velar length, shorter pharyngeal depth and a bigger Adequate ratio. Based on the above results, the Furlow palatoplasty should be preferred for patients with HSCP.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by This study was approved by the Ethics Committee, Nanjing Stomatological Hospital, Medical School of Nanjing University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

YL, YCD conceived and designed the research studies. XFF, WLL, JCN and XXC performed data collection and analysis; YL, YCD critically revised the manuscript. XFF, WLL and JCN wrote the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Dixon MJ, Marazita ML, Beaty TH, Murray JC. Cleft lip and palate: understanding genetic and environmental influences. *Nat Rev Genet*. (2011) 12:167–78. doi: 10.1038/nrg2933

2. JC M AJ. Orofacial clefting recent insights into a complex trait. *Curr Opin Genet Dev*. (2005) 15:270–8. doi: 10.1016/j.gde.2005.03.003

3. Eppley BL, van Aalst JA, Robey A, Havlik RJ, Sadove AM. The spectrum of orofacial clefting. *Plast Reconstr Surg*. (2005) 115:101e–114. doi: 10.1097/01.prs.0000164494.45986.91

4. Cheng X, Bo Z, Yin H, Yang K, Li J, Shi B. Age and preoperative velar closure ratio are significantly associated with surgical outcome of furlow double-opposing Z-plasty in palatal Re-repair. *J Oral Maxillofac Surg*. (2020) 78:431–9. doi: 10.1016/j.joms.2019.09.023

5. Wei Y, Zhong T, Yin X, Shi B, Zheng Q, Li J. Dynamic nasolabial growth after primary surgery for patients with bilateral cleft lip: a five-year follow-up study. *J Oral Maxillofac Surg*. (2019) 77:2125.e2121–2110. doi: 10.1016/j.joms.2019.05.013

6. Xu X, Cao C, Zheng Q, Shi B. The influence of four different treatment protocols on maxillofacial growth in patients with unilateral complete cleft lip, palate, and alveolus. *Plast Reconstr Surg*. (2019) 144:180–6. doi: 10.1097/prs.0000000000005711

7. Li F, Wang HT, Chen YY, Wu WL, Liu JY, Hao JS. Cleft relapse and oronasal fistula after furlow palatoplasty in infants with cleft palate: incidence and risk factors. *Int J Oral Maxillofac Surg*. (2017) 46:275–80. doi: 10.1016/j.ijom.2016.09.019

8. Williams WN, Seagle MB, Pegoraro-Krook MI, Souza TV, Garla L, Silva ML Prospective clinical trial comparing outcome measures between furlow and von langenbeck palatoplasties for UCLP. *Ann Plast Surg*. (2011) 66:154–63. doi: 10.1097/SAP.0b013e3181d60763

9. Sakran KA, Wu M, Alkebsi K, Mashrah MA, Al-Rokhami RK, Wang Y. The sommerlad-furlow modified palatoplasty technique: postoperative complications and implicating factors. *Laryngoscope*. (2022). doi: 10.1002/lary.30385. [Epub ahead of print]

10. Sakran KA, Yin J, Yang R, Elayah SA, Alkebsi K, Zhang S. Early cleft palate repair by a modified technique without relaxing incisions. *Cleft Palate Craniofac J*. (2022):10556656221135288. doi: 10.1177/10556656221135288. [Epub ahead of print]

11. Calis M, Ekin O, Kayikci ME, lcen M, Suslu N, Ozgur F. Does contribution of extended vomer flap to palatoplasty affects speech results. *J Craniofac Surg*. (2014) 25:1980–4. doi: 10.1097/SCS.0000000000001030

12. Prathanee B, Pumnum T, Seepuaham C, Jaiyong P. Five-year speech and language outcomes in children with cleft lip-palate. *J Craniomaxillofac Surg*. (2016) 44:1553–60. doi: 10.1016/j.jcms.2016.08.004

13. Devani P, Watts R, Markus AF. Speech outcome in children with cleft cleft palate: aerophonoscope assessment of nasal emission. *J Craniomaxillofac Surg*. (1999) 27:180–6. doi: 10.1016/S1010-5182(99)80048-1

14. Sommerlad BC. A technique for cleft palate repair. *Plast Reconstr Surg*. (2003) 112:1542–8. doi: 10.1097/01.PRS.0000085599.84458.D2

15. Furlow LT. Cleft palate repair by double opposing Z-plasty. *Plast Reconstr Surg*. (1986) 78:724–38. doi: 10.1097/00006534-198678060-00002

16. Khosla RK, Mabry K, Castiglione CL. Clinical outcomes of the furlow Z-plasty for primary cleft palate repair. *Cleft Palate Craniofac J*. (2008) 45:501–10. doi: 10.1597/07-063.1

17. Kara M, Calis M, Kara I, Kayikci ME, Gunaydin RO, Ozgur F. Comparison of speech outcomes using type 2b intravelar veloplasty or furlow double-opposing Z plasty for soft palate repair of patients with unilateral cleft lip and palate. *J Craniomaxillofac Surg*. (2021) 49:215–22. doi: 10.1016/j.jcms.2021.01.003

18. Wang K, Wang Q, He W, Wang F, Chen S, Zhang N. The effect of Zigzag palatoplasty on the repair of cleft palate and its comparative study with sommerlad palatoplasty and the double opposing Z palatoplasty. *J Craniofac Surg*. (2020) 31:e717–20. doi: 10.1097/SCS.0000000000006673

19. Li Y, Wu M, Yang C, Tsauo C, Li C, Liu R. Evaluation of fistula rates in three cleft palate techniques without relaxing incisions. *J Craniomaxillofac Surg*. (2021) 49:456–61. doi: 10.1016/j.jcms.2021.01.022

20. Perkins JA, Lewis CW, Gruss JS, Eblen LE, Sie KC. Furlow palatoplasty for management of velopharyngeal insufficiency: a prospective study of 148 consecutive patients. *Plast Reconstr Surg*. (2005) 116:72–80; discussion 81–74.doi: 10.1097/01.prs.0000169694.29082.69

21. Qiu Y, Zheng Q, Shi B, Li Y, Wang Y, Yin H. Influential factors affecting the postoperative velopharyngeal function among aged cleft palate patients. *Hua Xi Kou Qiang Yi Xue Za Zhi*. (2014) 32:54–7. doi: 10.7518/hxkq.2014.01.013

22. John A, Sell D, Sweeney T, Harding-Bell A, Williams A. The cleft audit protocol for speech-augmented: a validated and reliable measure for auditing cleft speech. *Cleft Palate Craniofac J*. (2006) 43:272–88. doi: 10.1597/04-141.1

23. Nam SM. Surgical treatment of velopharyngeal insufficiency. *Arch Craniofac Surg*. (2018) 19:163–7. doi: 10.7181/acfs.2018.02082

24. Collins J, Cheung K, Farrokhyar F, Strumas N. Pharyngeal flap versus sphincter pharyngoplasty for the treatment of velopharyngeal insufficiency: a meta-analysis. *J Plast Reconstr Aesthet Surg*. (2012) 65:864–8. doi: 10.1016/j.bjps.2012.01.020

25. Liu BY, Chen XX, Cao J, Lu Y. Analysis of velopharyngeal function and speech outcomes of sommerlad palatoplasty combined with sphincter pharyngoplasty in surgical repair of older patients with cleft palateexperience from a major craniofacial surgery centre in eastern China. *Br J Oral Maxillofac Surg*. (2020) 58:819–23. doi: 10.1016/j.bjoms.2020.04.026

26. Nguyen DC, Patel KB, Skolnick GB, Skladman R, Grames LM, Stahl MB. Progressive tightening of the levator veli palatini muscle improves velopharyngeal dysfunction in early outcomes of primary palatoplasty. *Plast Reconstr Surg*. (2015) 136:131–41. doi: 10.1097/PRS.0000000000001323

27. Chorney SR, Commesso E, Tatum S. Incidence of secondary surgery after modified furlow palatoplasty: a 20-year single-surgeon case series. *Otolaryngol Head Neck Surg*. (2017) 157:861–6. doi: 10.1177/0194599817703948

28. Dong Y, Dong F, Zhang X, Hao F, Shi P, Ren G. An effect comparison between furlow double opposing Z-plasty and two-flap palatoplasty on velopharyngeal closure. *Int J Oral Maxillofac Surg*. (2012) 41:604–11. doi: 10.1016/j.ijom.2012.01.010

29. Reddy RR, Gosla Reddy S, Vaidhyanathan A, Bergé SJ, Kuijpers-Jagtman AM. Maxillofacial growth and speech outcome after one-stage or two-stage palatoplasty in unilateral cleft lip and palate. A systematic review. *J Craniomaxillofac Surg*. (2017) 45:995–1003. doi: 10.1016/j.jcms.2017.03.006

30. Yin H, Ma L, Shi B, Guo C, Zhao S, Li Y. A study on the application of the perceptual assessment in the diagnosis of the velopharyngeal function. *Hua Xi Kou Qiang Yi Xue Za Zhi*. (2012) 30:197–200. doi: 10.3969/j.issn.1000-1182.2012.02.021

31. Perry JL, Sutton BP, Kuehn DP, Gamage JK. Using MRI for assessing velopharyngeal structures and function. *Cleft Palate Craniofac J*. (2014) 51:476–85. doi: 10.1597/12-083

32. Kuehn DP, Moon JB. Velopharyngeal closure force and levator veli palatini activation levels in varying phonetic contexts. *J Speech Lang Hear Res*. (1998) 41:51–62. doi: 10.1044/jslhr.4101.51

33. Huang H, Chen N, Yin H, Skirko JR, Guo C, Ha P, et al. Validation of the Chinese velopharyngeal insufficiency effects on life outcomes instrument. *Laryngoscope*. (2019) 129:E395–401. doi: 10.1002/lary.27792

34. Zong Y, Cheng X, Xia W, Xie Z, Yang Y, Shi B. The correlation between OSA-related quality of life and two mental statuses in adolescent Chinese patients with cleft palate: a comprehensive study. *Front Pediatr*. (2022) 10:985375. doi: 10.3389/fped.2022.985375

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Growth patterns of the nasolabial region following unilateral cleft lip primary repair

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Surgical correction is the optimal way of repairing a congenital cleft lip. Patients with this condition often undergo initial surgical treatment at an early age and achieve an acceptable outcome. However, their levels of satisfaction will decrease in later stages of life as facial growth and development will inevitably cause changes in long-term outcomes, especially in the nasolabial region. Therefore, it is important for surgeons to understand nasolabial development after primary treatment and tailor their surgical techniques appropriately. This review focuses on the growth patterns of the nasolabial region after primary repair, so as to provide references for operative strategy.

KEYWORDS

unilateral cleft lip, primary repair, primary rhinoplasty, nasolabial region, growth patterns

1. Introduction

Cleft lips (CLs) are the most common congenital deformities affecting the orofacial region; patients with CLs usually have significant orofacial deformities (1–3). Moreover, patients with a unilateral cleft lip and palate (UCLP) were detected with a more pronounced asymmetry than those with a bilateral cleft lip and palate (BCLP) (4). Significant differences between the cleft and the non-cleft sides existed only around the cleft but not in the broader regions of the maxillary complex (5). Therefore, the main orofacial deformities are manifested in soft tissue covering the nasolabial region (6), for example, a deviation of the columella toward the non-cleft side, widening of the nasal sill, displacement of the alar base, and flattening of the lower lateral cartilage (LLC) (7).

Deformities in soft tissue can be easily corrected compared with those in hard tissue (8). In order to improve the soft tissue profile, some researchers proposed that there was a close relationship among muscles in the nasolabial region, histologically and biomechanically, and the deformities of the cleft lip were the result of the joint actions of these muscles, which were caused by the uneven distribution of the nasolabial muscles (9–11).

Due to facial development and growth, the nasolabial morphology changes, eventually leading to significant residual asymmetry. Therefore, the main challenge in cleft lip primary reconstruction is to restore normal nasolabial morphology by taking into account various perspectives, with consideration given to the anticipated changes that occur over time (12). This places a great deal of responsibility on surgeons to accurately assess the anatomic deformity along with anticipated fourth-dimensional changes and improve and adjust their surgical strategy so as to optimize long-term postoperative outcomes (13, 14).

This review summarizes the growth patterns of the nasolabial region following unilateral cleft lip primary repair, in order to provide a reference for the surgical refinement of primary repair of CL so as to minimize facial asymmetry and guide secondary corrective surgery.

2. Landmarks and measurements of the nasolabial region

Some facial anatomical landmarks were used to quantitatively assess nasolabial growth patterns, such as crista philtri (cphi), cheilon (ch), subnasale (sn), alare (al), and subalare (sbal) (15). Labial width (cphi–ch), heminasal width (sn–al), medial-oblique labial height (sn–cphi), lateral-oblique labial height (sbal–cphi), and nasal sill width (sn–sbal) are the most globally and widely used evaluation indices, and these were used in this study (16) (**Figure 1**). In addition, nasal tip angle, columellar angle, columellar–labial angle, columellar height, and dome height were used as evaluation parameters (17).

3. Lip

3.1. Labial width

Primary repair leads to significant improvements in the morphology of the upper lip and nose (18). In order to study the labial growth changes in UCLP patients, Ayoub et al. analyzed the changes in crista philtri in 21 patients with unilateral CL who underwent primary repair at the age of 3 months. At 3 years postoperatively, the crista philtri on both the cleft and the non-cleft sides was displaced laterally and posteriorly, and philtrum width (cphi–cphi') and labial width (cphi–ch) increased significantly (19).

Mulliken and Labrie further measured and analyzed the labial width of 99 UCLP patients repaired by modified rotation advancement. The average labial width of the cleft side was about 8.36% shorter than that of the non-cleft side, but at a follow-up at 6 years of age, the gap was reduced to only 2.80%, which implied an asymmetrical growth pattern (16). Knight et al. re-evaluated a number of patients and extended the observation period, providing more details about the rate of change (20). They divided the follow-up periods into two phases: the first included all 99 patients from the operational age to an average age of 6.6 and the second involved a subset of 50 patients at an average age ranging from 6.6 to 11.5. They disclosed that immediately upon operation, the average labial width of the cleft side became 9.15% shorter than that of the non-cleft side, but the gap was narrowed to 4.39% and 2.75%, respectively, during the subsequent two follow-ups (20). Obviously, the labial width of the cleft side and the non-cleft side increased disproportionately, with a greater increase in the width of the cleft side during the growth phase. As time passed by, the gap in the labial width between the two sides gradually narrowed, and the labial width on the cleft side was closer to that on the non-cleft side.

The discordance in labial width will affect the sagittal and vertical positions of the philtrum, resulting in philtrum inclination to the cleft side after primary repair (16, 19). In patients with UCLP, the labial width on the non-cleft side increased at a slower pace than that on the cleft side, and the crista philtri on the cleft side will drift medially during the subsequent growth phase, gradually approaching the position that is almost symmetrical with that on the non-cleft side. Then, the philtrum on the cleft side will also rotate from the lateral inclination to the vertical direction (16, 20) (**Table 1**).

3.2. Labial height

Comparing the distance from the labialis superioris (the most prominent upper midline point of the vermilion border of the upper lip) to the subnasale with the labial height, Ayoub et al. found that there was no difference in the labial height between the operated CL patients and the non-cleft children at 3 years of life (19). This finding necessitated that labial height should be described in terms of two parameters, medial-oblique height (sn–cphi) and lateral-oblique height (sbal–cphi) (20).

Mulliken et al. disclosed that immediately after repair, the medial-oblique height on the cleft side became slightly longer and the lateral-oblique height became shorter, but 6 years later, the medial-oblique height eventually matched that on the non-cleft side, while the lateral-oblique height remained shorter. Thus, it could be speculated that the growth rate of the medial-oblique height on the cleft side was slower than that on the non-cleft side, whereas the growth rate of the lateral-oblique height was consistent on both sides (16). As evidenced by Knight et al., in the first phase (6.6 years), the medial-oblique height on the cleft side increased at a slower rate (5.2%) than that on the non-cleft side. In the second phase (11.5 years), the cleft and noncleft sides saw an almost equivalent growth at a rate of 3.53% and 3.02%, respectively. Specifically, the medial-oblique height on the cleft side was 7.14% longer than on the non-cleft side immediately upon operation, 2.08% longer at 6.6 years, and 2.61% longer at 11.5 years. The medial-oblique height on the cleft side increased at a slower pace initially but proportionately with the non-cleft side later on, finally increasing faster. As for the lateral-oblique height (sbal–cphi), it was on average 3.66% shorter on the cleft side than that on the non-cleft side immediately upon operation and remained significantly shorter on the cleft side by 3.12% at the age of 6.6 and by 2.47% at the age of 11.5 (20). There was no significant difference in the growth rate of the lateral-oblique height between the cleft side and the non-cleft side. In other words, the height of both sides increased equally all through the two follow-up periods.

Based on the above, and together with the rapid growth of the transverse labial width on the cleft side, it is meaningful to mark the lateral crista philtri on the cleft side closer to the commissure to ensure the restoration of the labial height on the non-cleft side (16) (**Table 1**). Generally, current methods of primary repair are able to restore labial height, labial width, and labial symmetry effectively.

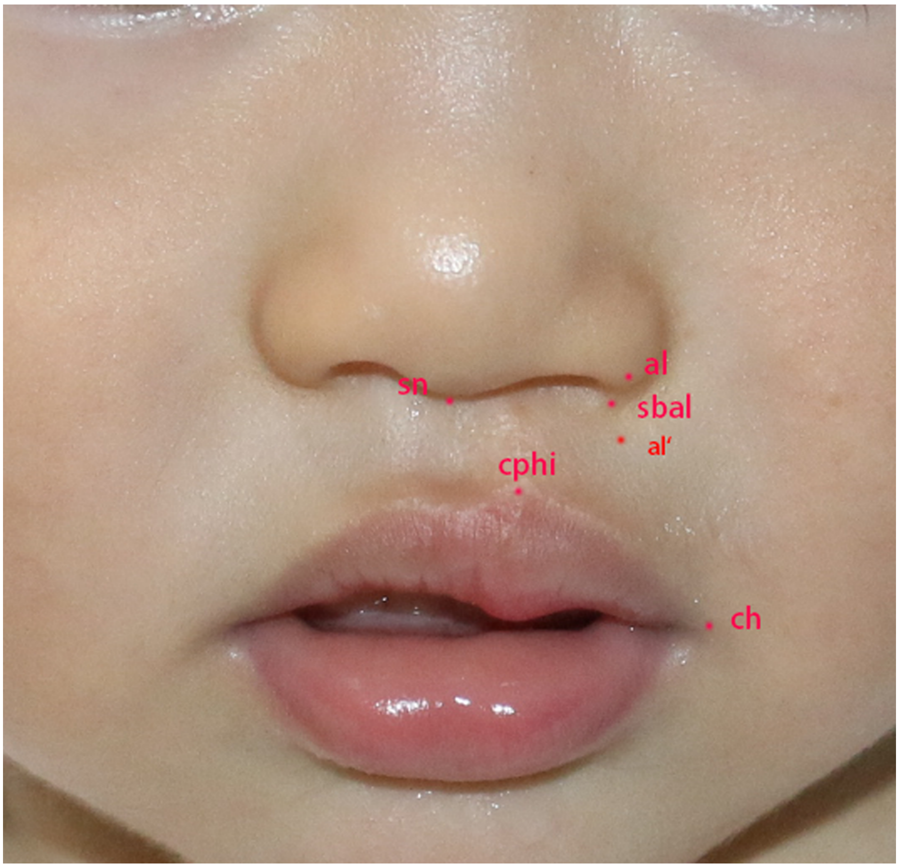

FIGURE 1
A patient with UCLP (right side) who underwent primary repair at 3 months of age showing the landmarks of anthropometric measurements. sn, the midpoint of the columellar base at which the lower border of the dorsal septum and the surface of the cutaneous upper lip meet; al, the most lateral point on each alar contour; al′, the dimension sn–al measured at sn–al′ along the perpendicular to the horizontal line through sbal; sbal, the medial point at the inferior limit of each alar base that is tangential to the cutaneous upper lip; cphi, the point on each elevated margin of the philtrum immediately above the vermilion line; ch, the point located at each labial commissure; sn–al, heminasal width; sn–cphi and sbal–cphi, labial height; cphi–ch, labial width; sn–sbal, nasal sill width . UCLP, unilateral cleft lip and palate.

4. Nose

4.1. Alar base

According to the anthropometric principle of Farkas, the malposition of the alare base has always been represented by the subalare (15, 27, 28). Traditional perspectives revealed that for a unilateral cleft lip, lateral and inferior deviation of the cleft alar base led to deformities. However, Tse et al. disputed this and certified upon a 3D image analysis that subalares on both sides were displaced, and compared with the cleft side, the non-cleft side alar base located more laterally to the facial midline. Surgical corrections involved an anterior rather than a horizontal movement of the subalare on the cleft side and an unexpected medial movement of the subalare on the non-cleft side considering that no dissection or suture was performed in that site (22) (**Table 1**). The position of the subalare on the cleft side in the sagittal direction was almost symmetrical to the non-cleft side immediately upon operation (16, 29, 30).

Three years after operation, the alar bases on the cleft side and the non-cleft side remained basically symmetrical, both drifting laterally and posteriorly but maintaining the vertical position (21). Even so, the nostril width (sbal–sbal') on both sides was significantly lower than that preoperatively (31) (**Table 1**). In the following age of 8–10 years, the width between the alare (al–al'), the width between the subalare (sbal–sbal'), and the ratio of the width of the subalare to the labial width (Sbal–Sbal'/Cphi–Ch) were significantly higher than those in the non-cleft population (20, 24). At the age of 10, the subalare of the cleft side in patients with a cleft palate drifted significantly more laterally than in the cleft lip–only group and normal control group (23, 32). However, the symmetrical results of repair, including retrusion of the alar base, were consistent over time and were unrelated to the fact whether alveolar cleft bone grafting was performed or not (22).

TABLE 1 Results of the main reviewed studies.

Reference	Country	Number of patients	Measurement methods	Patients age (years)	Follow-up	Associated procedures	Cleft type	Surgical techniques	Measurements
Ayoub et al. (19, 21)	Britain	21	3D images	3	Up to 3 years	McComb primary rhinoplasty	Unilateral (complete and incomplete)	Modified Millard cheiloplasty	Labial width and height; nasal base width; nasal height and projection; columellar length
Mulliken and Labrie (16)	United States	99	Direct anthropometry	6	Up to 6 years	Primary nasal correction	Unilateral (complete and incomplete)	Rotation advancement	Heminasal width; Labial height; labial width
Knight et al. (20)	United States	50	Direct anthropometry	11.5	Up to 11.5 years	Primary nasal repair	Unilateral (complete and incomplete)	Rotation advancement	Heminasal width; Labial height; labial width
Tse et al. (22)	United States	102	3D images	5	Up to 5 years	Foundation-based rhinoplasty	Unilateral (complete, incomplete and microform)	Cleft lip repair	Subalare; subnasale; alar base; nostril
Bell et al. (23)	Britain	95	3D facial models	10	Up to 10 years	McComb nose repair	UCLP (51); UCL (44)	Millard lip repair	Mean square distances between landmarks
Zreaqat et al. (24)	Malaysia	30	3D images	8–10	Up to 10 years	Not used	Unilateral (complete and incomplete)	Rotation advancement	Alar base root width; lip length; nose base/mouth width ratio
Chang et al. (25)	Taiwan	76	Photogrammetry	5	Up to 5 years	Primary rhinoplasty; nasoalveolar molding	Unilateral (complete and incomplete)	Modified rotation advancement (Mohler incision)	Nostril width and height; nasal sill height; nostril height-to-width ratio
Miyamoto and Nakajima (26)	Japan	31	3D computerized tomography	5–8	Up to early childhood	Primary rhinoplasty	Unilateral (complete and incomplete)	Rotation advancement	Nasal width; columellar length; nasal tip protrusion; vertical nasal tip projection
Moreira et al. (3)	Canada	70	Lateral cephalometric measurements	7–18	Up to 18 years	Not used	UCLP (complete)	Rotation advancement	Lip (nose) length and protrusion

UCLP, unilateral cleft lip and palate; UCL, unilateral cleft lip.

The subalare on the cleft side will continuously drift laterally from the postoperative period to adulthood (16, 23, 33) (**Table 1**). Therefore, it should be overcorrected medially and fixed on the nasal muscle or periosteum during primary repair (13, 16).

4.2. Nostril

Nostril height and nostril width were the most common parameters used to evaluate the changes in nostril morphology. The asymmetry of the nose improved immediately postoperatively, and there was a reduction of the total nostril width postoperatively compared with the preoperative period (31). The nostril height ratio significantly increased 4 years after McComb primary rhinoplasty (0.89 vs. 0.58), while there was no significant increase in nostril width (34). Chang et al. on one occasion measured and analyzed the photographs of 76 patients with CLP who were approximately 5 years old. He found that patients who underwent primary rhinoplasty (overcorrection) during CL primary repair showed the best postoperative results: the nostril height ratio 5 years postoperatively was significantly higher than that in those who did not undergo primary rhinoplasty (0.95 vs. 0.77), and the nostril width ratio was lower (1.21 vs. 1.36) although without any statistical significance (25) (**Table 1**). At 18–25 years of age, clinical differences still existed in the nasolabial region, which mainly manifested as a wider, larger, or flatter nostril (35).

The postoperative outcomes of the nostril depended not only on the preoperative severity of clefts but also on primary rhinoplasty (32). Evidence implied that rhinoplasty in infancy would not impair nasal growth and development (17). Accordingly, several surgeons advocated rhinoplasty simultaneously with primary lip repair (12, 13, 16, 30) and suggested 20% overcorrection to optimize the nostril height (7, 16, 25).

4.3. Nasal tip, columella, and nasolabial angle

Cerrati and Dayan observed a coordinated change between the nasal tip and the upper lip projection. As the nasal tip protruded, the upper lip projection increased (36), which would definitely cause changes to the nasolabial angle. The morphology of the nasal tip and columella is known to be braced mainly by LLC, so changes in LLC would possibly affect the morphology of the columella (7, 29). Therefore, we will discuss these three parameters together in this section.

At the postoperative 10 months, there was a partial improvement in the nasal tip and it was restored to a near normal position, but it was still lower and dislocated in the vertical direction (37). Then, at the postoperative 4 years, the average length of the columella on the cleft side was longer than that immediately upon operation, and the nasolabial angle and columellar angle increased, with the nasolabial angle showing the most significant increase (110.03 ± 3.31 vs. 94.62 ± 2.73) (34). At 5–8 years postoperatively, all other nasal measurements were satisfactory except for the vertical tip position (26). From 7 to 17.9 years of age, the columellar length in CLP patients averagely remained short of 2 mm, exhibiting a reduction of the nasolabial angle, especially between 11.1 and 17.9 years (105.34 ± 2.80 vs. 100.36 ± 2.97) (3) (**Table 1**).

These nasal changes might be attributed to the re-establishment of the muscle balance on both sides. After that, the nasolabial angle and columella could be corrected by growth and development (10, 28). Since there was a lack of muscle in the area near the nasal tip, this region was susceptible to scar contracture, which resulted in a downward rotation of the columella and the nasal tip. In addition, nasal tip and columella deformities were caused by a displacement of the anterior nasal spine and caudal septum (13), and therefore, an overcorrection of the nasal tip to an extremely forward sagittal position would be necessary during primary repair to compensate for its depression caused by an insufficient bone base (12, 13).

4.4. Overall symmetry of the nose

The soft tissue morphology of the nose and lip in patients with UCLP is more asymmetrical than that in patients with BCLP (4, 38). At 3–4 months postoperatively, the overall symmetry of the nose significantly improves (18, 39). However, the nostrils in patients with complete UCLP (all repaired at 6 months of age) are still largely asymmetrical at 3 and 6 months postoperatively, and the nasal tip inclines toward the non-cleft side at 9 months of age. The amount of edema decreases by two-thirds at 1 month, 95% at 6 months, and 97.5% at 1 year after rhinoplasty (40). Therefore, the appropriate time to evaluate the nostril morphology should be at least 6 months postoperatively. At 12 months of age, the symmetry of the nose ameliorates, with the remnant asymmetry observed on the nostril rim (41). In patients aged 6–12 years after primary repair, the nasal soft tissue exhibits a better symmetry than the hard tissue, and this could be attributed to the compensatory growth of the nasal soft tissue, especially in the vertical and sagittal dimensions (28). It is also believed that at this age, despite the nasal symmetry being close to "normal," the asymmetry persists in most patients (23, 42). In adulthood, however, assessed by 3D images in patients of the unilateral cleft lip–only group, no statistically significant asymmetry between the cleft side and the non-cleft side of the nose is identified (33, 43).

5. Summary

Surgical outcomes of cleft lip primary repair continue to improve with age, especially in the lip. However, the revision of nasal deformities remains a challenge, and this may be the last and most complicated aspect of cleft care, the reasons for which are traced to the multiple problems discussed in this review. Fortunately, primary rhinoplasty confirmed no significant impairment of the growth and development of the nose. Therefore, compared with secondary rhinoplasty, primary lip repair, combined with primary rhinoplasty, has more advantages in terms of establishing a new dynamic muscular balance around the nasolabial region, which may result in a more symmetrical nose during its growth and development, requiring less intervention at the time of definitive secondary rhinoplasty.

Author contributions

YX and NZ conceived the idea of writing this manuscript. YX, JL, and NZ drafted the manuscript and prepared the figure. QZ and BS critically revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Vyas T, Gupta P, Kumar S, Gupta R, Gupta T, Singh HP. Cleft of lip and palate: a review. *J Family Med Prim Care*. (2020) 9:2621–5. doi: 10.4103/jfmpc.jfmpc_472_20

2. Worley ML, Patel KG, Kilpatrick LA. Cleft lip and palate. *Clin Perinatol*. (2018) 45:661–78. doi: 10.1016/j.clp.2018.07.006

3. Moreira I, Suri S, Ross B, Tompson B, Fisher D, Lou W. Soft-tissue profile growth in patients with repaired complete unilateral cleft lip and palate: a cephalometric comparison with normal controls at ages 7, 11, and 18 years. *Am J Orthod Dentofacial Orthop*. (2014) 145:341–58. doi: 10.1016/j.ajodo.2013.11.018

4. Trotman CA, Faraway J, Hadlock T, Banks C, Jowett N, Regan D. Quantifying soft tissue shape and symmetry: patients with cleft lip/palate and facial paralysis. *Plast Reconstr Surg Glob Open*. (2018) 6:e1715. doi: 10.1097/GOX.0000000000001715

5. Yang L, Chen Z, Zhang X. A cone-beam computed tomography evaluation of facial asymmetry in unilateral cleft lip and palate individuals. *J Oral Sci*. (2016) 58:109–15. doi: 10.2334/josnusd.58.109

6. Suri S, Utreja A, Khandelwal N, Mago SK. Craniofacial computerized tomography analysis of the midface of patients with repaired complete unilateral cleft lip and palate. *Am J Orthod Dentofacial Orthop*. (2008) 134:418–29. doi: 10.1016/j.ajodo.2006.09.065

7. Sykes JM, Tasman AJ, Suarez GA. Cleft lip nose. *Clin Plast Surg*. (2016) 43:223–35. doi: 10.1016/j.cps.2015.09.016

8. Wu Y, Yang Y, Chen Y, Zhang Y, Wang G. Measurement and evaluation of the alar base in unilateral secondary lip nasal deformities by three-dimensional computed tomography. *Cleft Palate Craniofac J*. (2013) 50:696–703. doi: 10.1597/11-144.1

9. Huang H, Han Y, Akinade T, Li J, Shi B, Li C. Force balance reconstruction of the orbicularis oris in unilateral incomplete cleft lip. *J Plast Reconstr Aesthet Surg*. (2020) 73:1717–22. doi: 10.1016/j.bjps.2020.03.010

10. Mooney MP, Siegel MI, Kimes KR, Todhunter J. Development of the orbicularis oris muscle in normal and cleft lip and palate human fetuses using three-dimensional computer reconstruction. *Plast Reconstr Surg*. (1988) 81(3):336–45. doi: 10.1097/00006534-198803000-00004

11. Ningbei Y, Wu J, Chen B, Wang Y, Song T, Ma H. Nasolabial muscle finite-element study and clinical application. *Zhonghua Kou Qiang Yi Xue Za Zhi*. (2015) 50:278–85. Chinese. PMID: 26082049

12. Kamel GN, Segal RM, Tsai C, Kordahi A, Gosman AA. How to get consistently good results in cleft lip repair. *Plast Reconstr Surg Glob Open*. (2021) 9:e3677. doi: 10.1097/GOX.0000000000003677

13. Fisher MD, Fisher DM, Marcus JR. Correction of the cleft nasal deformity: from infancy to maturity. *Clin Plast Surg*. (2014) 41:283–99. doi: 10.1016/j.cps.2014.01.002

14. Ayeroff JR, Volpicelli EJ, Mandelbaum RS, Pfaff MJ, Asanad S, Bradley JP, et al. Component restoration in the unilateral intermediate cleft tip rhinoplasty: technique and long-term outcomes. *Plast Reconstr Surg*. (2019) 143:572e–80e. doi: 10.1097/PRS.0000000000005367

15. Farkas LG. Clinical evaluation of facial morphology in cleft lip palate patients. *Plast Reconstr Surg*. (1997) 99:262–3. doi: 10.1097/00006534-199701000-00053

16. Mulliken JB, Labrie RA. Fourth-dimensional changes in nasolabial dimensions following rotation-advancement repair of unilateral cleft lip. *Plast Reconstr Surg*. (2012) 129:491–8. doi: 10.1097/PRS.0b013e31822b69b4

17. Seo HJ, Denadai R, Lo LJ. Long-term nasal growth after primary rhinoplasty for bilateral cleft lip nose deformity: a three-dimensional photogrammetric study with comparative analysis. *J Clin Med*. (2019) 8(5):602. doi: 10.3390/jcm8050602

18. Al-Rudainy D, Ju X, Stanton S, Mehendale FV, Ayoub A. Assessment of regional asymmetry of the face before and after surgical correction of unilateral cleft lip. *J Craniomaxillofac Surg*. (2018) 46:974–8. doi: 10.1016/j.jcms.2018.03.023

19. Ayoub A, Garrahy A, Millett D, Bowman A, Siebert JP, Miller J, et al. Three-dimensional assessment of early surgical outcome in repaired unilateral cleft lip and palate: part 2. Lip changes. *Cleft Palate Craniofac J*. (2011) 48:578–83. doi: 10.1597/09-148

20. Knight ZL, Ganske I, Deutsch CK, Mulliken JB. The changing nasolabial dimensions following repair of unilateral cleft lip: an anthropometric study in late childhood. *Plast Reconstr Surg*. (2016) 138:879e–86e. doi: 10.1097/PRS.0000000000002655

21. Ayoub A, Garrahy A, Millett D, Bowman A, Siebert JP, Miller J, et al. Three-dimensional assessment of early surgical outcome in repaired unilateral cleft lip and palate: part 1. Nasal changes. *Cleft Palate Craniofac J*. (2011) 48:571–7. doi: 10.1597/09-147

22. Tse RW, Knight R, Oestreich M, Rosser M, Mercan E. Unilateral cleft lip nasal deformity: three-dimensional analysis of the primary deformity and longitudinal changes following primary correction of the nasal foundation. *Plast Reconstr Surg*. (2020) 145:185–99. doi: 10.1097/PRS.0000000000006389

23. Bell A, Lo TW, Brown D, Bowman AW, Siebert JP, Simmons DR, et al. Three-dimensional assessment of facial appearance following surgical repair of unilateral cleft lip and palate. *Cleft Palate Craniofac J*. (2014) 51:462–71. doi: 10.1597/12-140

24. Zreaqat M, Hassan R, Halim AS. Facial dimensions of Malay children with repaired unilateral cleft lip and palate: a three dimensional analysis. *Int J Oral Maxillofac Surg*. (2012) 41:783–8. doi: 10.1016/j.ijom.2012.02.003

25. Chang CS, Por YC, Liou EJ, Chang CJ, Chen PK, Noordhoff MS. Long-term comparison of four techniques for obtaining nasal symmetry in unilateral complete cleft lip patients: a single surgeon's experience. *Plast Reconstr Surg*. (2010) 126:1276–84. doi: 10.1097/PRS.0b013e3181ec21e4

26. Miyamoto J, Nakajima T. Anthropometric evaluation of complete unilateral cleft lip nose with cone beam CT in early childhood. *J Plast Reconstr Aesthet Surg*. (2010) 63:9–14. doi: 10.1016/j.bjps.2008.08.071

27. Farkas LG, Lindsay WK. Morphology of the adult face following repair of unilateral cleft lip and palate in childhood. *Plast Reconstr Surg*. (1973) 52:652–5. doi: 10.1097/00006534-197312000-00009

28. Huang L, Wang Z, Shan Z, Yeung AWK, Yang Y, Liang Z, et al. Nasal asymmetry changes during growth and development in 6- to 12-year-old children with repaired unilateral cleft lip and palate: a 3D computed tomography analysis. *J Anat*. (2022) 240:155–65. doi: 10.1111/joa.13538

29. Tan SPK, Ganske IM, Mulliken JB. Nasolabial revisions in unilateral incomplete cleft lip: one surgeon's 28-year experience. *Plast Reconstr Surg*. (2020) 145:1477–85. doi: 10.1097/PRS.0000000000006831

30. Haddock NT, Mcrae MH, Cutting CB. Long-term effect of primary cleft rhinoplasty on secondary cleft rhinoplasty in patients with unilateral cleft lip-cleft palate. *Plast Reconstr Surg*. (2012) 129:740–8. doi: 10.1097/PRS.0b013e3182402e8e

31. Feijo MJ, Brandao SR, Pereira RM, Santos MB, Silva HJD. Nostril morphometry evaluation before and after cleft lip surgical correction: clinical evidence. *Int Arch Otorhinolaryngol*. (2014) 18:192–7. doi: 10.1055/s-0033-1352506

32. Mercan E, Oestreich M, Fisher DM, Allori AC, Beals SP, Samson TD, et al. Objective assessment of the unilateral cleft lip nasal deformity using three-dimensional stereophotogrammetry: severity and outcome. *Plast Reconstr Surg*. (2018) 141:547e–58e. doi: 10.1097/PRS.0000000000004233

33. Lee D, Tanikawa C, Yamashiro T. Impairment in facial expression generation in patients with repaired unilateral cleft lip: effects of the physical properties of facial soft tissues. *PLoS One*. (2021) 16(4):e0249961. doi: 10.1371/journal.pone.0249961

34. Mirashrafi F, Rahavi-Ezabadi S, Tavakolnejad F, Amali A. Primary rhinoplasty in unilateral incomplete cleft lip nose: a 4-year follow up. *Int J Pediatr Otorhinolaryngol*. (2021) 145:110717. doi: 10.1016/j.ijporl.2021.110717

35. Othman SA, Ahmad R, Asi SM, Ismail NH, Rahman ZA. Three-dimensional quantitative evaluation of facial morphology in adults with unilateral cleft lip and palate, and patients without clefts. *Br J Oral Maxillofac Surg*. (2014) 52:208–13. doi: 10.1016/j.bjoms.2013.11.008

36. Cerrati EW, Dayan SH. Association of increasing nasal tip projection with lip position in primary rhinoplasty. *JAMA Facial Plast Surg*. (2017) 19:323–6. doi: 10.1001/jamafacial.2017.0070

37. Xu Y, Li J, Zhao S, Shi B, Zheng Q, Wang Y, et al. Four-dimensional changes of nasolabial positions in unilateral cleft lip and palate. *J Craniofac Surg*. (2013) 24:473–8. doi: 10.1097/SCS.0b013e318275ee3b

38. Bugaighis I, Mattick CR, Tiddeman B, Hobson R. 3D asymmetry of operated children with oral clefts. *Orthod Craniofac Res*. (2014) 17:27–37. doi: 10.1111/ocr.12026

39. Van Loon B, Maal TJ, Plooij JM, Ingels KJ, Borstlap WA, Kuijpers-Jagtman AM, et al. 3D stereophotogrammetric assessment of pre- and postoperative volumetric changes in the cleft lip and palate nose. *Int J Oral Maxillofac Surg*. (2010) 39:534–40. doi: 10.1016/j.ijom.2010.03.022

40. Pavri S, Zhu VZ, Steinbacher DM. Postoperative edema resolution following rhinoplasty: a three-dimensional morphometric assessment. *Plast Reconstr Surg*. (2016) 138:973e–9e. doi: 10.1097/PRS.0000000000002760

41. Brons S, Meulstee JW, Loonen TGJ, Nada RM, Kuijpers MAR, Bronkhorst EM, et al. Three-dimensional facial development of children with unilateral cleft lip and palate during the first year of life in comparison with normative average faces. *PeerJ*. (2019) 7:e7302. doi: 10.7717/peerj.7302

42. Linden OE, Taylor HO, Vasudavan S, Byrne ME, Deutsch CK, Mulliken JB, et al. Three-dimensional analysis of nasal symmetry following primary correction of unilateral cleft lip nasal deformity. *Cleft Palate Craniofac J*. (2017) 54:715–9. doi: 10.1597/16-073

43. Schwenzer-Zimmerer K, Chaitidis D, Berg-Boerner I, Krol Z, Kovacs L, Schwenzer NF, et al. Quantitative 3D soft tissue analysis of symmetry prior to and after unilateral cleft lip repair compared with non-cleft persons (performed in Cambodia). *J Craniomaxillofac Surg*. (2008) 36:431–8. doi: 10.1016/j.jcms.2008.05.003

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Correction of narrow nostril deformity secondary to cleft lip: indications for different surgical methods and a retrospective study

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Background: Cleft lip and/or palate (CLP) can lead to severe nasolabial deformities that significantly affect the appearance of the patient. Among all types of nasolabial deformities, narrow nostril deformities are the most troublesome, causing poor and unstable surgical outcomes. The purpose of this study was to develop an algorithm for surgical method selection for revision of narrow nostril deformities secondary to CLP based on retrospective clinical data.
Materials and methods: Patients with narrow nostril deformities secondary to CLP were enrolled in the study. Before surgery, patients' clinical data were collected and the width of the nasal floor and the length of the alar rim were measured. Surgical methods were determined according to the measurements. After surgery, a nostril retainer was applied for 6 months to consolidate and maintain the nostril shape. The surgical method and postsurgical changes were recorded for the final summary of the algorithm to select surgical methods for narrow nostril deformities.
Results: The data from 9 patients were analyzed. According to the width of the nasal floor and the length of the alar rim, correct surgical methods were determined. Four patients received nasolabial skin flaps to widen the soft tissue of the nasal floor. Three patients received upper lip scar tissue flaps to treat the narrow nasal floor. For the short alar rim, free alar composite tissue flap or narrowing of the nostril of the noncleft side was recommended.
Conclusion: The width of the nasal floor and the length of the alar rim are critical elements to consider when selecting the correct surgical method for revising narrow nostril deformities secondary to CLP. The proposed algorithm provides a reference for selecting surgical methods in future clinical practice.

KEYWORDS
cleft lip, narrow nostril deformities, diagnosis, rhinoplasty, surgical method selection

1. Introduction

Cleft lip and/or palate (CLP) is the most common birth defect in the world (1, 2). CLP causes morbidity to patients and imposes financial risks for families. With the popularization of prenatal diagnosis, the incidence of CLP in newborns is decreasing (3, 4). However, improvements in living standards have gradually increased people's aesthetic requirements. Secondary facial deformities after CLP include nasal and labial deformities.

Although clefts and deformities are revised in the first stage of surgery, differences in growth rates still exist in bilateral tissues during the growth period (5, 6). The existence of scars and the asymmetry of the lip and nose can distress patients when interacting with other people (7). Thus, secondary rhinocheiloplasty performed in adulthood is regarded as the last surgery in a cleft patient's management timeline (8).

Nasal deformities secondary to CLP include asymmetry of the nostrils, deviations of the septum, and collapse of the nasal tip (8). Nostril asymmetry is the most common deformity in patients with unilateral cleft lip. The typical clinical characteristics of nostril asymmetry include collapse of the nostril on the cleft side combined with an increased base width and decreased height (9). However, the cleft side nostril is sometimes narrow; this type of nostril asymmetry is rare. The main cases of narrow nostril deformity secondary to cleft lip may include the following aspects. Firstly, the improper surgical correction to remove excessive tissue may be dominant reason for it. Besides that, irregular applying of nasal retainer after the primary open rhinoplasty and postoperative scar contracture may also contribute to the occurrence of deformity (5, 6, 9).

Few studies have focused on the causes and treatments of narrow nostril deformities secondary to CLP. Thus, the surgical results for this deformity are often unsatisfactory. In this study, we summarize the causes of narrow nostril deformities secondary to CLP and propose corresponding surgical techniques.

2. Materials and methods

From February 2010 to July 2021, 9 consecutive patients with narrow nostril deformities secondary to CLP who underwent surgical treatment at the Department of Oral and Craniomaxillofacial Surgery, Shanghai Ninth People's Hospital were enrolled in this retrospective case series. Informed consent was obtained from all study subjects before participating in the study. The protocol of this retrospective case series was approved by the institutional ethics committee of Shanghai Ninth People's Hospital.

Inclusion criteria were: ①Patients with narrow nostril deformity secondary to unilateral clefts lip and palate. The narrow nostril deformity was defined as the differences of bilateral nasal floor or alar rim was more than 2 millimeters. ②According to the requirements of patients and their families. All patients underwent open rhinoplasty to revise the narrow nostril deformity. ③Considering that the growth and development of the nose are basically completed by the age of 16, the minimum age for revision surgery of narrow nostril deformity was set as the age of 16. ④Patients had adequate and complete presurgical and postsurgical follow-up clinical records for at least 12 months. Exclusion criteria were a history of nasal trauma and incomplete medical records.

Surgeons fully communicated with the patient before surgery. Complete clinical data, including previous surgical history and facial photos, were collected. The surgery was performed under general anesthesia. After disinfecting, presurgical photos were taken and the presurgical deformity was measured before the surgery. To quantitatively measure the degree of deformity, we use a syringe needle to dip with methylene blue to locate the landmark point. The landmark point we used include bilateral lip peak point, philtrum point and bilateral cheilion point. By penetrating the skin with a syringe, the methylene blue is then stained in the subcutaneous tissue. In this way, we can locate landmark point and perform corresponding measurements. The alar rim was encircled with a steel wire and the length of the steel wire was measured to determine the length of the alar rim. The width of the nasal floor and the breadth of the vermilion and scar were measured using castroviejo calipers. After evaluating the degree of the deformity, various surgical methods were performed to correct the nasal and labial deformities secondary to CLP.

Two days after surgery, a nostril retainer was placed to consolidate and maintain the nostril shape. Patients were instructed to remove and clean the nostril retainer after 6 consecutive hours. Seven days after the surgery, sutures were removed and patients were instructed to apply the nostril retainer for 6 months. Postsurgical photographs were taken immediately, 1 month, 3 months, and 6 months after the surgery.

In all these patients, the surgical revision methods and the presence of postsurgical complications, such as infection and deformity recurrence, were monitored. During the follow-up, patient satisfaction and treatment outcomes were recorded and evaluated.

3. Results

Nine patients with narrow nostril deformities secondary to unilateral CLP were enrolled in the study. No recurrence of deformity occurred post surgically in all patients. And all patients were satisfied with the postsurgical results. Characteristics of the patient population, patient diagnosis, and surgical methods are summarized in **Table 1**. Since all these patients' primary surgeries had been performed for more than 15 years and were not performed in our center, it is not possible to obtain the surgical procedures and specific surgical technique of the primary surgery at this time. The mean age of the patients was 20.67 years (range 17–30 years, median 21 years). The mean age of the primary cheiloplasty was 5.89 months (range 3–12 months, median 6 months). The male: female ratio was 2:7. Five patients had left nasal deformities secondary to CLP and four patients had right nasal deformities secondary to CLP. Seven patients had unilateral cleft lip, cleft palate, and alveolar cleft; the other two patients only had unilateral cleft lip and cleft palate.

Based on a specific summarization of this group of cases, we further classify the narrow nostril deformity into three main categories according to the morphological differences of bilateral nostrils. The first type is the narrow nostril deformity caused by narrow nasal floor, which characterized by the difference of bilateral nasal floor greater than 2 mm, while the alar rim of the affected side is normal. The second one is the

TABLE 1 Demographics, diagnosis, patient features and final surgical methods.

Patient No	Age	Gender	Age of cheiloplasty	Diagnosis	Combined cleft palate and alveolar cleft or not	Surgical time of rhinoplasty	Surgical methods of rhinoplasty
1	17	Male	8 months	L. Nasal deformity secondary to CLP	Cleft lip + cleft palate + alveolar cleft	August 10, 2013	Nasolabial skin flap
2	22	Female	4 months	R. Nasal deformity secondary to CLP	Cleft lip + alveolar cleft	June 22, 2010	Nasolabial skin flap
3	18	Female	3 months	R. Nasal deformity secondary to CLP	Cleft lip + cleft palate + alveolar cleft	July 23, 2013	Nasolabial skin flap
4	21	Female	7 months	L. Nasal deformity secondary to CLP	Cleft lip + cleft palate + alveolar cleft	May 8, 2014	Nasolabial skin flap
5	30	Female	4 months	L. Nasal deformity secondary to CLP	cleft lip + alveolar cleft	March 18, 2014	Upper lip scar tissue flap
6	17	Female	6 months	L. Nasal deformity secondary to CLP	Cleft lip + cleft palate + alveolar cleft	August 7, 2012	Upper lip scar tissue flap
7	22	Male	1 year	R. Nasal deformity secondary to CLP	Cleft lip + cleft palate + alveolar cleft	March 2, 2010	Upper lip scar tissue flap
8	22	Female	3 months	R. Nasal deformity secondary to CLP	Cleft lip + cleft palate + alveolar cleft	July 18, 2011	Free alar composite tissue flap + narrow the nostril of non-cleft side
9	17	Female	6 months	L. Nasal deformity secondary to CLP	Cleft lip + cleft palate + alveolar cleft	April 9, 2021	narrow the nostril of non-cleft side

narrow nostril deformity caused by short alar rim. Such patients are with extremely short alar rim and the difference of bilateral alar rim is greater than 2 mm, while the nasal floor of the affected side is normal. The third type is the combination of the two-above type. Such patients are characterized by having both a narrow nasal floor and short alar rim at the same time. The deformity of this type is troublesome and requires a combination of various methods to revise the severe deformity.

3.1. Clinical presentation 1

A 17-year-old female patient was referred to our department for the management of left nasal and labial deformities secondary to CLP. This patient underwent cheiloplasty at the age of 6 months at a local hospital. She received palatoplasty at the age of 6 years in our department. Repair of the left alveolar cleft with iliac bone harvest was conducted at the age of 12 years at another hospital. As the child grew, the nasal and labial tissue grew and changed. The repaired lip was affected and the deformity become more apparent. Thus, the patient was referred to our department to revise the nasal and labial deformities. Physical examination revealed a wide postoperative scar on the left upper lip. The left vermilion was hypertrophic, the left lip peak was raised, and the lip bread structure did not show. The left nasal tip was collapsed, and the nostril sizes were asymmetric. The asymmetry of bilateral nostrils was particularly evident in this patient from the bottom view. The surgical objectives included excision of the residual scar, repositioning of key anatomic landmarks, including the vermilion-cutaneous junction, leveling of the vertical lip lengths, enlargement of the nostril on the affected side, and repositioning of the alar cartilage. Before surgery, the width of the nasal floor and the length of the alar rim were measured to confirm the causes of the narrow nostril and establish a reasonable treatment strategy. The main cause of the narrowed nostril was a narrow nasal floor, according to the presurgical measurements. Thus, the wide residual scar was not completely resected during surgery, and the residual pedicle scar tissue flap was transposed and transplanted to repair the narrow nasal floor. This surgical technique would resect the scar on the upper lip, adjust the shape of the upper lip, broaden the nasal floor tissue, and resolve the narrow nasal floor at the same time. Besides that, to solve the problem of nasal alar lateral malposition, open rhinoplasty was performed meanwhile to reposition the nasal alar cartilage. During the surgery, the bilateral nasal alar cartilage was freely dissociated and anatomically reduced through the bilateral tajima incision and the inverted V-shaped incision on the nasal columella. The patient was instructed to apply the nostril retainer for 6 months after the surgery to reposition the alar cartilage and maintain the nostril size. After the secondary rhinocheiloplasty, a good nasolabial profile was acquired. The photos before and after the surgery and the schematic diagram of the surgery are shown in **Figure 1**.

3.2. Clinical Presentation 2

A 20-year-old female patient with a chief complaint of nasal and labial deformities was presented to correct the deformities in our department. This patient received cheiloplasty at the age of 4 months at a local hospital. As the child grew, the nasal and labial tissue grew and changed and the deformity become more apparent. The patient was referred to our department for the urgent need to revise the nasal and labial deformities. The physical examination revealed a wide postoperative scar on the right upper lip. The vermilion-cutaneous junction was disrupted. The right nasal alar was malpositioned downward, and the nasal nostril was asymmetric with a narrow right nostril. The width of

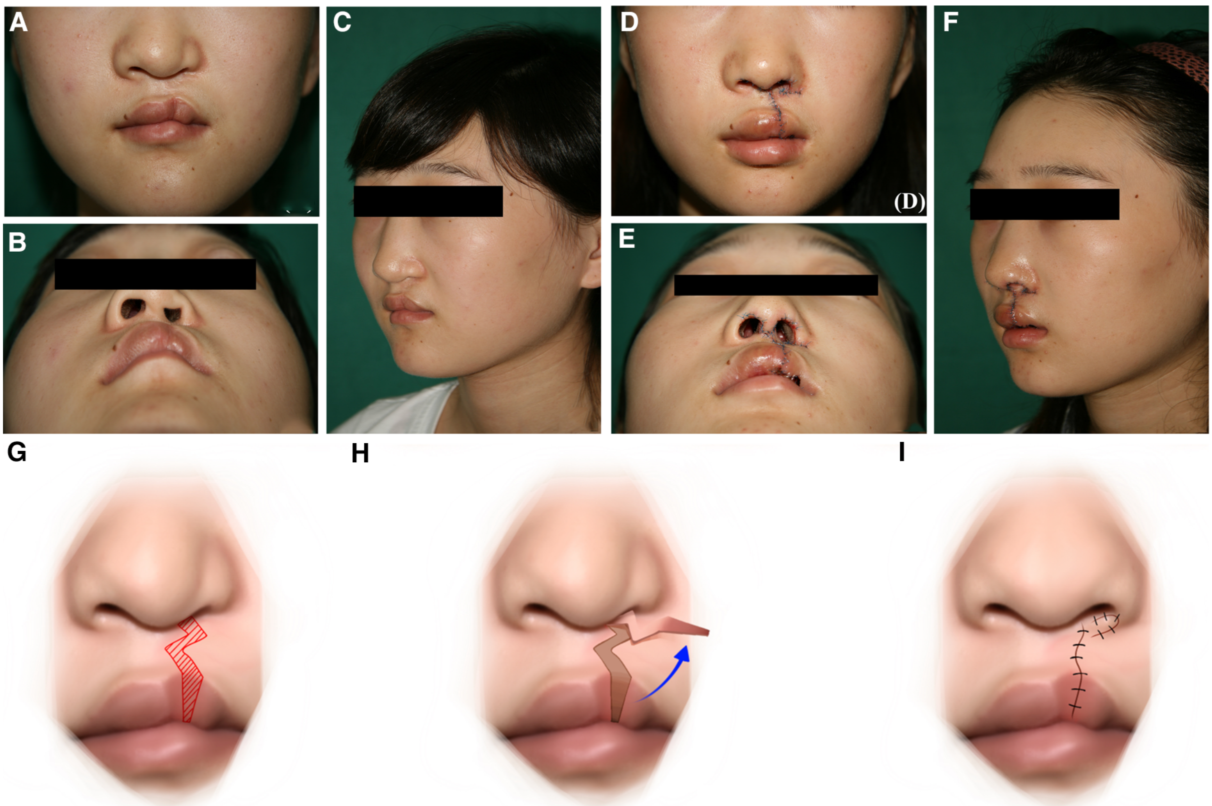

FIGURE 1
Clinical Presentation 1: A 17-year-old female patient with a narrow nostril secondary to cleft lip and palate corrected by the upper lip scar tissue flap. (A) Preoperative frontal view of the patient. (B) Preoperative bottom view of the patient. (C) Preoperative profile view of the patient. (D) Postoperative frontal view of the patient. (E) Postoperative bottom view of the patient. (F) Postoperative profile view of the patient. (G–I) Schematic presentation of the upper lip scar tissue flap.

the nasal floor and the length of the alar rim were measured to determine the causes of the narrow nostril. In this patient, the main cause of the narrow nostril was a narrow nasal floor. A nasolabial skin flap was designed, transposed, and transplanted to repair the narrow nasal floor of the affected side. Additionally, open rhinoplasty was applied to reposition the nasal alar cartilage and nostril retainer was utilized to maintain the position and shape of the nasal alar. Thus, resection of the residual scar, anatomical reduction of the nasal alar cartilage, repositioning of key anatomic landmarks, and leveling of vertical lip lengths were achieved at the same time during the surgery. In this case, the upper lip scar was an irregular polyline, so the upper lip scar could not be applied to enlarge the nostril. Thus, a nasolabial skin flap was designed and applied to enlarge the nostril on the affected side. Similarly, the nasal alar of the affect side was lateral malposition. To solve this problem, the bilateral tajima incision and the inverted V-shaped incision on the nasal columella was utilized in the surgery to dissociate and reposition the nasal alar cartilage anatomically. The nostril retainer was also applied to maintain the nostril size and alar cartilage position after the surgery for 6 months. A good nasolabial appearance was achieved after surgery. And the photos before and after the secondary rhinocheiloplasty are shown in Figure 2.

3.3. Clinical presentation 3

A 22-year-old female patient was diagnosed with right nasal and labial deformities secondary to CLP and presented at our hospital to resolve the narrow nostril of the affected side. This patient underwent cheiloplasty at the age of 3 months and palatoplasty at the age of 10 years at a local hospital. However, a palatal fistula remained after the surgery. The patient underwent surgery to repair the palatal fistula in our hospital at the age of 16 years. The nasal and labial deformities become more apparent with growth and development, and the patient was referred to our department for revision of these deformities. The physical examination revealed collapse of the nasal tip, asymmetry of the nostrils, and deviation of the septum to the left side. The asymmetry of the bilateral nostrils was particularly evident from the bottom view. Before surgery, the length of the alar rim and the width of the nasal floor were measured to establish a reasonable treatment plan. The alar rim on the noncleft side was 38 mm, and the alar rim on the cleft side was only 22 mm. Thus, a huge difference existed between the bilateral perimeters of the alar rims. A free alar composite tissue flap from the noncleft side was used to extend the perimeter of the cleft side alar rim. During the surgery, a wedge-shaped flap was designed and resected from the lateral one-

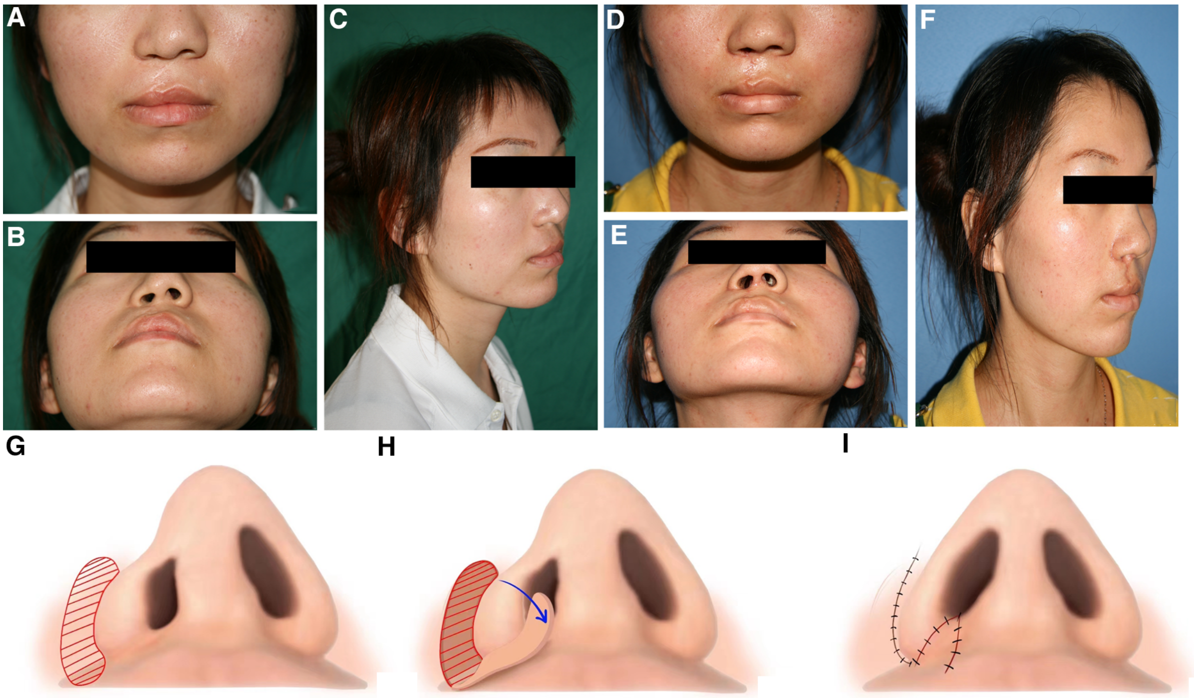

FIGURE 2
Clinical presentation 2: A 20-year-old female patient with a narrow nostril secondary to cleft lip and palate corrected by a nasolabial skin flap. (A) Preoperative frontal view of the patient. (B) Preoperative bottom view of the patient. (C) Preoperative profile view of the patient. (D) Frontal view of the patient 1 month after surgery. (E) Bottom view of this patient 1 month after surgery. (F) Profile view of this patient 1 month after surgery. (G–I) Schematic presentation of the nasolabial skin flap.

third of the alar rim on the noncleft side. Subsequently, the resected wedge-shaped flap was inserted into the corresponding position on the lateral one-third of the alar rim on the cleft side to lengthen the alar rim on that side. To ensure the survival of the free flap, the nasal alar cartilage was not anatomically repositioned during the primary rhinoplasty. Only the enlargement of the cleft side nostril was performed at this stage. Local compression was performed with vaseline gauze for 14 days. After the primary rhinoplasty, the asymmetry of the nostrils was revised. However, the collapse of the nasal tip and the malposition of the nasal alar cartilage still remained. The revision of nostril asymmetry provided better conditions for further revision of the nasal deformity. One year later, a secondary rhinoplasty with cartilage from the nasal septum was performed. During the secondary rhinoplasty, the bilateral nasal alar cartilage was also freely dissociated and anatomically reduced to remodel the shape of nasal tip and bilateral nasal alar. The bilateral tajima incision and the inverted V-shaped incision on nasal columella was applied this time for anatomic dissection of nasal alar cartilage. A satisfactory aesthetic and functional result was achieved ultimately. The schematic diagram of the surgery is shown in **Figure 3**.

4. Discussion

Nasolabial morphology is the key to facial aesthetics, and the existence of nasolabial deformities and upper lip scars secondary to CLP trigger great distress in human relationships (7). Although congenital clefts are repaired during infancy and childhood, nasal and labial deformities remain in adolescence and even into adulthood. Nasal deformities associated with cleft lip are characterized by a lack of symmetry, alar collapse on the affected side, loss of tip definition, and obtuse nasal labial angles (10–12). These troublesome maxillofacial deformities result not only from the baseline congenital deformities and deformational changes during craniofacial growth, but also from surgical procedure flaws, poor adherence to instructions in childhood, and maxillary deficiency secondary to CLP (6, 8, 13, 14). These deformities involve abnormalities in all layers, including nasal alar cartilage, nasal septal cartilage, skin, subcutaneous tissue, and even the basal bone (15). Thus, cleft rhinoplasty is regarded as a tough and vital reconstructive procedure. Several factors, such as scars from previous surgeries, insufficient soft tissue for tension-free closure, and displaced and deformed cartilage, might contribute to the final poor postsurgical results (16).

Among all these clinical characteristics, nostril asymmetry is the most common nasolabial deformity secondary to CLP and manifests as increased base width and decreased height (9). However, in clinical practice, the cleft side nostril is sometimes narrow due to improper surgery or overcorrection in a previous surgery. This condition is extremely troublesome due to insufficient soft tissue for nostril augmentation. In addition to the soft tissue defect, scars at the base of the nose and columella, the tight skin envelope, and the intrinsic memory of displaced

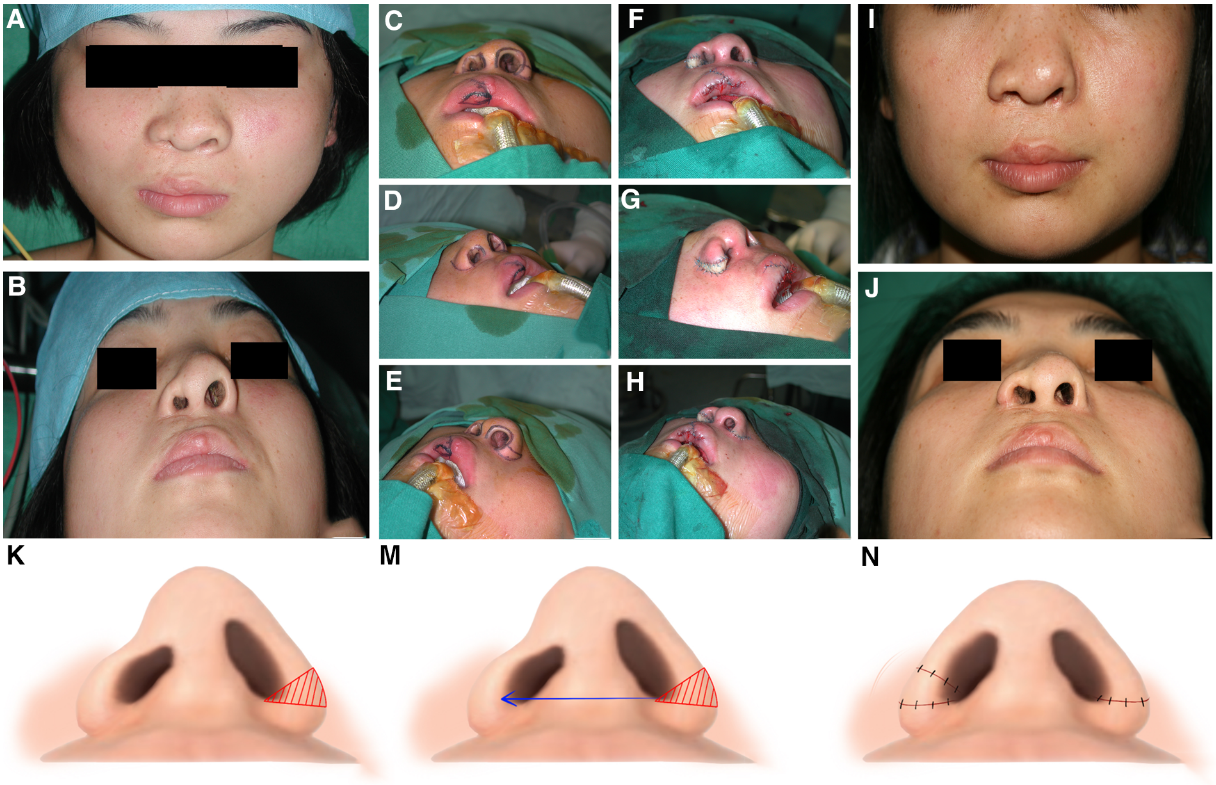

FIGURE 3
Clinical presentation 3: A 22-year-old female patient with a narrow nostril secondary to cleft lip and palate corrected by a free alar composite tissue flap. (A) Preoperative frontal view of the patient. (B) Preoperative bottom view of the patient. (C–H) Photos during the surgery. A wedge-shaped flap was designed and resected from the lateral one-third of the noncleft side alar rim. This free alar composite tissue flap was inserted into the corresponding position of the cleft side alar rim to lengthen the alar rim. (I) Frontal view of the patient 1 year after surgery. (J) Bottom view of the patient 1 year after surgery. (K–N) Schematic presentation of the free alar composite tissue flap.

and deformed cartilage might also cause deformity relapse (17). To resolve this troublesome situation, surgeons have tried various methods to revise this deformity and published some relevant case reports. Several surgical methods, including V-Y advancement flap or *Z*-plasty, are effective in correcting this rare deformity (18, 19). Additionally, Matsuya et. al applied a "flaying-bird" incision in the nostril tip to revise the cleft nasal deformity during open rhinoplasty (20). This procedure widens the nostril from the nostril tip but does not significantly improve the width of the nasal base. Essentially speaking, narrow nostrils are soft tissue deficiencies; thus, these methods result in only short-term improvements in the nasal shape. Slight deformities can be revised by local tissue modifications on the affected side. However, recurrence of the deformity is more likely for severe deformities due to postsurgical scar contracture. Therefore, some surgeons utilize composite tissue flap transplantation during the surgical procedure to revise narrow nostril deformities. To widen the alar base width during post-CLP rehabilitation, Balaji used a typical nasolabial flap to correct the narrow alar base deformity and achieve outstanding esthetic and functional outcomes (21). To restore the symmetry of bilateral nostrils, Suh et. al applied full-thickness skin grafts harvested from the postauricular region to widen the stenotic cleft nostril (18). Although skin grafts appeared as red and elevated scars during the early remodeling period, the transplant area eventually became similar to the surrounding tissues. Lee et. al utilized the subalar grafting technique to improve the symmetry of nostrils and achieved striking results in the immediate postsurgical period and beyond 1 year after surgery (22).

In this study, we summarized the algorithm for the selection of surgical methods for treating narrow nostril deformities secondary to CLP based on the literature and our clinical experience (**Figure 4**). While designing the surgical plan, all clinical data should be collected, including the patient's chief complaint, medical history, and facial photography. In addition, accurate clinical measurements are important in establishing a surgical plan. We used a steel wire to encircle the alar rim and measured the length of the steel wire to precisely determine the length of the alar rim. Besides that, we used castroviejo calipers to precisely measure the width of the nasal floor and the breadth of the vermilion and scar. Based on the clinical data, the causes of narrow nostril deformities can be divided into three main categories, including a narrow nasal floor, a short alar rim, and a combination of both. When the nasal floor is narrow while the alar rim is normal, a nasolabial skin flap or upper lip scar tissue flap is recommended to utilized for enlarging the width of the nasal floor. To be specific, when there is a broad scar on the upper lip, an upper lip scar tissue flap is recommended to

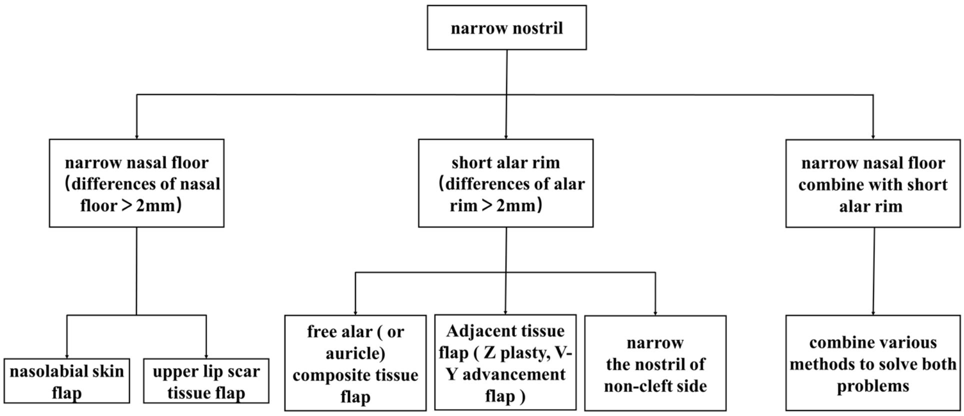

FIGURE 4
Algorithm for surgical method selection for revising narrow nostril deformities secondary to cleft lip and palate.

applied priority to avoid opening a second surgical area in the nasolabial fold region. If the upper lip scar is slight and does not need to be revised or the upper lip scar was irregular, a nasolabial skin flap is recommended because the resulting wound is more concealed. When the alar rim is slightly shorter than the other side, adjacent tissue flaps, such as *Z*-plasty or a V-Y advancement flap, are recommended. If the alar rim is significantly shorter than the other side while the nasal floor is

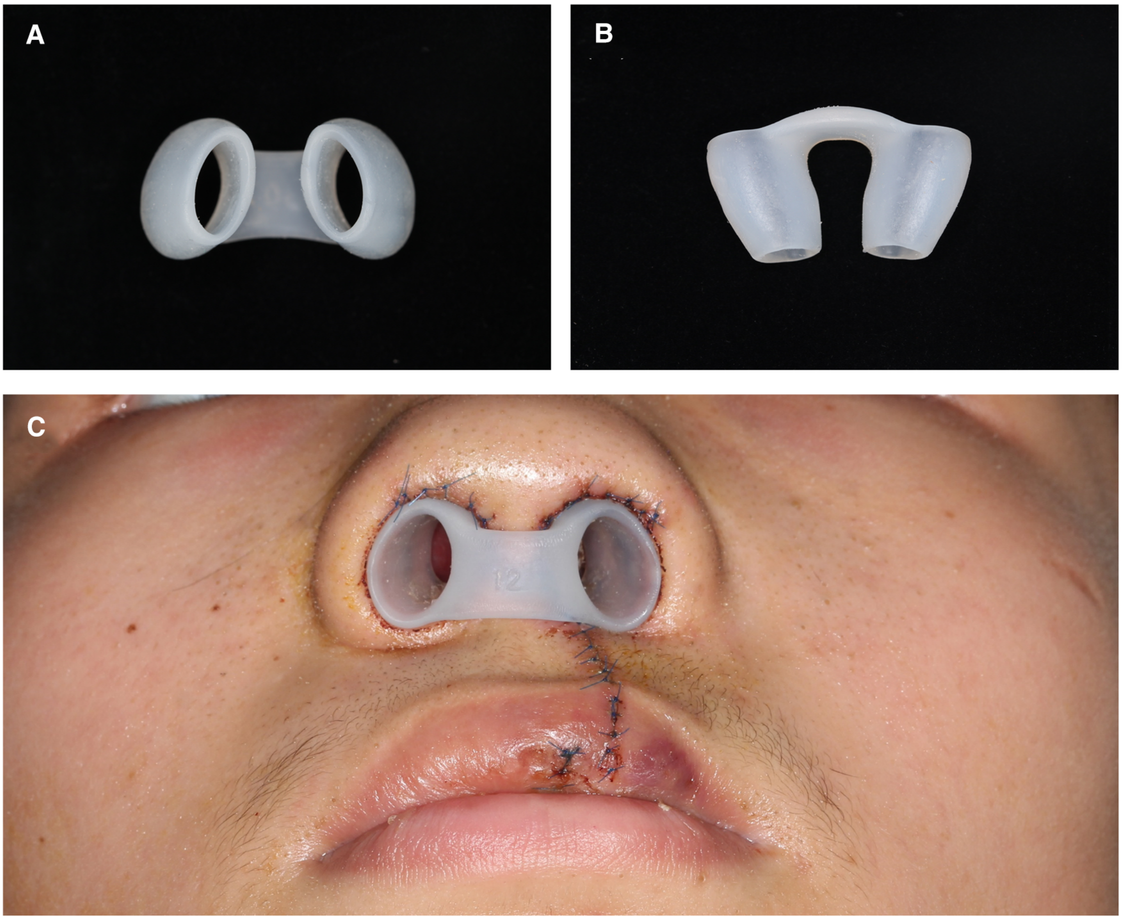

FIGURE 5
(A) and (B) the nostril retainer applied after the surgery. (C) The nostril retainer placed in bilateral nasal nostril to maintains the alar cartilage and the alar wing in the desired positions.

normal, free composite tissue flap transplantation, such as a free alar tissue flap or a free auricle tissue flap, is recommended. If the patient is unwilling to receive free tissue flap transplantation and the patient's nostril on the noncleft side is too large, a simple partial resection to narrow the noncleft side nasal alar can also result in a harmonious and symmetrical nasal profile. Finally, when a narrow nasal floor coexists with a short alar rim, a combination of various methods is recommended. The selection algorithm of surgical methods for revising narrow nostril deformities secondary to CLP is shown in **Figure 4**.

Of note, the nostril retainer (**Figure 5**), which maintains the alar cartilage and the alar wing in the desired positions, is widely applied in surgeries involving the alar cartilage and nostril to prevent alar collapse or nostril stenosis (23–25). However, diversity exists in the literature regarding to the time of postoperative nasal retainer should be applied. Most studies recommend using the nasal retainer for at least six months to maintain the desired surgical outcome (26, 27). However, in our patients, significant recurrence was observed even after the application of the nasal retainer for six months. Severe tissue deficiencies and scar hyperplasia may lead to this phenomenon. Thus, a prolonged application of the nasal retainer is recommended in such patients.

5. Conclusions

Narrow nostril deformities secondary to CLP are rare and troublesome in clinical practice. In this study, we summarized the treatment of these deformities and proposed an algorithm for surgical method selection for revising these deformities. According to this algorithm, the width of the nasal floor and the length of the alar rim are crucial in selecting the correct surgical method. Based on this algorithm, an appropriate surgical method was ascertained and favorable surgical outcomes were achieved.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board of Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine. The patients/participants provided their written informed consent to participate in this study.

Author contributions

HW contributed to the conception, design, data acquisition, analysis, interpretation, and drafted the manuscript; XX contributed to data acquisition and analysis; TW participated in post-surgical follow-up of patients and collation of clinical data; YY., YW and YZ performed the surgeries and critically revised the manuscript; YL contributed to the conception, design, and critically revised the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Neiswanger K, Mukhopadhyay N, Rajagopalan S, Leslie EJ, Sanchez CA, Hecht JT, et al. Individuals with nonsyndromic orofacial clefts have increased asymmetry of fingerprint patterns. *PLoS One*. (2020) 15(3):e0230534. doi: 10.1371/journal.pone.0230534

2. Dixon MJ, Marazita ML, Beaty TH, Murray JC. Cleft lip and palate: understanding genetic and environmental influences. *Nat Rev Genet*. (2011) 12 (3):167–78. doi: 10.1038/nrg2933

3. Zhu Y, Miao H, Zeng Q, Li B, Wang D, Yu X, et al. Prevalence of cleft lip and/or cleft palate in guangdong province, China, 2015–2018: a spatio-temporal descriptive analysis. *BMJOpen*. (2021) 11(8):e046430. doi: 10.1136/bmjopen-2020-046430

4. Salari N, Darvishi N, Heydari M, Bokaee S, Darvishi F, Mohammadi M. Global prevalence of cleft palate, cleft lip and cleft palate and lip: a comprehensive systematic review and meta-analysis. *J Stomatol Oral Maxillofac Surg*. (2022) 123 (2):110–20. doi: 10.1016/j.jormas.2021.05.008

5. Feijo MJ, Brandão SR, Pereira RM, Santos MB, Justino da Silva H. Nostril morphometry evaluation before and after cleft lip surgical correction: clinical evidence. *Int Arch Otorhinolaryngol*. (2014) 18(2):192–7. doi: 10.1055/s-0033-1352506

6. Knight ZL, Ganske I, Deutsch CK, Mulliken JB. The changing nasolabial dimensions following repair of unilateral cleft lip: an anthropometric study in

late childhood. *Plast Reconstr Surg*. (2016) 138(5):879e–86e. doi: 10.1097/PRS.0000000000002655

7. Dissaux C, Diop V, Wagner D, Talmant JC, Morand B, Bruant-Rodier C, et al. Aesthetic and psychosocial impact of dentofacial appearance after primary rhinoplasty for cleft lip and palate. *J Craniomaxillofac Surg*. (2021) 49(10):914–22. doi: 10.1016/j.jcms.2021.06.004

8. Rohrich RJ, Benkler M, Avashia YJ, Savetsky IL. Secondary rhinoplasty for unilateral cleft nasal deformity. *Plast Reconstr Surg*. (2021) 148(1):133–43. doi: 10.1097/PRS.0000000000008124

9. Zhang Z, Huang TC, He Y, Li S, Li Z, Chen J, et al. Modified use of costal cartilage in asians for the correction of nostril asymmetry in unilateral secondary cleft lip nasal deformity. *Ann Plast Surg*. (2021) 86(2):175–81. doi: 10.1097/SAP.0000000000002503

10. Tiong WH, Zain MA, Basiron NH. Augmentation rhinoplasty in cleft lip nasal deformity: preliminary patients' perspective. *Plast Surg Int*. (2014) 2014:202560. doi: 10.1155/2014/202560

11. van Loon B, Maal TJ, Plooij JM, Ingels KJ, Borstlap WA, Kuijpers-Jagtman AM, et al. 3D Stereophotogrammetric assessment of pre- and postoperative volumetric changes in the cleft lip and palate nose. *Int J Oral Maxillofac Surg*. (2010) 39 (6):534–40. doi: 10.1016/j.ijom.2010.03.022

12. Vass G, Mohos G, Bere Z, Ivan L, Varga J, Piffko J, et al. Secondary correction of nasal deformities in cleft lip and palate patients: surgical technique and outcome evaluation. *Head Face Med*. (2016) 12(1):34. doi: 10.1186/s13005-016-0132-y

13. Huang L, Wang Z, Shan Z, Yeung AWK, Yang Y, Liang Z, et al. Nasal asymmetry changesduring growth and development in 6- to 12-year-old children with repaired unilateral cleft lip and palate: a 3D computed tomography analysis. *J Anat*. (2022) 240(1):155–65. doi: 10.1111/joa.13538

14. Zhou F, Lin W, Du Y, Li S, Jiang H, Wan L, et al. Single-stage repair of secondary unilateral cleft lip-nose deformity in adults. *J Craniomaxillofac Surg*. (2020) 48 (1):83–9. doi: 10.1016/j.jcms.2019.12.004

15. Nguyen HL, Hoang MP, Nguyen VM, Tran TT, Le VS. Use of septal cartilage in rhinoplasty to correct nasal deformity after unilateral cleft lip and palate surgery. *Clin Cosmet Investig Dent*. (2022) 14:131–40. doi: 10.2147/CCIDE.S364332

16. van Zijl FVWJ, Versnel S, van der Poel EF, Baatenburg de Jong RJ, Datema FR. Use of routine prospective functional and aesthetic patient satisfaction measurements in secondary cleft lip rhinoplasty. *JAMA Facial Plast Surg*. (2018) 20(6):488–94. doi: 10.1001/jamafacial.2018.0876

17. Jackson O, Wingate N, Lee A, Kaye AE. The conchal butterfly graft in secondary reconstruction of the bilateral cleft lip nasal deformity. *Int J Pediatr Otorhinolaryngol*. (2020) 129:109737. doi: 10.1016/j.ijporl.2019.109737

18. Suh JM, Uhm KI. Change in nostril ratio after cleft rhinoplasty: correction of nostril stenosis with full-thickness skin graft. *Arch Craniofac Surg*. (2021) 22 (2):85–92. doi: 10.7181/acfs.2021.00010

19. Cho BC. Correction of unilateral cleft lip nasal deformity in preschool and school-aged children with refined reverse-U incision and V-Y plasty: long-term follow-up results. *Plast Reconstr Surg*. (2007) 119(1):267–75. doi: 10.1097/01.prs.0000237015.45614.7a

20. Matsuya T, Iida S, Kogo M. Secondary rhinoplasty using flying-bird and vestibular tornado incisions for unilateral cleft lip patients. *Plast Reconstr Surg*. (2003) 112(2):390–5. doi: 10.1097/01.PRS.0000070723.17041.4D

21. Balaji SM. Cleft-Rhinoplasty constricted nasal floor reconstruction. *Ann Maxillofac Surg*. (2014) 4(2):182–5. doi: 10.4103/2231-0746.147121

22. Wu L, Wang H, You J. The utility of the subalar graft in nostril symmetry in rhinoplasty. *Plast Reconstr Surg*. (2022) 150(5):1108e. doi: 10.1097/PRS.0000000000009582

23. Ozkan B, Albayati A, Akinci K, Uysal CA, Ertas NM. A custom-made nostril retainer for adult population. *J Craniofac Surg*. (2020) 31(6):e533–4. doi: 10.1097/SCS.0000000000006462

24. Oh JS, Chung J, Ha JH, Yoo HK, Kim S. Custom-Made nasal retainer using latex NelatonUrine catheter after the cheiloplasty. *Cleft Palate Craniofac J*. (2021) 58 (11):1443–5. doi: 10.1177/1055665621992673

25. Al-Qatami F, Avinoam SP, Cutting CB, Grayson BH, Shetye PR. Efficacy of postsurgical nostril retainer in patients with unilateral cleft lip and palate treated with presurgical nasoalveolar molding and primary cheiloplasty-rhinoplasty. *Plast Reconstr Surg*. (2022) 150(3):623–9. doi: 10.1097/PRS.0000000000009426

26. Phannarus K, Jaijakul S. An innovation of postsurgical nasal retainer in a unilateral cleft lip and palate patient. *J Craniofac Surg*. (2021) 32(8):2833–4. doi: 10.1097/SCS.0000000000007724

27. Luo D, Li T, Wang H, Chen Y. Three-Dimensional printing of personalized nasal stents forPatients with cleft lip. *Cleft Palate Craniofac J*. (2019) 56(4):521–4. doi: 10.1177/1055665618782804

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Application of vertical transposition flap in closure for large facial soft tissue defects in children

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Background: While transposition flap is widely used for the repairs of facial defects, few studies has reported its application among children with large defects. In this study, we aimed to investigate the surgical techniques and principles in different locations on face of vertical transposition flap in children.
Methods: We retrospectively reviewed our hospital database and identified children who were treated with vertical transposition flap for large facial defects between January 2014 and December 2021. Information was collected including patients' demographics, location and dimension of the lesion, surgical procedure, additional surgeries, complications, and outcomes.
Results: A total of 122 patients (77 boys, 63.1%) were included in this study. The average age for participants was 3.3 years (3 months to 9 years). One hundred and four (85.3%) patients had melanin nevus and 18 (14.8%) had sebaceous nevus. The average size of defects was 5.8 cm^2 (ranging from 0.8–16.5 cm^2). Ten patients (8.2%) suffered from dermal layer or full-thickness necrosis in the distal part of their flaps, They all recovered after conservative treatment and there were noticeable scars at discharge. Five patients (4.1%) had slight traction of the mouth and eyelid, all recovered about 2 week after surgery. An acceptable cosmetic outcome was achieved for all the patients at last time follow-up.
Conclusions: Repairing large facial defects with vertical transposition flap is effective in Children, especially on forehead, cheek and mandible. However, this technique is far from perfect. Careful selection of appropriate patients and flap design might be needed.

KEYWORDS

children, facial defects, transposition flap, vertical, reconstruction

Introduction

Facial defects resulting from the excision of skin lesions such as melanin nevus, sebaceous nevus, or scars are relatively common in children. Face is the center of communication and emotion expression. Therefore, large lesions of the face may lead to devastating emotional and psychological outcomes among some sensitive populations such as children, who developed self-esteem and a sense of self-image at around 5 years of age (1, 2). Reconstruction of facial defects should consider cosmetic and functional results, such as skin texture, color match, and blood supply (3, 4). A local flap comprises skin and subcutaneous tissue with a direct vascular supply. It has several advantages including reliable blood supply, good skin texture and color match, and a single stage procedure (4).

Transposition flaps are among one of the most widely used local flaps for the repairs of facial defects. Larger defects can be better closed when the angle of the flap to the defect is increased to a right angle (5). Numerous studies have reported transposition flaps for reconstructing facial defects, including the area, angle, shape, and outcomes (6–9). However, few articles have discussed the surgical application in children. This article discusses the surgical techniques and application locations site of the vertical translocation flap in children.

Methods

Participants

A retrospective study was conducted for patients admitted to Department of Burn and Plastic Surgery, Beijing Children's Hospital, Capital Medical University, between January 2014 and December 2021 who were treated by 90° transposition flap for large facial defects. Clinical information concerning the patients' demographics, location and dimension of the lesion, surgical procedure, additional surgeries, complications, and outcomes were collected. The study was approved by the ethical review board of Beijing Children's Hospital, and informed consent was waived due to the retrospective nature of the study.

Surgical procedure

Before surgery, the individual facial skin was examined carefully to check if the primary closure was possible. Preoperative assessment of the lesion size, laxity of surrounding tissues, the possible flap length was made for all patients. Under general anesthesia, skin lesions were excised with a margin of clinically normal appearing skin to ensure complete removal. The depth of the excision was extended into the subcutaneous tissue. After excision, the defects often exhibited a circular or oval shape. The long (a) and short (b) axis of the defect was decided (**Figure 1**). A line extended from the long axis was drawn and the length of this extended line was half of the short axis (b/2). Another line that was vertical to the extended line was drawn at its end and the length of this vertical line was decided at the sum of long axis and half of the short axis (a + 2/b). Then the border of the flap was designed based on the extended and vertical line, and the size of flap was slightly larger than that of defect. After that, we incised the skin along the margins of the flap and separate it at the layer of Superficial Musculo-Aponeurotic System to ensure sufficient perfusion through subcutaneous vessels. The donor site was closed first. Then the elevated flap was transferred by 90 degrees to cover the defect and sutured in different layers with tension. Minor modifications would be made during the procedure if the flap wasn't able to be transposed freely or there was a limitation in arc of rotation.

Results

A total of 122 children were included in this study, with 77 (63.1%) being male. The average age for participants was 3.3 years (interquartile range: 3 months to 9 years). One hundred and four (85.3%) patients had melanin nevus and 18 (14.8%) had sebaceous nevus. The average size of defects was 5.8 cm^2 (ranging from 0.8–16.5 cm^2). Forty-eight (37.7%) patients had the defects on the cheek, 26 (27.4%) on the forehead, 22 (19.4%) on the mandible, 17 (13.9%) on the eyelid, 9 (7.4%) on the nose (**Table 1**).

All patients had successful lesion excision and vertical transposition flap to close the wound in single procedure. Three patients (4.8%) had incomplete eyelid closure, and 2 patients had slight traction of the upper lip immediately after surgery. All of them were fully recovered 2 week later. At discharge, one

TABLE 1 Basic information and follow-up of flaps in different locations.

	Cases	Average size (cm^2)	Flap necrosis	Thicker flap
Cheek	48	6.6	3	3
Forehead	26	8.1	2	1
Mandible	22	5.9	1	1
Eyelid	17	2.3	0	3
Nose	9	1.3	0	0

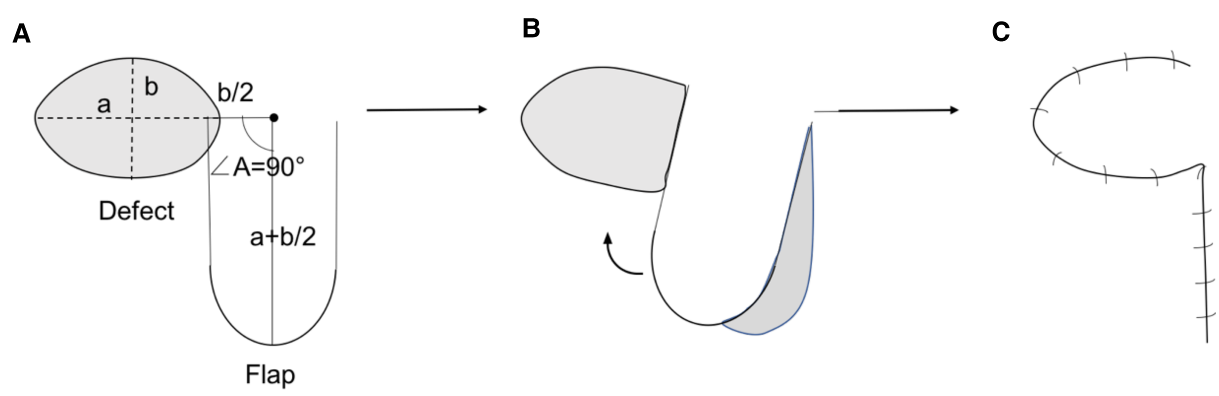

FIGURE 1
(A) Design of the flap. The angle A is nearly 90 degree. The length of two legs of ∠A are approximately sum of a and 2/b(a + 2/b). (B) Rotate the flap to cover the defect. (C) Close the wound from donor area.

hundred and twelve (91.8%) patients had their flaps survived. Four subjects (3.2%) suffered from dermal layer necrosis with pigment differences between the flap and surrounding skins. Another six subjects (4.8%) had full-thickness skin necrosis with noticeable scars left at discharge. Eight patients (6.6%) had a thicker flap than the surrounding tissues and 2 of them underwent flap thinning one year later. The average clinical follow-up was 8 months (Range: 3 to 24 months). An acceptable cosmetic outcome was achieved for all the patients.

Illusive case 1

This was 3-month-old boy with melanin nevi (6.0 * 3.0 cm) on forehead. His parents requested a single surgical repair because they were concerned about the effect of multiple anesthesia on the child's central system development. He had vertical transposition flap to cover the defect. However, removal of standing cutaneous deformities (dog-ear) led to de-vascularization of the flap and the distal part of the flap suffered partial-dermal necrosis two weeks later. He recovered well at discharge after conservative treatment. Last time follow-up at 8 months after surgery showed light scar and pigment left (Figure 2). The local hairs were removed by laser therapy (Intense pulsed light).

Illusive case 2

An 1-year-old boy presented with melanin nevi (4.0 * 3.0 cm) on the left cheek. His parents rejected serial incision, so we designed vertical transposition flap to cover the defect within the right cheek aesthetic subunit. The patient healed uneventfully, and the follow-up 1 month later showed acceptable scar (Figure 3).

Illusive case 3

An 9-year-old girl presented with melanin nevi (4.5*3.5 cm) on the lower left jaw region. She requested a single operation to achieve a good cosmetic result because of limited time. We designed a vertical transposition flap to cover her defect within the left aesthetic subunit of mandible. The patient recovered uneventfully and was satisfied with the final result (Figure 4).

Discussion

Facial lesions or defects affect children's appearance, which would have long-term effects on the mental health and life quality of both children and parents (8, 10, 11). Special consideration should be given when reconstructing facial defects

FIGURE 2
(A) Intraoperative lesion skin before excision. (B) Defect closure by 90° transposition flap. (C) 8 months after the surgery with light scar and pigment left because of partial-dermal necrosis of flap.

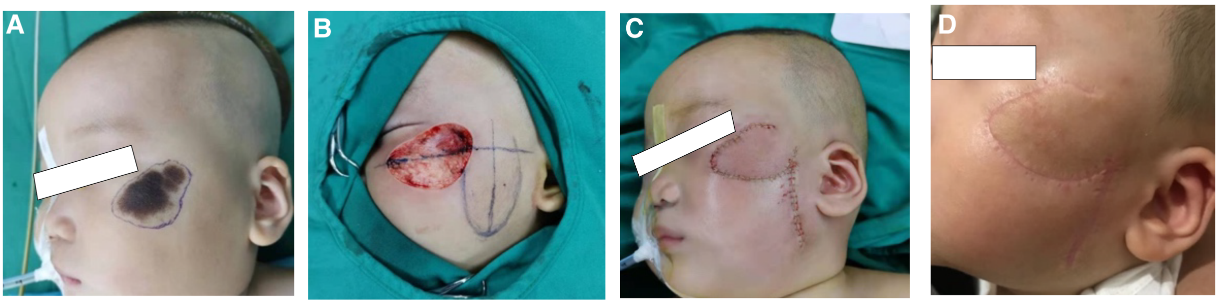

FIGURE 3
(A) Design of excision area preoperative. (B,C) Defect closure by vertical transposition flap. (D) 1 month after the surgery.

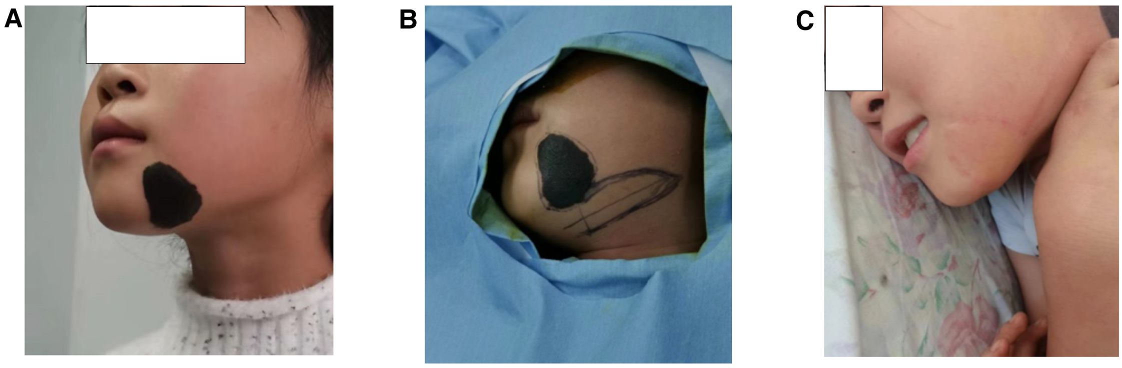

FIGURE 4
(A) Preoperative lesion skin. (B) Design of excision and flap area. (C) 10 months after the surgery.

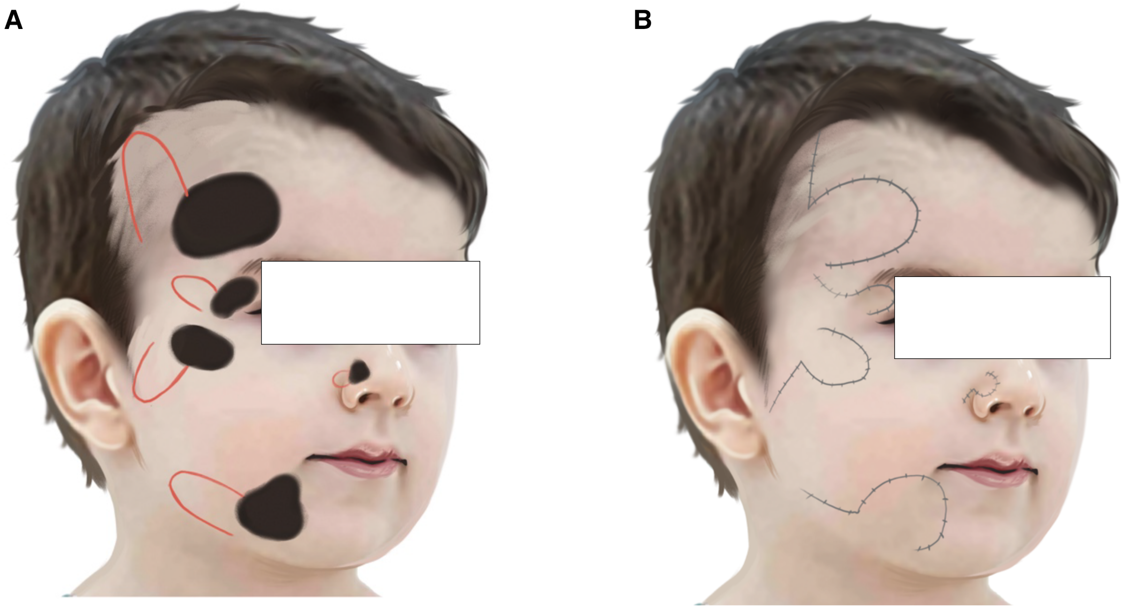

FIGURE 5
(A) Vertical flap design for different locations on face. (B) Secondary incisions should left in hairline, nasolabial fold, mandibular line or pre-auricular line.

in pediatrics. Generally, the facial skin of children has more elasticity and is growing with the growth centers of the facial skeleton. It is difficult to conceal a surgical scar in the pediatrics as there are no distinct borders between aesthetic subunits. Thus, primary wound closure is less likely to produce an acceptable cosmetic result among children, especially for the large defects (12, 13). We use transposition flaps in pediatric patients with large facial defects rather than the most commonly used expansion flaps due to their higher complications. In addition, many parents request a single surgical including excision and construction for many reasons, such as limited time, cost, concerns about the damage to their child's central system development from multiple anesthesia. As powerful reconstructive tools, transposition flaps are frequently used in cutaneous reconstruction. During the closure of defects, transposition flaps borrow skin laxity from adjacent areas and redirect the vectors of tension. This allows the primary defect to be closed with a few or even no wound edge tensions (15). Transposition flaps have been modified over time and are now used in a variety of locations due to their versatility (16). Defects on forehead, eyelid, outer canthus, cheek and mandible allow surgeons to position the flap in hairline, nasolabial fold, mandibular line or neck. So it's easier for surgeons to conceal the flap incision scars and reduce the occurrence of pulling of the facial features (**Figure 5**). We found that flaps located in eyelid and nose can cover smaller defects and are more likely to show distraction of eyelid and lips.

Transposition flaps were frequently to be rotated between 45° and 90°. However, there was a tension overlap between primary and secondary defects if the angle was too small, resulting in limited extent of flap and heavy scar (17, 18). When the transposition angle was larger than 90°, the effective length of the flap would decrease significantly and a larger flap was thus needed (15, 16). In our center, we increase the transposition angle to 90°. It decreased the tension between flap and defect while having a larger flap. In addition, we found that the donor site and the defect can be closed more easily. Our results showed that most of children achieved a satisfied cosmetic and functional outcome. However, it should be noted that the increased angle will lead to an increased flap length and a higher incidence of flap necrosis (17). In our case series, 6 patients suffered from partial or full-thickness skin necrosis. Even though they recovered well in the end after careful management, skin necrosis is an important complication that should be pay attention to.

Important points of operation in our center were as follows: (1) Flaps selection: The defects should be repaired in the same facial subunit with local flaps. Cross-facial aesthetic unit flaps like expanded flaps were utilized for larger defects only when local flaps are not sufficient (18). Efforts should be made to feel for areas with a greater laxity and examine the effects of different tension vectors on adjacent skins. (2) Flap position selection: The long axis of skin flap should be placed along relaxed skin tension line (RSTL) so that the incisions can be less conspicuous. The incision should be left in the concealed part like hairline, nasolabial fold, mandibular line, pre-auricular line for greater scar camouflage. (3) Flap design: To ensure the survival of distal part of flap, the length-width ratio of the flap should be less than 3:1. The length of flap is the sum of long axis and 1/2 of the short axis. (4) Skin flap thickness: While thinner flaps usually allow better cosmetic facial landmarks, a certain thickness of fat layer should be preserved to avoid the damage of subdermal vascular network. (5) Dog-ear deformities: Significant dog-ear deformities should be corrected appropriately. However, the minor deformities could be preserved to avoid insufficient blood supply. (6) Postoperative caring: A surgical drain or needle aspiration could be applied for the drainage of accumulated blood or fluid under the flap (13, 19).

In conclusion, vertical transposition flap is effective in repairing large facial soft tissue defects in children, showing acceptable functional and aesthetic outcomes. However, this technique is far from perfect. Careful selection of appropriate patients and flap design might be needed.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by Beijing Children's Hospital Ethics Committee. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

RF: Performed the research, collected and analysed data, wrote the initial draft of the paper. JC: Discussed the results and revised the manuscript. YW: Designed the study and collected the data all authors contributed to the writing and revisions. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2023.1171092/full#supplementary-material.

References

1. Giugliano C, Andrades PR, Benitez S. Nasal reconstruction with a forehead flap in children younger than 10 years of age. *Plast Reconstr Surg.* (2004) 114(2):316–25. doi: 10.1097/01.PRS.0000131870.52649.98

2. Kung TA, Gosain AK. Pediatric facial burns. *J Craniofac Surg.* (2008) 19(4):951–9. doi: 10.1097/SCS.0b013e318175f42f

3. Rohere TE, Bhatia A. Transposition flaps in cutaneous surgery. *Am Soc Dermatol Surg.* (2005) 31:1014–23. doi: 10.1111/j.1524-4725.2005.31826

4. Maciel-Miranda A, Morris SF, Hallock GG. Local flaps, including pedicled perforator flaps: anatomy, technique, and applications. *Plast Reconstr Surg.* (2013) 131(6):896e–911e. doi: 10.1097/PRS.0b013e31828bd89f

5. Starkman SJ, Williams CT, Sherris DA. Flap basics I. *Facial Plast Surg Clin North Am.* (2017) 25(3):313–21. doi: 10.1016/j.fsc.2017.03.004

6. Scott JF, Bordeaux JS. A conceptual approach to designing transposition flaps. *Dermatol Surg.* (2020) 46(1):9–19. doi: 10.1097/DSS.0000000000002011

7. Aizawa T, Hirayama T, Tojo S, Kiyosawa T. A banner flap with adjacent rotation flap for closure of circular skin defects: a schematic comparison with conventional rotation flap technique. *J Plast Surg Hand Surg*. (2021) 55(5):278–83. doi: 10.1080/2000656X.2021.1873797

8. Mann JA. Update on pediatric dermatologic surgery from tots to teens. *Curr Opin Pediatr*. (2014) 26(4):452–9. doi: 10.1097/MOP.0000000000000123

9. Steele RB, Jellinek NJ, Foy A, Lee K, Vij A, Knackstedt TJ. Use of extranasal bilobed transposition flaps in cutaneous reconstructive surgery at 2 institutions. *Dermatol Surg*. (2020) 46(10):1279–85. doi: 10.1097/DSS.0000000000002319

10. Masnari O, Neuhaus K, Aegerter T, Reynolds S, Schiestl CM, Landolt MA, et al. Predictors of health-related quality of life and psychological adjustment in children and adolescents with congenital melanocytic nevi: analysis of parent reports. *J Pediatr Psychol*. (2019) 44(6):714–25. doi: 10.1093/jpepsy/jsz017

11. Goel P, Wolfswinkel EM, Fahradyan A, Tsuha M, Hough M, Magee W, et al. Sebaceous nevus of the scalp. *J Craniofac Surg*. (2020) 31(1):257–60. doi: 10.1097/SCS.0000000000006007

12. Kung TA, Gosain AK. Pediatric facial burns. *J Craniofac Surg*. (2008) 19(4) 19 (4):951–9. doi: 10.1097/SCS.0b013e318175f42f

13. Hogg N. Primary and secondary management of pediatric soft tissue injuries. *Oral Maxillofac Surg Clin North Am*. (2012) 24(3):365–75. doi: 10.1016/j.coms.2012.04.007

14. Blake BP, Simonetta CJ, Maher IA. Transposition flaps: principles and locations. *Dermatol Surg*. (2015) 41:S255–64. doi: 10.1097/DSS.0000000000000479

15. Pepper J-P, Baker SR. Local flaps: cheek and lip reconstruction. *JAMA Facial Plast Surg*. (2013) 15(5):374–82. doi: 10.1001/jamafacial.2013.1608

16. Schultz TA, Cunningham K, Bailey JS. Basic flap design. *Oral Maxillofac Surg Clin North Am*. (2014) 26(3):277–303. doi: 10.1016/j.coms.2014.05.001

17. Hankinson A, Holmes T. Repair of defects of the central forehead with a modified banner transposition flap. *Am Soc Dermatol Surg*. (2017) 0:1–3. doi: 10.1097/DSS.0000000000001318

18. Reckley LK, Peck JJ, Roofe SB. Flap basics III: interpolated flaps. *Facial Plast Surg Clin North Am*. (2017) 25(3):337–46. doi: 10.1016/j.fsc.2017.03.006

19. Talbot SG, Pribaz JJ. First aid for failing flaps. *J Reconstr Microsurg*. (2010) 26 (8):513–5. doi: 10.1055/s-0030-1261697

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Pearls and pitfalls in contemporary management of marginal velopharyngeal inadequacy among children with cleft palate

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Marginal velopharyngeal inadequacy (MVPI) is a particular status of velopharyngeal closure after cleft palate repair. The physiological and phonological characteristics of patients with MVPI are significantly different from those with typical velopharyngeal insufficiency. The pathological mechanisms and diagnostic criteria of MVPI are still controversial, and there is limited evidence to guide the selection of surgical and non- surgical management options and a lack of recognized standards for treatment protocols. Based on a systematic study of the relevant literatures, this review identifies specific problems that are currently under-recognized in the diagnosis and treatment of MVPI and provides guidelines for further exploration of standardized and reasonable intervention protocols for MVPI.

KEYWORDS
cleft palate, velopharyngeal dysfunction, speech therapy, pharyngoplasty, palate lengthening

1. Introduction

Congenital cleft palate is one of the most common craniomaxillofacial birth defects in humans and may affect important physiological functions including speech, mastication, swallowing, hearing, and maxillofacial growth and development. Although primary cleft palate repair restores the continuity of soft and hard tissue and physiological anatomy of the palate, a significant percentage of patients still fail to fully close the velopharyngeal port during speech after surgery. The state coined as velopharyngeal inadequacy (VPI) results in varying degrees of speech dysfunction, seriously affects the quality of life and requires further medical intervention (1, 2). More specifically, the speech of patients with VPI is usually characterized by nasal emission, hypernasality and compensatory errors in articulation. And the severity of speech abnormality is associated with the extent of incomplete velopharyngeal closure.

There is no clear-cut distinction between normal and abnormal velopharyngeal closure, and a borderline closure exists between typical VPI and definitive velopharyngeal competent (VPC), which may appear as a mildly incomplete or unstable closure. Since the speech performance and treatment prognosis under the borderline state are significantly different from typical VPI or VPC, it has been classified as a separate diagnostic category as marginal velopharyngeal inadequacy (MVPI), which is widely used to date to evaluate the outcome of cleft palate management. However, there is no unified standard for the diagnosis of MVPI, and different studies not only use drastically different criteria but also differ in defining MVPI as a treatment success or failure, which seriously undermines the cross-sectional comparability of data related to cleft palate treatment outcomes. In addition, intervention options for MVPI are controversial. While the selection of surgery for typical VPI and speech training for VPC with articulation error are indisputable, the structural, physiological, and habitual factors affecting velopharyngeal fuction are often intertwined in MVPI (3). The differences in the willingness to improve speech among patients and the health economic considerations make the choice of surgical and non-surgical treatments for MVPI even more complicated (4–7).

In concern of the controversies in the management of MVPI, we systematically reviewed the research progress related to the pathological mechanism, diagnostic criteria and treatment outcomes of MVPI, so as to clarify the existing research difficulties, misunderstandings and shortcomings and provide reference for further improvement of MVPI treatment protocol.

2. Pathogenesis of MVPI

The concept of MVPI was first defined in 1976 as "mild or intermittent incomplete closure" and "a borderline status between complete and incomplete closure" (8). Among patients with MVPI, structural, physiological and habitual factors affecting velopharyngeal closure are intertwined. For example, articulatory errors and mild soft palate elevation deficits may be of reverse causality. It is often difficult to clearly distinguish the various pathological causes of speech intelligibility.

Smith Guyette (1996) suggested that the status of MVPI is where the velopharyngeal closure system demonstrates different degrees of competence in response to speech tasks of varying difficulty. Using sounds of /Pa/ and /Pi/ as a criterion, he observed complete closure of the /Pa/ sound and incomplete closure of the /Pi/ sound in some patients and speculated that there may be antagonistic action of the palatoglossal muscle against the levator veli palatini in /Pi/ sound, resulting in increased resistance to soft palate uplift and incomplete closure (9).

Warren made close observation on the timing of nasal emission and found that the closure phase in patients with MVPI was about 50 ms behind the normal population, resulting in a longer duration of nasal emission and a shorter duration of closure during functional speech. He then suggested that the pathological basis of MVPI may be related to the response timing of the velopharyngeal closure system (10).

Karnell et al. analyzed the pathological characteristics of velopharyngeal closure based on objective nasometer values and observed that some patients showed normal values when completing high-pressure test sentences containing stress consonants and abnormal values when completing low-pressure test sentences containing only vowels and semivowels. On this basis, they proposed the pressure-sensitive theory, suggesting that the velopharyngeal performance of patients with MVPI was influenced by the oronasal pressure associated with the speech task, showing "mixed" nasometer results (3, 11).

Morris hypothesized that MVPI might be categorized into two subtypes: the structural and functional. In the former, complete closure is not possible due to the structural constraints and should be manifested as persistent mild nasal emission, while in the latter, the velopharyngeal mechanism meets the requirements for closure but is affected by poor articulatory habits and demonstrates incomplete closure during difficult speech tasks, which should be manifested as intermittent nasal emission (12). This subtype classification hypothesis, however, has not yet been supported by adequate research data.

To date, there is no uniform understanding of the pathological mechanisms underlying the development of MVPI. Different studies often focused on only one aspect of speech performance. The lack of an exact pathological mechanism also leads to controversies regarding the diagnostic criteria for MVPI.

3. Diagnostic criteria of MVPI

Early in the introduction of the MVPI concept, there was debate on whether it should be classified as a transitional state on the continuous spectrum of VPI or as a third diagnostic classification distinct from typical VPI and VPC. With increasing evidence suggesting distinct performance in hypernasality and speech among patients with MVPI from those with VPI and VPC, and the clinical significance of MVPI diagnosis to treatment options and prognosis, MVPI became recognized as an independent diagnostic category and widely used in the evaluation of cleft palate treatment outcomes (3, 13). The diagnostic criterion of MVPI is yet to be unified. Accordingly, the identification between MVPI and mild VPI becomes critical to their clinical management.

The tools for velopharyngeal function evaluation include subjective evaluation, endoscopy, radiography, nasometer, and oronasal pressure test. Early studies mostly used a single examination for diagnosis, such as classifying patients with a velopharyngeal gap less than 2 mm on lateral radiographs as MVPI (14). Although diagnostic methods based on a single examination generally showed good internal consistency, the agreement between the results of different examination methods is often low. For example, more than half of the patients with a velopharyngeal gap less than 2 mm turned out to be definitive VPI or VPC (15).

Laine et al. made definitive diagnosis on velopharyngeal function basing solely on the ventilation port size deduced from nasometer values: a port less than 0.05 cm^2 was diagnosed as VPC, 0.05–0.09 cm^2 as marginal complete velopharyngeal closure, 0.10–0.19 cm^2 as marginal incomplete velopharyngeal closure, and more than 0.20 cm^2 as VPI (16). Warren et al. based their diagnosis algorithm on the severity of the hypernasality on a scale of 1–4, with VPC below 1.676, marginal complete velopharyngeal closure from 1.677 to 2.368, marginal incomplete velopharyngeal closure from 2.369 to 2.5, and VPI above 3.273 (17). Morris relied entirely on subjective evaluation for diagnosis, using a speech scale to obtain an overall score for nasal emission, resonance, and articulation. A score of 3–4 on the scale (1 for normal and 7 for severe abnormalities) was used as diagnostic criterion for MVPI (13). In addition, Morris (18) proposed to divide MVPI into two subtypes: "almost but not quite" (ABNQ) and "sometimes but not always" (SBNA). In the former, the velopharyngeal closure is always incomplete and there is a consistent mild nasal emission during pronunciation, whereas in the latter, complete closure can be achieved occasionally but not consistently (19). However, mild and intermittent incomplete closure could not simply equate to structural and functional causes (20). Although this subtype classification has potential value to intervention selection, its existence is not supported by the currently available data.

Concerning the limitations of a single examination, it is now believed that the diagnosis of MVPI should combine subjective and objective findings, and a three-dimensional and dynamic endoscopic evaluation of velopharyngeal port is generally recommended (21, 22). There are still drastic differences in the diagnostic criteria of MVPI reported in the literature, and more studies involving MVPI did not even clearly describe their diagnostic criteria (23–25). Moreover, there is no agreement on whether to classify MVPI as a successful or unsuccessful outcome for cleft palate treatment, which seriously affects the comparability among studies (26–28). A definite and explicit diagnosis criterion is prerequisite to intervention selection, and inconsistency in diagnosis inevitably leads to different management protocols for MVPI in different institutions.

4. Disagreements on the management philosophy of MVPI

The treatment options for typical VPI and VPC are relatively clear, with the former requiring further surgery to restore the velopharyngeal mechanism and the latter relying on speech training to correct habitual errors (29). In contrast, it is often difficult to draw a definitive line between structural velopharyngeal abnormalities and articulation abnormalities in patients with MVPI (30). Mild closure inadequacy may force compensatory articulation, and normal articulation may be restored after surgery without speech training, while abnormal articulatory habits may affect velopharyngeal closure and velopharyngeal closure insufficiency may disappear after correction of articulation (31, 32). In addition, MVPI status may be less stable during the follow-up as compared to VPI and VPC, further complicating the clinical decision-making (33, 34).

In an idealized medical setting, it seems reasonable to firstly prescribe speech training for all patients with MVPI and subsequently schedule surgery according to the training outcome. Speech training can determine whether articulation error is the initiating factor in causing speech problems and does not cause structural changes at the velopharyngeal port (4). In a realistic medical setting, however, the time and financial costs associated with speech training are not affordable for all families, especially in remote regions where speech therapy is not yet available (35–37).

The other extreme of the MVPI management is to prescribe indiscriminate surgery. Some scholars believed that patients with MVPI generally yielded poor outcomes to speech training and prefer to perform surgical intervention first (5, 12, 38). Some studies found that re-palatoplasty improves the outcome of speech training among patients with MVPI, probably because surgery makes it easier for them to achieve complete closure and master the correct articulation techniques with resonance and emission eliminated (5, 6). However, this strategy is at risk of overtreatment and complications to patients who may be potentially cured by speech training alone.

Thus, assessment of the sensitivity of MVPI patients to speech training seems to be an important prerequisite for the development of an accurate treatment plan. This philosophy was reflected in the ABNQ and SBNA category proposed by Morris, who suggested that the former is difficult to achieve further improvement through training and therefore suitable for surgical treatment, while the latter has more potential in velopharyngeal mechanism that could be activated by speech training (12, 18, 19). However, there are no reliable data to support the accuracy and reliability of Morris' subtype classification to guide clinical treatment.

In addition, the willingness of patients with MVPI patients is polarized. Some patients get along well with mild speech abnormalities in daily life and are not willing to undergo surgery, while some patients believe that their speech is close to completely normal and hold high expectations for the last step of treatment. Patients' attitude and expectation also play an important role in making treatment decisions (39, 40).

In view of the above-mentioned issues, the literatures have not yet formed a well-recognized standard treatment standard for MVPI. The identification of MVPI from mild VPI and the decision on corresponding management protocol are still highly subjective. Physicians are generally suggested to develop individualized treatment plans depending on their experience, which obviously lacks practical guidance. The lack of evidence for the clinical management of MVPI is the main reason for the absent of standardized protocols.

5. Clinical intervention options for MVPI

5.1. Speech therapy

Patients with MVPI are of their own characteristics in speech, usually not demonstrating all the typical problems of VPI in terms of hypernasality, emission and articulatory error, and their speech performance may vary in coping with different speech tasks. For example, Karnell et al. concluded that low-pressure test sentences were more likely to induce hypernasality in patients with MVPI. Speech spectrum analysis likewise suggested that pressure consonants were most likely to be abnormal in patients with MVPI (21, 41). It has been shown that about 80% of patients with MVPI demonstrated phonological problems (13, 21) and their common articulation errors included vowel omission and post-phonological articulation. Therefore, individualized speech therapy should be design for each patient. For example, the treatment of vowel omission should focus on target sound elicitation, and the treatment of post-phonological articulation should focus on moving the articulation position forward.

In addition, Continuous Positive Airway Pressure (CPAP) has also been used to assist speech training. Theoretically, CPAP provides a resistance training scenario for velopharyngeal closure and helps to strengthen the relevant muscles (42). It has been shown that CPAP could be potentially effective in improving the efficiency of speech training and reducing the difficulty of eliciting target sounds (36). This instrument, however, has not been widely employed among cleft centers. Accordingly, publications concerning the effectiveness of CPAP in facilitating cleft speech training are highly limited. Further studies with decent patient volume and well-controlled design are required.

Although some small-sample studies reported good speech training outcome in all included patients with MVPI (43–45), cases with poor outcomes would be more valuable from the perspective of clinical guidance. For example, it was found that MVPI patients who responded poorly to speech therapy and required surgery intervention tended to have articulation errors in low-pressure speech-length sentences (21), which was consistent with the pressure-sensitivity theory. Analysis of the prognostic factors of speech training has significant medical-economic value and can help in the choice between surgical and non-surgical strategies in the treatment of MVPI. However, such relevant studies are currently scarce and the findings of individual studies need further validation.

5.2. Surgical intervention

Surgical interventions become necessary when speech therapy fails to correct the closure insufficiency or when the patient is unwilling to take speech training. The surgical options for VPI after cleft palate repair include palatal lengthening and pharyngoplasty (46). Given the potential risk of nasal airway obstruction after pharyngoplasty and the high velopharyngeal closure rate in patients with MVPI, palatal lengthening generally preferred.

The most widely used technique for MVPI in the literature is the reverse double-Z approach proposed by Furlow and its modifications (38, 47, 48). This procedure effectively lengthens the soft palate and tightens the musculature posteriorly to improve velopharyngeal closure. Sommerlad's technique has also been used in the treatment of MVPI. This technique is more radical in soft palate muscle reconstruction than the double-Z technique (49). Mann et al. proposed to transfer the buccal mucomuscular flap to better lengthen the soft palate and has also been successfully used in the treatment of VPI after cleft palate repair (50). In addition, posterior pharyngeal wall augmentation by filling of various materials has been reported to be successful in managing VPI but is currently not the first-line option for MVPI treatment in most cleft centers due to the resorption, translocation of fillers as well as related biosafety risks (51–53).

Yamaguchi et al. reported that 78.57% of 42 patients with MVPI had complete velopharyngeal closure after Furlow procedure as evidenced by endoscopic examination (29). Hsu et al. reported satisfactory velopharyngeal function in 13 patients who underwent the Furlow procedure, with 69% of them achieving normal resonance and 80% of them having resolution of nasal emission (26).

Otherwise, studies are highly limited on the outcome and prognosis-related factors of MVPI management. Notably, the inconsistency of diagnostic criteria for MVPI seriously affects the comparability across studies. Clinical studies on MVPI treatment needs to incorporate a comprehensive panel of measurements including time-economic burden, surgical risk, and speech benefit.

The limitations of this review must be noted. The largest limitation is the controversial diagnostic standards employed in different studies, which significantly debilitated the inter-study comparability. Most studies simply provided no or vague description on their MVPI diagnostic methods. Second, the sample sizes are generally small in studies concerning MVPI outcomes. Third, no study comparing different management protocol or surgical techniques has been reported, forcing the authors to speculate the most appropriate suggestion on several cricical decision-making points in MVPI management. These limitations exist throughout the discussion in this manuscript.

6. Conclusions

The diagnostic criteria and treatment protocols of MVPI are currently controversial. Studies on variables that may influence the outcome of speech assessment will help to clarify the mechanisms underlying the possible discrepancy between speech performance and velopharyngeal function. Clinicians should base their MVPI management protocol on the most repeatable and reliable diagnostic criteria in their institutions. Speech therapy for either diagnostic or treatment purpose is suggested prior to surgery. Palate lengthening is preferred over pharyngoplasty in the surgical management of MVPI. Explorations on the prognostic factors will provide further evidence-based guides for MVPI management.

Author contributions

QM and XY contributed to the conception and writing of this review. JL and XY Contributed to the literature review and revision of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Kuehn DP, Moller KT. Speech and language issues in the cleft palate population: the state of the art. *Cleft Palate Craniofac J*. (2000) 37(4):1–35. doi: 10.1597/1545-1569_2000_037_0348_saliit_2.3.co_2

2. Johns DF, Rohrich RJ, Awada M. Velopharyngeal incompetence: a guide for clinical evaluation. *Plast Reconstr Surg*. (2003) 112(7):1890–7. doi: 10.1097/01.PRS.0000091245.32905.D5

3. Karnell MP, Schultz K, Canady J. Investigations of a pressure-sensitive theory of marginal velopharyngeal inadequacy. *Cleft Palate Craniofac J*. (2001) 38(4):346–57. doi: 10.1597/1545-1569_2001_038_0346_ioapst_2.0.co_2

4. Smith B, Guyette TW. Evaluation of cleft palate speech. *Clin Plast Surg*. (2004) 31 (2):251–60. doi: 10.1016/S0094-1298(03)00123-8

5. Riski JE, Delong E. Articulation development in children with cleft lip/palate. *Cleft Palate J*. (1984) 21(2):57–64.

6. Kummer AW. Speech therapy for errors secondary to cleft palate and velopharyngeal dysfunction. *Semin Speech Lang*. (2011) 32(2):191–8. doi: 10.1055/s-0031-1277721

7. Smith BE, Kuehn DP. Speech evaluation of velopharyngeal dysfunction. *J Craniofac Surg*. (2007) 18(2):251–61. doi: 10.1097/SCS.0b013e31803ecf3b

8. Krause C, Tharp R, Morris H. A comparative study of results of the von langenbeck and the V-Y pushback palatoplasties. *Cleft Palate J*. (1976) 13:11–9.

9. Smith BE, Guyette TW. Pressure-flow differences in performance during production of the CV syllables Ipil and Ipal. *Cleft Palate Craniofac J*. (1996) 33 (1):74–6.

10. Warren DW, Dalston RM, Mayo R. Hypernasality in the presence of "adequate" velopharyngeal closure. *Cleft Palate Craniofac J*. (1993) 30(2):150–4.

11. Karnell M. Nasometric discrimination of hypernasality and turbulent nasal airflow. *Cleft Palate Craniofac J*. (1995) 32(2):145–8. doi: 10.1597/1545-1569_1995_032_0145_ndohat_2.3.co_2

12. Kummer AW. A pediatrician's guide to communication disorders secondary to cleft lip/palate. *Pediatr Clin N Am*. (2018) 65(1):31–46. doi: 10.1016/j.pcl.2017.08.019

13. Hardin MA, Van Demark DR, Morris HL. Long-term speech results of cleft palate speakers with marginal velopharyngeal competence. *J Commun Disord*. (1990) 23(6):401–16. doi: 10.1016/0021-9924(90)90027-V

14. Neely B, Bradley D. A rating scale for evaluation of video tape recorded x-ray studies. *Cleft Palate J*. (1964) 16:88–94.

15. Hardin MA, Morris HL, Van Demark DR. A study of cleft palate speakers with marginal velopharyngeal competence. *J Commun Disord*. (1986) 19(6):461–73. doi: 10.1016/0021-9924(86)90021-3

16. Warren DW, Dalston RM, Trier WC, Holder MB. A pressure-flow technique for quantifying temporal patterns of palatopharyngeal closure. *Cleft Palate J*. (1985) 22 (1):11–9.

17. Warren DW, Dalston RM, Mayo R. Hypernasality and velopharyngeal impairment. *Cleft Palate Craniofac J*. (1994) 31(4):257–62. doi: 10.1597/1545-1569_1994_031_0257_havi_2.3.co_2

18. Morris HL. Marginal velopharyngeal competence. In: H. Winitz, editors. *For clinicians by clinicians, articulation disorders [M]*. Baltimore: University Park Press (1984). p. 211–22.

19. Jones DL, Morris HL, Van Demark DR. A comparison of oral-nasal balance patterns in speakers who are categorized as "almost but not quite" and "sometimes but not always". *Cleft Palate Craniofac J*. (2004) 41(5):526–34. doi: 10.1597/03-075.1

20. Patel KB, Sullivan SR, Murthy AS, Marrinan E, Mulliken JB. Speech outcome after palatal repair in nonsyndromic versus syndromic robin sequence. *Plast Reconstr Surg*. (2012) 130(4):577e–84e. doi: 10.1097/PRS.0b013e318262f2e4

21. Ma SW, Ren ZP, Wen YX, Li JF, Hou YX. Articulation of 65 patients with MVPI and the speech therapy approach after repair of cleft palate. *J Pract Stomatol*. (2013) 29 (06):844–7.

22. Ma L, Shi B, Li Y, Zheng Q. Velopharyngeal function assessment in patients with cleft palate: perceptual speech assessment versus nasopharyngoscopy. *J Craniofac Surg*. (2013) 24(4):1229–31. doi: 10.1097/SCS.0b013e31828a7877

23. Jackson O, Stransky CA, Jawad AF, Basta M, Solot C, Cohen M, et al. The children's hospital of Philadelphia modification of the furlow double-opposing Z-palatoplasty: 30-year experience and long-term speech outcomes. *Plast Reconstr Surg*. (2013) 132(3):613–22. doi: 10.1097/PRS.0b013e31829ad109

24. Barbosa DA, Scarmagnani RH, Fukushiro AP, Trindade IE, Yamashita RP. Surgical outcome of pharyngeal flap surgery and intravelar veloplasty on the velopharyngeal function. *CoDAS*. (2013) 25(5):451–5. doi: 10.1590/S2317-17822013000500009

25. Basta MN, Silvestre J, Stransky C, Solot C, Cohen M, McDonald-McGinn D, et al. A 35-year experience with syndromic cleft palate repair: operative outcomes and long-term speech function. *Ann Plast Surg*. (2014) 73(Suppl 2):S130–5. doi: 10.1097/SAP.0000000000000286

26. Hsu PJ, Wang SH, Yun C, Lo LJ. Redo double-opposing Z-plasty is effective for correction of marginal velopharyngeal insufficiency. *J Plast Reconstr Aesthet Surg*. (2015) 68(9):1215–20. doi: 10.1016/j.bjps.2015.05.014

27. Chim H, Eshraghi Y, Iamphongsai S, Gosain AK. Double-opposing Z-palatoplasty for secondary surgical management of velopharyngeal incompetence in the absence of a primary furlow palatoplasty. *Cleft Palate Craniofac J*. (2015) 52 (5):517–24. doi: 10.1597/13-187

28. Scarmagnani RH, Barbosa DA, Fukushiro AP, Salgado MH, Trindade IE, Yamashita RP. Relationship between velopharyngeal closure, hypernasality, nasal air emission and nasal rustle in subjects with repaired cleft palate. *CoDAS*. (2015) 27 (3):267–72. doi: 10.1590/2317-1782/20152014145

29. Yamaguchi K, Lonic D, Lee CH, Wang SH, Yun C, Lo LJ. A treatment protocol for velopharyngeal insufficiency and the outcome. *Plast Reconstr Surg*. (2016) 138 (2):290e–9e. doi: 10.1097/PRS.0000000000002386

30. Heng Y, Chunli G, Bing S, Yang L, Jingtao L. Morphological classification and velopharyngeal function analysis of submucous cleft palate patients. *West China J Stomatol*. (2016) 34(05):488–92.

31. Denadai R, Sabbag A, Raposo-Amaral CE, Filho JCP, Nagae MH, Raposo-Amaral CA. Bilateral buccinator myomucosal flap outcomes in nonsyndromic patients with repaired cleft palate and velopharyngeal insufficiency. *J Plast Reconstr Aesthet Surg*. (2017) 70(11):1598–607. doi: 10.1016/j.bjps.2017.06.029

32. Elsherbiny A, Amerson M, Sconyers L, Grant JH 3rd. Time course of improvement after re-repair procedure for VPI management. *J Plast Reconstr Aesthet Surg*. (2018) 71(6):895–9. doi: 10.1016/j.bjps.2018.01.029

33. Vella J, Tatum S. Risk factors for velopharyngeal dysfunction following orthognathic surgery in the cleft population. *Curr Opin Otolaryngol Head Neck Surg*. (2019) 27(4):317–23. doi: 10.1097/MOO.0000000000000553

34. Dempsey RF, Elsherbiny A, Amerson M, Sconyers L, Grant J. Normal speech should be the expected outcome in the adopted cleft child. *Ann Plast Surg*. (2019) 82:S370–3. doi: 10.1097/SAP.0000000000001751

35. Alaluusua S, Turunen L, Saarikko A, Geneid A, Leikola J, Heliövaara A. The effects of Le fort I osteotomy on velopharyngeal function in cleft patients. *J Craniomaxillofac Surg*. (2019) 47(2):239–44. doi: 10.1016/j.jcms.2018.11.016

36. Yang YY, Ma SW, Ren ZP, Yang BT. The effectiveness of CPAP in speech therapy for cleft palate patients with margin al vealopharyngeal dysfunction. *Med Aesthet Beauty*. (2020) 29(09):49–53.

37. Carr M, Skarlicki M, Palm S, Bucevska M, Bone J, Gosain AK, et al. Through-and-through dissection of the soft palate for pharyngeal flap inset: a "good-fast-cheap" technique for any etiology of velopharyngeal incompetence. *Cleft Palate Craniofac J*. (2022) 59(6):785–93. doi: 10.1177/10556656211021738

38. Glade RS, Deal R. Diagnosis and management of velopharyngeal dysfunction. *Oral Maxillofac Surg Clin North Am*. (2016) 28(2):181–8. doi: 10.1016/j.coms.2015.12.004

39. Pamplona C, Ysunza A, Patiño C, Ramírez E, Drucker M, Mazón JJ. Speech summer camp for treating articulation disorders in cleft palate patients. *Int J Pediatr Otorhinolaryngol*. (2005) 69(3):351–9. doi: 10.1016/j.ijporl.2004.10.012

40. Derakhshandeh F, Nikmaram M, Hosseinabad HH, Memarzadeh M, Taheri M, Omrani M, et al. Speech characteristics after articulation therapy in children with cleft palate and velopharyngeal dysfunction—a single case experimental design. *Int J Pediatr Otorhinolaryngol*. (2016) 86:104–13. doi: 10.1016/j.ijporl.2016.04.025

41. Zhu HP, Sun YG, Wang GH, et al. The study on the acoustic-phonetic features of marginal velopharyngeal closure. *Chin J Stomatol*. (1998) 03:50–2.

42. Schenck GC, Perry JL, Kollara L, Kuehn DP. Effects of surgical intervention and continuous positive airway pressure therapy on velopharyngeal structure and function:

a case report. *Cleft Palate Craniofac J*. (2019) 56(4):525–33. doi: 10.1177/1055665618787688

43. Liu Q, Jiang LP, Chen Y, Yang YS. A preliminary study on speech therapy for marginal velopharyngeal insufficiency. *Shanghai J Stomatol*. (2011) 20(06):611–4.

44. Chen XR, Zhao B, Yin H. The charactristics of speech training for postoperation cleft palate patients who have marginal velopharyngeal insufficiency after palatoplasty. *Int J Stomatol*. (2011) 38(3):279–82.

45. Li B, Shi B, Yin H, Li Y. Effects of speech training on velopharyngeal insufficiency in patients with cleft palate. *West China J Stomatol*. (2010) 28(06):623–5.

46. Gart MS, Gosain AK. Surgical management of velopharyngeal insufficiency. *Clin Plast Surg*. (2014) 41(2):253–70. doi: 10.1016/j.cps.2013.12.010

47. Furlow LT Jr. Cleft palate repair by double opposing Z-plasty. *Plast Reconstr Surg*. (1986) 78(6):724–38. doi: 10.1097/00006534-198678060-00002

48. Dailey SA, Karnell MP, Karnell LH, Canady JW. Comparison of resonance outcomes after pharyngeal flap and furlow double-opposing z-plasty for surgical management of velopharyngeal incompetence. *Cleft Palate Craniofac J*. (2006) 43 (1):38–43. doi: 10.1597/04-118r.1

49. Elsherbiny A, Amerson M, Sconyers L, Grant JH 3rd. Outcome of palate re-repair with radical repositioning of the levator muscle sling as a first-line strategy in postpalatoplasty velopharyngeal incompetence management protocol. *Plast Reconstr Surg*. (2018) 141(4):984–91. doi: 10.1097/PRS.0000000000004236

50. Robertson AGN, McKeown DJ, Bello-Rojas G, Chang YJ, Rogers A, Beal BJ. Use of buccal myomucosal flap in secondary cleft palate repair. *Plast Reconstr Surg*. (2008) 122(3):910–7. doi: 10.1097/PRS.0b013e318182368e

51. Impieri D, Tønseth KA, Hide Ø, Feragen KJB, Høgevold HE, Filip C. Autologous fat transplantation to the velopharynx for treating mild velopharyngeal insufficiency: a 10-year experience. *J Plast Reconstr Aesthet Surg*. (2019) 72 (8):1403–10. doi: 10.1016/j.bjps.2019.03.040

52. Cofer SA, Baas B, Strand E, Cockerill CC. Augmentation pharyngoplasty for treatment of velopharyngeal insufficiency in children: results with injectable dextranomer and hyaluronic acid copolymer. *Laryngoscope*. (2016) 126:S5–13. doi: 10.1002/lary.26227

53. Lu LD, Xu H. Research progress on autologous fat transplantation in the treatment of velopharyngeal insufficiency. *J Prevent Treat Stomatol Dis*. (2021) 29(2):135–9.

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Case report: Hereditary sensory autonomic neuropathy presenting as bifid deformity to the tongue

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Hereditary sensory autonomic neuropathy (HSAN) is a group of rare genetic disorders in which affected patients have a diminished capacity to feel pain. Patients with HSAN may present with a wide range of factitial injuries, where injury to the oral cavity may be an early presenting sign. While existing literature on HSAN is scant, many reports highlight the long-term outcomes that may include enucleation of eyes, amputation of fingers and limbs, and disfigurement of the tongue. This case describes a five-month-old female with repetitive injury to the tongue causing it to heal with a bifid deformity. The patient was later diagnosed with HSAN type 4. This case highlights the importance of recognition of extensive oral trauma as one of the early signs of HSAN that should provoke a timely referral for neurological assessment.

KEYWORDS

pediatric dentistry, congenital insensitivity to pain, hereditary sensory autonomic neuropathy, tongue ulceration, bifid deformity of the tongue

Introduction

Hereditary sensory autonomic neuropathy (HSAN) is a group of rare genetic disorders that are characterized by the inability to perceive noxious stimuli (1). HSAN is divided into eight subtypes based on clinical phenotype (2). The pathophysiology of HSAN has been linked to more than 12 genes (3, 4). HSAN Type 4 is characterized by the inability to feel pain or thermal stimuli as well as anhidrosis and intellectual disability. The pattern of inheritance for HSAN Type 4 is autosomal recessive with approximately 50 per cent of cases associated with parental consanguinity (5). Its prevalence is estimated to be 1/600,000–950,000 (5). Patients with HSAN are susceptible to a variety of physical injuries that can lead to permanent disability. The clinical manifestations of HSAN generally appear in infancy and include self-mutilating injuries to the oral cavity, eyes, and hands (6, 7). Repetitive bone fractures can also lead to Charcot joints and osteomyelitis. Intellectual disability, anhidrosis, and lack of olfaction are also common phenotypes (symptoms) of HSAN. Affected children present with a higher incidence of *staphylococcus aureus* infections and delayed wound healing (8). As a result of complications related to injuries and fractures, patients with more severe presentations of HSAN rarely survive to adulthood.

There is no cure for HSAN and management is focused on the prevention of physical injuries and the subsequent complications to those injuries. Diagnosis of HSAN early in life coupled with increased attentiveness to injury prevention and medical surveillance may improve long-term health and quality of life. The literature highlights the potentially devastating effects of HSAN when affected patients are not closely followed by a medical team. In this report, we present the case of a female infant who initially presented with repeated self-mutilation of the tongue and was diagnosed with HSAN Type 4 at 10 months of age.

Case description

A 5-month female patient presented to the Emergency Department at The Hospital for Sick Children with a chief complaint of bleeding from the tongue. The patient was the first child of healthy, non-consanguineous parents and had no other comorbid conditions. The patient was born full term and her birth height and weight were within normal limits. The parents reported that the child's first four months of life were uneventful until her primary mandibular incisor teeth erupted.

Clinical examination revealed partially erupted mandibular primary central incisors as well as a large ulceration on the ventral surface with significant tissue loss at the midline (**Figure 1**). The dorsal surface of the tongue was within normal limits. The child was eating and feeding normally. A provisional diagnosis of traumatic ulcerative granuloma with stromal eosinophilia was made at the time of the emergency department assessment.

The parents were provided with recommendations for non-invasive management of the tongue ulcerations such as using a pacifier to prevent the tongue from interfering with the teeth and changes to how the infant was fed to avoid trauma to the tongue. Reduction of the incisal edge of the incisors or application restorations were offered as temporary solutions with low likelihood of success. Intraoral appliances such as bite guards and splints have been used in patients with pathological chewing secondary to brain trauma (9). In this case, secure retention of the appliance would be compromised by the very small number of teeth to aid with mechanical retention of a bite guard or splint. Extraction of the mandibular incisors was discussed but the parents opted for modifications to nursing bottles, pacifier use and follow-up in the Dental Clinic in one-week.

No apparent signs of healing were noted at the one-week follow-up (**Figure 2**). The parents reported that the patient did not appear to be in pain and was still feeding and sleeping normally. A diagnosis of Riga Fede disease was made. Riga Fede disease (syndrome) is "an ulceration of the ventral surface of the tongue, often caused by repetitive traumatic injuries due to backward and forward movements of the tongue over the mandibular anterior incisors" (10). Extraction of the mandibular primary central incisors was recommended. The parents declined extraction in anticipation of laboratory results from their child's pediatrician who had undertaken blood work to assess for underlying medical conditions.

Four weeks after the initial emergency room visit, after the blood work was determined to be normal, the parents consented to the extraction of the mandibular primary central incisors. A week postoperatively, the extraction site healing was uneventful, and the tongue ulceration demonstrated signs of resolution. A midline defect involving the tip of the tongue was noted (**Figure 3**). The parents were cautioned that further trauma to the tongue was likely to occur with the eruption of additional teeth.

Three months later, the patient presented to the Dental Clinic with partially erupted maxillary central and mandibular lateral primary incisors. A new traumatic tongue ulcer measuring 0.5 cm on the right dorsal surface and tip of the tongue as well as buccal ulcerations were present (**Figure 4**). The parents declined extractions at this time. Given the extent and recurrent

FIGURE 1
Intraoral photo showing ulceration of the tongue following the eruption following the eruption of the mandibular primary central incisors.

FIGURE 2
Intraoral photo of the tongue showing persistent ulceration of the tongue at the one-week follow-up visit.

FIGURE 3
Intraoral photo showing the permanent bifid deformity of tongue healing four weeks after the extraction of mandibular primary incisors.

FIGURE 4
Intraoral photo of recurrent ulcerations on the tongue and buccal mucosa following eruption of posterior primary molars.

nature of the oral injuries, the patient was referred for neurological testing.

The Division of Neurology administered sensory testing and a nerve conduction study. The resultant report indicated that the patient had a decreased response to temperature and decreased response to electrical shock. The sympathetic skin response was also abnormal. A provisional diagnosis of hereditary sensory and autonomic neuropathy was made and genetic testing recommended. A molecular HSAN genetic testing demonstrated that the patient had two pathological variants in the *NTRK1* gene (c.2066C>T (p.Pro689Leu), c.851-33T>A (intronic) compound heterozygous), resulting in faulty or deficient neurotrophic tyrosine receptor type 1. This protein is found on certain cells, especially nerve cells that transmit pain, temperature, and touch sensations. These genetic results are consistent with a diagnosis of HSAN type 4. Due to the autosomal recessive nature of the disease, genetic testing was also performed on the parents to confirm carrier status. The parents were informed of the other clinical manifestations of the disease including intellectual disability, anhidrosis, and decreased lacrimation. The patient was 10 months of age when the diagnosis of HSAN Type 4 was made.

Shortly after the diagnosis of HSAN Type 4, the parents consented to extractions of the mandibular primary lateral incisors. The parents expressed concern over the esthetic appearance of the bifid tongue and whether it would interfere with their child's speech. The patient was referred to the Division of Plastic Surgery for consultation with regard to surgical correction of the tongue deformity. Due to the risk of continued traumatic injury to the tongue with eruption of additional primary teeth, it was recommended that correction be deferred until the child is 5–6 years of age.

The parents indicated that no other injuries, bruises, or cuts were noted anywhere else on the patient's body. The patient's developmental milestones were all normal and no signs of intellectual deficits or developmental delay were noted. Assessment in the Department of Ophthalmology detected no traumatic eye injuries. Currently, the patient's parents have declined further extractions. Follow-up appointments continue.

Discussion

HSAN Type 4 is a rare genetic disorder which is characterized by the impairment of pain sensation leading to self-mutilating behaviors. This case of HSAN Type 4 was diagnosed at 10 months of age after repeated episodes of self-mutilation to the tongue. Following the eruption of primary incisors, the patient repeatedly traumatized the tongue causing it to heal with a bifid deformity, which to our knowledge has not yet been previously reported. It is important to note that during periods of extensive tongue ulceration, the patient did not appear to show any signs of discomfort or difficulty feeding. This lack of reaction to such severe oral injuries should prompt the clinician to pursue further clinical investigations specifically neurological assessment.

Initially, this patient's oral condition was managed primarily as Riga Fede disease. Dental interventions to prevent Riga Fede disease referenced in the literature include smoothing sharp edges of teeth, placement of composite resin or other restorative materials to sharp edges of teeth, intraoral appliances (such as mouth guards), and extraction of primary teeth (9).

It is plausible that earlier extraction of the mandibular primary central incisors may have mitigated the damage to the tongue. Although recommended on multiple occasions, the family declined extractions. Studies that examined parental decision-making preferences of ill children suggests that parental perception of urgency can sometimes differ from that of the medical team. Specifically, when a child is given a significant medical diagnosis, the parent is more likely to view treatment and management as urgent (11). Therefore, it is plausible to infer that the parents may have consented to definitive treatment options if the diagnosis of HSAN was made earlier.

At present, the tongue cleft defect is being monitored by the Division of Plastic Surgery and will be surgically repaired when the patient is at an age when she is less likely to re-traumatize the tongue. The surgical correction of median tongue clefts can yield satisfactory result in cases of congenital tongue clefts (12). The outcome for remediation of a traumatically induced tongue cleft deformity is not certain.

The strength of this current case report lies in the relatively early diagnosis of this rare syndrome. The diagnosis of HSAN at ten months of age prompted dental interventions paired with routine follow up visits with dentistry, ophthalmology, and occupational therapy for counselling and injury surveillance, with the hope of preventing long term complications of the disease. Limitations of this report include no long-term follow up of this case to build on the success of her dental and oral growth and general development. There is no single consensus on the dental management best practices for patients with HSAN. The limited pool of patients with HSAN creates an obstacle for clinicians to offer a consensus on the most suitable treatment options.

Conclusion

To our knowledge this case is the first describing a bifid tongue as a presenting feature of HSAN4. Oral trauma is one of the earliest symptoms of the disease and pediatric dentists may be one of the first healthcare providers to assess the condition. Early diagnosis of HSAN may potentially allow for interventions that mitigate more extensive injuries.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

KO-W and DS conceptualized the case report and performed the clinical treatment. MC supervised the clinical treatment and contributed to treatment planning. KO and DS wrote the initial draft of this manuscript. MC critically reviewed the manuscript. HG performed neurological testing and assisted with editing the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The author MC declared that they were an editorial board member of Frontiers at the time of submission. This had no impact on the peer review process and the final decision.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Nagasako EM, Oaklander AL, Dworkin RH. Congenital insensitivity to pain: an update. *Pain*. (2003) 101(3):213–9. doi: 10.1016/S0304-3959(02)00482-7

2. Schwartzlow C, Kazamel M. Hereditary sensory and autonomic neuropathies: adding more to the classification. *Curr Neurol Neurosci Rep*. (2019) 19(8):52. doi: 10.1007/s11910-019-0974-3

3. Davidson G, Murphy S, Polke J, Laura M, Salih M, Muntoni F, et al. Frequency of mutations in the genes associated with hereditary sensory and autonomic neuropathy in a UK cohort. *J Neurol*. (2012) 259(8):1673–85. doi: 10.1007/s00415-011-6397-y

4. Lischka A, Lassuthova P, Çakar A, Record CJ, Van Lent J, Baets J, et al. Genetic pain loss disorders. *Nat Rev Dis Primers*. (2022) 8(1):41. doi: 10.1038/s41572-022-00365-7

5. Haga N, Kubota M, Miwa Z. Epidemiology of hereditary sensory and autonomic neuropathy type IV and V in Japan. *Am J Med Genet A*. (2013) 161a(4):871–4. doi: 10.1002/ajmg.a.35803

6. Almutairi MM, Tabassum S. Congenital insensitivity to pain with anhidrosis: a case report and review of the pertinent literature. *Cureus*. (2022) 14(11):e31019. doi: 10.7759/cureus.31019

7. Soussou R, Cheung WS, Campbell KM. Congenital insensitivity to pain with anhidrosis: a case with self-inflicted oral ulcerations. *J Dent Child (Chic)*. (2019) 86 (2):109–12. PMID: 31395116.

8. Fruchtman Y, Perry ZH, Levy J. Morbidity characteristics of patients with congenital insensitivity to pain with anhidrosis (CIPA). *J Pediatr Endocrinol Metab*. (2013) 26(3-4):325–32. doi: 10.1515/jpem-2012-0151

9. Ngan PW, Nelson LP. Neuropathologic chewing in comatose children. *Pediatr Dent*. (1985) 7(4):302–6.

10. Costacurta M, Maturo P, Docimo R. Riga-Fede disease and neonatal teeth. *Oral Implantol*. (2012) 5:26–30.

11. Carlisle EM, Klipowicz CJ, Shinkunas LA, Scherer AM, Kaldjian LC. Discrepancies in decision making preferences between parents and surgeons in pediatric surgery. *BMC Med Inform Decis Mak*. (2021) 21(1):42. doi: 10.1186/s12911-021-01414-z

12. Surej KL, Kurien NM, Sivan MP. Isolated congenital bifid tongue. *Natl J Maxillofac Surg*. (2010) 1:187–9. doi: 10.4103/0975-5950.79228

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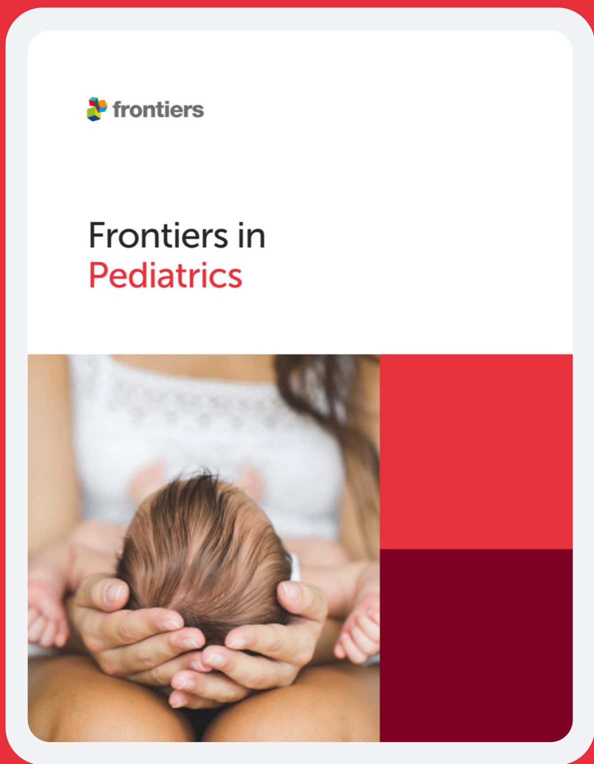

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