Radiographic Evaluation of Second Molar Substitution

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Katherine Anne Nordeen DDS, MSD

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DEDICATION

I would like to dedicate this thesis to my family who truly made it possible for me to complete a second residency and, ultimately, this research. To my husband, Kyle, thank you for supporting my decision to pursue orthodontic residency while you simultaneously completed your own residency in pediatric dentistry and then opened our dental practice. To our two sons, James and Teddy, thank you for your patience, flexibility and resilience during this busy time in your young lives. To my parents, Bill and Betsy Wild, thank you will never be enough for the endless support you provided us in every possible way; without you both, none of these dreams would be a reality. To my siblings, Chrissy, Laura, Dan and Kelly Wild, thank you for always being my biggest cheerleaders. To my parents-in-law, Pete and Lynda Michielutti and Mark and Elise Whitehill Nordeen, thank you for the support and encouragement you've shown Kyle and me every step along the way on our personal and professional journey.

ABSTRACT

INTRODUCTION: Extraction of first permanent molars (FPM) is unavoidable in pediatric dental patients considering their high rate of caries and enamel hypoplasia. The national guidelines in the United Kingdom recommend extracting the FPM between 8-10 years of age, and when the second molar (SPM) demonstrates early root bifurcation development. Several recent retrospective studies reported contradictory findings and identified additional predictive variables. **Aims:** 1) to evaluate the outcome of spontaneous SPM substitution following extraction of FPMs in pediatric patients, and identify pre-extraction radiographic variables associated with success; 2) to test the variables described by Patel et al 2017 in their predictive model for success in the mandibular arch: mesial angulation of the SPM and presence of the third molar (TPM) (1).

METHODS: The charts of 162 patients were assessed for a total of 138 maxillary quadrants and 168 mandibular quadrants. A pre-extraction panoramic radiograph was evaluated for 1) SPM developmental stage, 2) presence or absence of a developing TPM and 3) angle of the mandibular SPM relative to the occlusal plane. Chronological age at time of extraction and gender were recorded. A post-extraction radiograph was used for outcome assessment.

RESULTS: Successful space closure was observed in 82 percent of maxillary quadrants and 51 percent of mandibular quadrants. In the maxillary arch the SPM developmental stage was statistically significant, with the highest odds for success associated with the earlier stages of SPM development compared to the later stages of development ($p < 0.05$). In the mandibular arch, the chronological age at time of extraction was statistically significant, with the highest odds for success associated with the younger ages compared to the older ages ($p < 0.05$). Mesial angulation of the mandibular SPM combined with presence of a TPM did not result in the highest probability for success.

CONCLUSIONS: The Patel et al predictive model was not validated in this study population. The results suggest the primary importance of chronological age and SPM developmental stage for predicting a successful outcome. Extraction at a younger chronological age and earlier SPM developmental stage are significantly associated with success compared to extraction at later ages and stages.

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ABBREVIATIONS

First permanent molar (FPM)

Second permanent molar (SPM)

Third permanent molar (TPM)

The Royal College of Surgeons of England (FDSRCS)

Guidelines (FDSRCS National Clinical Guidelines for the extraction of first permanent molars in children)

United Kingdom (UK)

Early Childhood Caries (ECC)

Molar-incisor hypomineralization (MIH)

Molar hypomineralization (MH)

University of Minnesota (UM)

Virginia Commonwealth University (VCU)

University of Iowa (UI)

Date of pre-extraction panoramic radiograph (T1)

Date of extraction (T2)

Date of post-extraction radiograph (T3)

Upper right first permanent molar (1)

Upper left first permanent molar (2)

Lower left first permanent molar (3)

Lower right first permanent molar (4)

INTRODUCTION

The first permanent molar (FPM) presents numerous challenges for both general dentists and specialists alike (2–5). It is one of the first permanent teeth to erupt, and experiences the highest incidence of caries in the permanent dentition (6,7). The FPM typically erupts at approximately six years of age, when caries risk is primarily determined by the caries status of the primary dentition (8,9). The presence of one or more decayed, missing, or filled tooth surfaces in children under six years of age is referred to as early childhood caries (ECC) (10). According to recent epidemiological data, the overall prevalence of ECC in the United States (US) is 22 percent, but disproportionately affects children of lower socioeconomic levels (11). As the first permanent tooth to erupt, the FPM is exposed longest to the preponderance of caries risk factors that exist during the mixed dentition, when oral hygiene tends to be poor and diet is increasingly cariogenic (8,12). The prevalence of caries in the US rises to 50 percent in children between 6-11 years of age, coinciding with the mixed-dentition years (11,13,14). The FPM has proven to be the tooth with the highest risk for caries in both the mixed and permanent dentition (15–17). Not surprisingly, the FPM is both the most heavily restored and most commonly extracted permanent tooth due to caries in adolescence and early adulthood (6,9,18).

The enamel of the FPM is also uniquely susceptible to a common developmental disturbance known as enamel hypomineralization. Upon eruption, the hypomineralized enamel presents as an area of white, yellowish or brown discoloration with considerable variation in the extent of the defect (19). While mildly hypomineralized areas typically pose minimal concern, the severely affected FPMs are particularly prone to caries and/or structural breakdown shortly after eruption (20). Prevalence data on MIH ranges from 5.9 percent to 38 percent in the European populations studied, but is reportedly as high as 42 percent in a population of Mexican children (21–23). Molar hypomineralization (MH) describes the condition when one or more FPMs are affected, whereas molar-incisor hypomineralization (MIH) is used when the incisors are affected in addition to the FPMs (24). While the etiology of MIH in humans is still unknown, some animal models suggest an increased risk of hypomineralization following exposure to various events such as hypoxia, high fever, hypocalcemia, and amoxicillin, all of which can occur perinatally, when the human FPM undergoes calcification (25). Bisphenol-A exposure in rats resulted in enamel hypomineralization, similar to that observed in the human condition, by modulation of the genes responsible for enamel formation (26). More recently, the role of genetics has been studied as a possible component to the etiology of hypomineralization (25). At present, MH and MIH are suspected to be the result of a combination of genetic factors and conditions and/or exposures to harmful agents during enamel development and maturation (20).

Patients with hypomineralized FPMs present unique challenges for the clinician. Severely hypomineralized molars will present with structural breakdown and/or caries soon after eruption, thus requiring complex, early restorative treatment for a patient as young as six years of age (27). Restorative challenges are often compounded by the fact that hypomineralized molars demonstrate heightened sensitivity upon eruption to seemingly benign stimuli, such as toothbrushing, and seem to be more difficult to anesthetize, which seems to be attributed to inflammation of the pulp tissue due to the increased porosity of the enamel (3,4,28). Additionally, hypomineralized FPMs often require subsequent restorations due to inherent difficulty in bonding to the altered enamel structure and the unusual shape of the lesion (3,4,29). In their retrospective study, Jalevik and Klingberg demonstrated the cumulative economic and psychological burden that hypomineralized molars impart on pediatric dental patients (4). The authors observed that by the age of nine, children with hypomineralized molars underwent restorative treatment ten times more frequently than matched controls. Additionally, behavior management problems and dental fear/anxiety were increased in children with hypomineralized molars compared to controls, suggesting that additional pain and anxiety control measures beyond local anesthesia, such as sedation or general anesthesia, may be warranted (4). For pediatric patients requiring advanced behavior management techniques, the benefit in restoring the FPM must be weighed against the inherent risk of sedation or anesthesia, as well as the potential need for retreatment (30). In cases of severe FPM hypomineralization, early FPM extraction with spontaneous substitution of the SPM has proven to be a superior treatment modality compared to restorative treatment (29).

The concept of early FPM extraction is hardly new, as carious FPMs were even more problematic prior to systemic water fluoridation (5,31). During the first half of the 20th century, proponents of early FPM extraction cited multiple benefits including caries-prevention, alleviation of crowding, and prevention of malocclusion (32). Contemporaneously, Edward Angle was establishing the specialty of orthodontics and centered his malocclusion classification around the FPMs, which he considered to be the keystone of the dental arch. Opponents to early FPM extraction cited that it increased the incidence of caries and periodontal disease, and led to significant negative orthodontic sequelae including spacing, rotations, tipping, increased overbite and asymmetries (33–

37). Regardless of the side taken in the FPM extraction debate, the publications at the time were often observation studies lacking sufficient information about the study population, such as age at time of extraction. Furthermore, none of the early articles were subjected to statistical analysis, but instead included the author's opinion regarding the treatment modality (32–36). In the first half of the 20th century, Richardson succinctly described the eventual waning of the debate:

> "as is common in biological debates the argument, which was sustained initially by sweeping generalizations, subsided into surly silence with the realization that none of the major protagonists was completely correct and none was completely wrong. The reason was that not every patient responded in the same way to molar extractions. In some the results were excellent in others disastrous but in the majority there were some benefits and some untoward sequelae." (31)

Despite the introduction of fluoridated drinking water in the second half of the 20th century and significant public health efforts directed toward caries prevention and control, clinical problems regarding the FPM are still prevalent today (5). Given the relatively common occurrence of hypomineralized and carious FPMs, together with the restorative challenges they present in young patients, early FPM extraction remains a viable and often essential treatment modality. The Royal College of Surgeons of England (FDSRCS) first published national clinical guidelines, hereafter referred to as guidelines, regarding the extraction of FPMs in children in 2008 and updated them in 2014 (38). The guidelines are based on the best available evidence, although inclusive of some of the older, observational studies from the early 20th century (38). Nonetheless, the guidelines aim to support clinicians in treatment planning for compromised FPMs with the ideal outcome being successful, spontaneous space closure of the SPM.

The current guidelines state that the unerupted maxillary second permanent molar (SPM) will achieve ideal position and space closure with high predictability, with a success rate of approximately 80-90 percent reported in the literature (1,39). The mandibular FPM extraction, however, requires careful evaluation as the rates of spontaneous space closure are significantly lower than in the maxillary arch, with an overall success rate of approximately 50 percent (1,39,40). Per the guidelines, the most favorable time for successful space closure is when the extraction of the lower FPM is performed between 8-10 years of age, before the eruption of the SPM but after the eruption of the lateral incisors. Other favorable parameters include evidence of bifurcation development of the mandibular SPM, and an SPM completely housed in bone at the time of FPM extraction. Extraction of a mandibular FPM earlier than 8 years of age is said to be unfavorable due to lack of evidence of third permanent molar formation (TPM), and increased risk of the second premolar drifting distally into the extraction space. Later extraction, after 10 years of age, is said to result in increased mesial tipping of the SPM, lack of space closure and unfavorable occlusion. With many children experiencing caries and enamel hypoplasia of their FPMs soon after they erupt at approximately six years of age, and the optimal window of time for the mandibular FPM extraction is thought to be 8-10 years of age for spontaneous SPM space closure, it is then prudent that the clinician weigh the benefits and risks of maintaining or extracting a compromised FPM (38,41).

Again, the guidelines are based primarily on retrospective studies, including observational studies with results untested by statistical analysis (34,35,38,40,42,43). The publications of Thilander and Skagius, as well as Thunold, although not subject to statistical analysis, provided sufficient information in longitudinal, retrospective studies to draw associations between pre-extraction variables and the outcome of spontaneous

SPM eruption (40,43). Both studies found that the maxillary arch posed little issue if the FPM is extracted prior to eruption of the SPM but observed that the same extraction plan in the mandibular arch resulted in lower rates of successful spontaneous space closure. Additionally, both studies are referenced in the guidelines regarding optimal extraction timing in the mandibular arch; between 8-10 years of age per Thunold, and after the lateral incisors erupt but before the SPM or second premolar per Thilander and Skagius (38,40,43). Both studies also investigated the influence of several other pre-extraction variables on outcome in the mandibular arch, including presence or absence of the third molar (TPM), crowding, and occlusion. In a longitudinal study spanning 25 years, Thunold observed acceptable space closure in 70 percent of mandibular quadrants following extraction of FPMs in 52 children between the ages of 8-14 years at time of extraction (43). Thunold noted success in the mandibular arch occurred more frequently in patients with a normal skeletal base relationship, but also found the TPM seemed to have no effect on successful space closure.

Thilander and Skagius retrospectively investigated the influence of dental developmental stage, presence of the TPM, crowding, and skeletal base relationships on the outcome of the mandibular arch in 254 quadrants among 175 children (40). They reported a range of "acceptable to good" space closure in just 54 percent of the cases. Interestingly, Thilander and Skagius did not report chronological age at time of extraction for their subjects, just dental developmental stage, ranging from just 3 subjects who had extractions prior to eruption of the lateral incisors, up to 30 subjects with all permanent teeth erupted, including SPMs. Accounting for dental developmental stage, the highest frequency of success was observed when the FPM was extracted after the eruption of the lateral incisors, but before the eruption of the second premolar and/or second molar. Based on their observations, Thilander and Skagius stated that extractions completed at the most successful dental developmental stage, in combination with presence of a TPM and crowding, seemed to be most predictive of successful space closure in the mandibular arch. Of the patients with all three of these parameters, 80 percent had a good result. Although Thilander and Skagius were unable to run complex statistical analyses due to the technological limitations of the time, many of the variables they investigated would eventually be subject to statistical analysis in similarly designed, retrospective studies (40,43).

In 2013 Teo et al investigated the influence of the dental developmental stage of the SPM at time of extraction (39). Primarily, the authors wanted to know if the ideal timing per the guidelines, when the SPM demonstrates the earliest stage of bifurcation development, resulted in the highest frequency of success. Dental maturity systems were primarily designed to correlate dental development with chronological age in the context of physiologic maturity in a growing child. The dental maturity system commonly used in studies on SPM substitution is the Demirjian system, which describes an 8-stage scale based on relative dental development of the teeth using a panoramic radiograph (Appendix 1, figure 1) (44). Stage A represents the earliest sign of calcification and stage H represents complete closure of the root apices. Demirjian stage E represents the earliest sign of bifurcation development in molars, and therefore is referenced in the guidelines as the ideal stage of SPM development for extraction of the FPM (38,44). Using pre-extraction panoramic radiographs for SPM Demirjian staging and clinical examination for outcome assessment, the authors retrospectively assessed 236 quadrants in 63 patients with extraction of FPMs between 7-13 years of age, with a mean age of 8.9 years and mean follow-up time of 4.8 years. Although only 54 percent of both the upper and lower SPMs were identified as stage E at time of extraction, the Demirjian stage of the SPM was not statistically significant with respect to outcome. Among all Demirjian stages D-G studied, overall success in the maxillary arch was 92 percent, compared to 61 percent in the mandibular arch. Among subjects with SPM at stage E, the maxillary SPMs erupted successfully at a rate of 94 percent, whereas the mandibular SPMs demonstrated a significantly lower rate of successful eruption at 66 percent, only slightly better than the 61 percent observed across all stages. Notably, Teo et al observed that Demirjian stage F SPMs had the highest frequency of success in both arches. Successful outcomes occurred when the SPM was observed at both earlier and later Demirjian stages than the "ideal" time of stage E, and their findings were acknowledged in the revised 2014 guidelines, but did not result in a change in recommendation for extraction timing in the mandibular arch (38,39). Furthermore, since dental developmental stage of the SPM failed to be predictive of space closure, and the mandibular arch has a significantly lower incidence of success compared to the maxillary arch, the authors concluded that other parameters should be investigated to better predict success in the mandibular arch (39).

In 2016, Teo et al reassessed the mandibular quadrants in the previously referenced patients/study to investigate other parameters in addition to SPM Demirjian stage that may be associated with a higher rate of successful SPM substitution (39,45). The authors investigated the influence of the following radiographic parameters: 1) evidence of the developing second premolar crown within the bifurcation of the primary second molar; 2) mesial angulation of the developing SPM in relation to the FPM; and 3) presence or absence of TPM and its influence on SPM eruption. From the previous study, 127 lower SPMs with dental developmental stage ranging from D-G at time of extraction were investigated. The authors found that the most favorable combination of parameters resulting in successful SPM eruption were: 1) SPM developmental stage not equal to G; 2) Mesial angulation of the SPM in relation to the FPM; 3) presence of TPM. Of the 61 quadrants studied with all three pre-extraction parameters present, 85 percent demonstrated a successful outcome, which was statistically significant compared to the other combinations of variables studied. The authors suggest that the parameters of SPM angulation and presence/absence of a TPM should be evaluated in addition to the SPM Demirjian developmental stage when predicting outcome for successful SPM substitution in the mandibular arch (45).

Patel et al in 2017 investigated similar pre-extraction radiographic parameters that Teo et al found to be significantly associated with success in the mandibular arch: 1) overall/composite dental age, 2) Demirjian stage of the SPM by category: early (stages A-D) ideal (stage E) and late (stages F-H); 3) angulation of the maxillary and mandibular second premolar relative to the occlusal plane; 4) angulation of the maxillary and mandibular SPM relative to the occlusal plane; and 4) presence or absence of the TPM (1). The authors analyzed the pre-extraction panoramic radiographs of 81 patients with a total of 148 maxillary FPMs and 153 mandibular FPMs, ranging from 5-15 years at time of extraction, mean age 9.6 years and with a mean follow up time of 4 years. Outcome was assessed clinically, radiographically or through study casts, and determined to be successful if the contact was closed between the SPM and second premolar and without marginal ridge discrepancy. Consistent with previous research, the maxillary SPMs erupted successfully in 90 percent of the quadrants evaluated. Conversely, only 49 percent of the mandibular quadrants demonstrated successful SPM eruption, lower than the 61 percent observed in the Teo studies (39,45). After analyzing the explanatory variables with multilevel modeling, overall dental age was the only statistically significant parameter predictive of success in the maxillary arch. However, because of the high success rate in the maxillary arch, the predicted probability for success only decreases by less than one percent for every increase in dental age by one year. For this reason, the authors question whether overall dental age has clinical significance with respect to decision making. Regarding the mandibular arch, the authors found that the combination of a mesially-angulated SPM and the presence of a TPM resulted in 89 percent predictive probability of achieving successful space closure, similar to the predictive probability described by Teo et al when similar pre-extraction parameters were observed (45). As a result of their findings, Patel et al created a toolkit (figure 1) to assist the clinician in assessing the angulation of the SPM in relation to the occlusal plane, and suggested that the toolkit required additional validity testing in another study population (1).

SPECIFIC AIMS

The purpose of this study was to test the toolkit developed by Patel et al in a similar retrospective study population. The specific aims of the study were as follows:

1) Evaluate on a pre-extraction panoramic radiograph the following factors and their influence on successful space closure of the maxillary and mandibular SPM:

a) Demirjian stage of the maxillary or mandibular SPM.

b) Angle of the mandibular SPM relative to the occlusal plane.

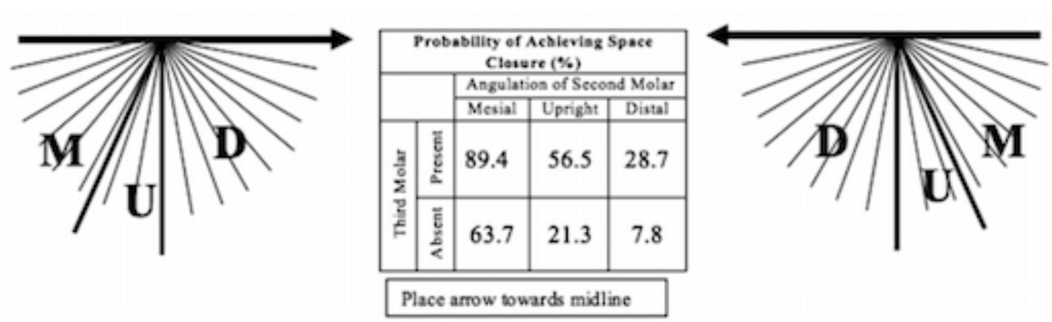
c) Presence or absence of a developing maxillary or mandibular TPM.

2) Evaluate the influence of chronological age and gender at time of extraction on successful space closure.

3) Test the toolkit designed by Patel et al 2017 and the parameters most predictive of success in the mandibular arch: presence of TPM in combination with mesial angulation of the SPM (1).

HYPOTHESIS

The primary null hypothesis for the study is that the presence of a mandibular TPM combined with mesial angulation of the SPM relative to the occlusal plane have no influence on the successful space closure of the mandibular SPM. The secondary null hypothesis is that none of the other variables studied would influence successful space closure.



Probability of Achieving Space Closure (%)				
		Angulation of Second Molar		
		Mesial	Upright	Distal
Third Molar	Present	89.4	56.5	28.7
	Absent	63.7	21.3	7.8

Figure 1. Clinical toolkit by Patel et al to predict success of mandibular second permanent molar substitution (1).

MATERIALS & METHODS

To validate the clinical toolkit (figure 1) described by Patel et al, the study must closely resemble their research design with respect to population, measurement, recording of variables, and statistical methods. To address the hypothesis and specific aims, this study employed a retrospective cohort design.

Inclusion criteria for the study population:

- Pediatric patients between 5-15 years of age at time of extraction of FPM.
- Pre-extraction panoramic radiograph.
- Post-extraction panoramic radiograph or intraoral radiograph of SPM and second premolar after their complete eruption.

Exclusion criteria for the study population:

- Patients with craniofacial syndromes or anomalies of eruption.
- Patients with extractions or hypodontia of other permanent teeth in the same quadrant as FPM extraction.
- Patients who initiated orthodontic treatment prior to post-extraction radiograph.
- Patients lacking pre-extraction panoramic radiograph and/or post-extraction radiograph following complete eruption of the SPM.

The charts of 162 patients were assessed for a total of 138 maxillary quadrants and 168 mandibular quadrants. The charts were obtained from three University-based pediatric dental residency programs: the University of Minnesota (UM), Virginia Commonwealth University (VCU) and University of Iowa (UI). Institutional Review Board (IRB) approval was obtained from each university committee independently (UM IRB ID:

00009442, VCU IRB ID: HM20020705, University of Iowa IRB ID: 202011095). All radiographs were analyzed with MiPACs software, and all patient-level data was obtained from AxiUm electronic dental record. The following descriptive data for each patient was obtained:

- Gender (male/female)
- Ethnicity if available
- Date of birth
- Date of pre-extraction panoramic radiograph (T1), date of extraction (T2), and date of post-extraction radiograph (T3)
- University clinic location (UM, VCU, or UI)

Ethnicity data was recorded according to the following categories: White, Black, Hispanic/Latin American, American Indian, Asian/Pacific Islander, or unreported.

Date of birth was recorded to determine the age at T1, T2 and T3. The variable chronological age at T2 was assessed by category according to the age recommendations per the current guidelines: early: <8 years, ideal: 8-10 years, and late: >10 years.

If more than one pre-extraction panoramic radiograph was available, the panoramic radiograph taken closest to the extraction timepoint (T2) was used. If more than one post-extraction radiograph was available, the radiograph which best demonstrated complete eruption of the SPM and angulation was used for evaluation of the outcome timepoint (T3); secondarily, the post-extraction radiograph furthest from the extraction timepoint was selected to best evaluate long-term outcome.

Dental stage of the SPM was assessed on the pre-extraction panoramic radiograph using the parameters of Demirjian et al's 8-stage scale and recorded as A-H (Appendix 1, figure 1) (44). Consistent with the methodology in Patel et al, the Demirjian stage was further categorized as early (stage A-D), ideal (E), and late (F-H) for statistical analysis (1).

Angulation of the SPM was determined by the toolkit angulation template (figure 1). The toolkit was traced in Microsoft Powerpoint software and then superimposed on the pre-extraction panoramic images. The occlusal plane was determined first, and then the template was adjusted along the occlusal plane to find the sector which most closely matched the long axis of the SPM (Appendix 1, figure 2). The occlusal plane parameters were not explicitly defined by Patel et al; instead, they demonstrated an occlusal plane reference line on one sample panoramic image, which seemed to prioritize the cusp tips of the posterior teeth rather than the incisors (Appendix 1, figure 3) (1). The SPM angulation relative to the occlusal plane was recorded according to its individual sector on the toolkit template, 1-18, and then further categorized as mesial, upright, or distal as delineated by the toolkit boundaries (figure 1). Sectors 1-7 represented mesial angulation, sectors 8-9 represented upright angulation, and sectors 10-18 represented distal angulation. The SPM angulation measurements were categorical variables based on the pre-determined boundaries of the toolkit.

TPM was a binary variable, marked as present or absent. At minimum, observation of the TPM crypt was required for it to be marked as present. If no crypt formation was observed, the TPM was marked as absent.

The dependent variable, outcome of spontaneous SPM substitution, was determined using the post-extraction radiograph (T3) and defined as successful (Appendix 1, figure 4) or unsuccessful (Appendix 1, figure 5), and therefore is a binary variable. Consistent with the criteria for success described by Patel et al, successful substitution was defined as the presence of a visible contact between the second premolar and SPM and without significant marginal ridge discrepancy (1).

All data were obtained and assessed by the primary researcher (KN). Demirjian dental age of the SPM, angulation of the mandibular SPM, presence/absence of the TPM and outcome were reassessed for intra-rater reliability in 40 quadrants by the primary researcher after a 4-week washout period. Dental age of the SPM, angulation of the SPM, presence/absence of the TPM and outcome were also assessed in all study patients by a second evaluator (AR), a third-year pre-doctoral dental student, for inter-rater reliability using the deidentified radiographs.

The intra and inter-rater reliability variables were categorical variables (angulation of mandibular SPM, dental stage of the SPM, presence/absence of TPM and outcome) and were assessed using kappa statistics.

STATISTICAL ANALYSIS

Statistical analyses for the outcome assessment were performed in SAS system version 9.4. All patient identifiers were removed from the dataset. A study number was assigned to each patient, known only to the primary researcher. Logistic regression models with generalized estimating equations were conducted to examine the association between the explanatory variables and the outcome. Statistical models were adjusted for locations and accounted for correlations among multiple observations (up to 4 quadrants) in the same patient. Maxillary and mandibular quadrants were analyzed separately. Nonsignificant variables ($p>0.05$) were removed from the model and rerun. Odds ratio, 95 percent confidence intervals, and p value were reported.

The following analyses were used to test for differences among the populations of the three clinic sites: chi square test (number of patients, gender, TPM), Fisher's exact test (race/ethnicity, chronological age group at T2, Demirjian category, Demirjian stage, SPM angulation) and ANOVA (chronological age, mean value).

RESULTS

A total of 162 patients were included in the study from the three clinic locations (figure 2), with 52 percent females and 48 percent males (Appendix 2, table 1).

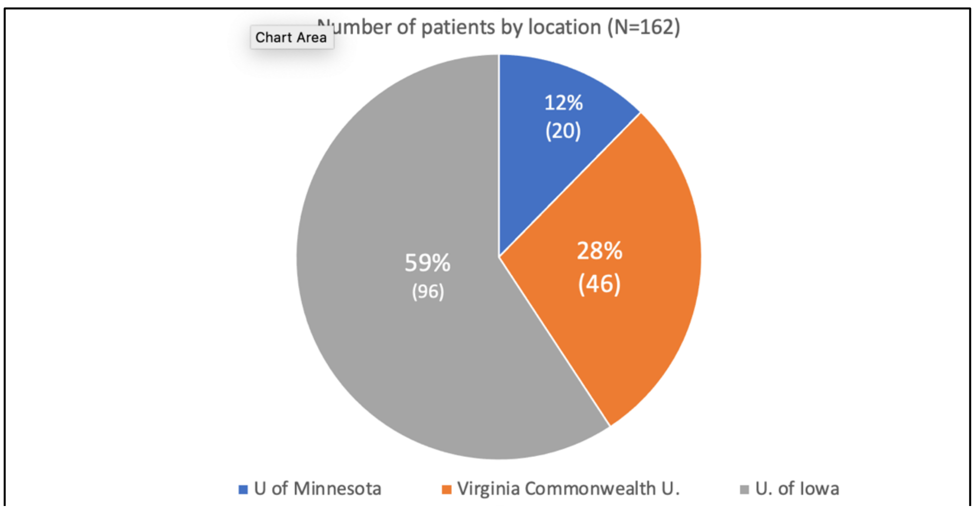


Figure 2. Number of patients by location.

Most patients had only one FPM extracted (53 percent), while 24 percent had 2 FPMs extracted, 4 percent had 3 FPMs extracted, and 19 percent hada all 4 FPMs extracted (figure 3).

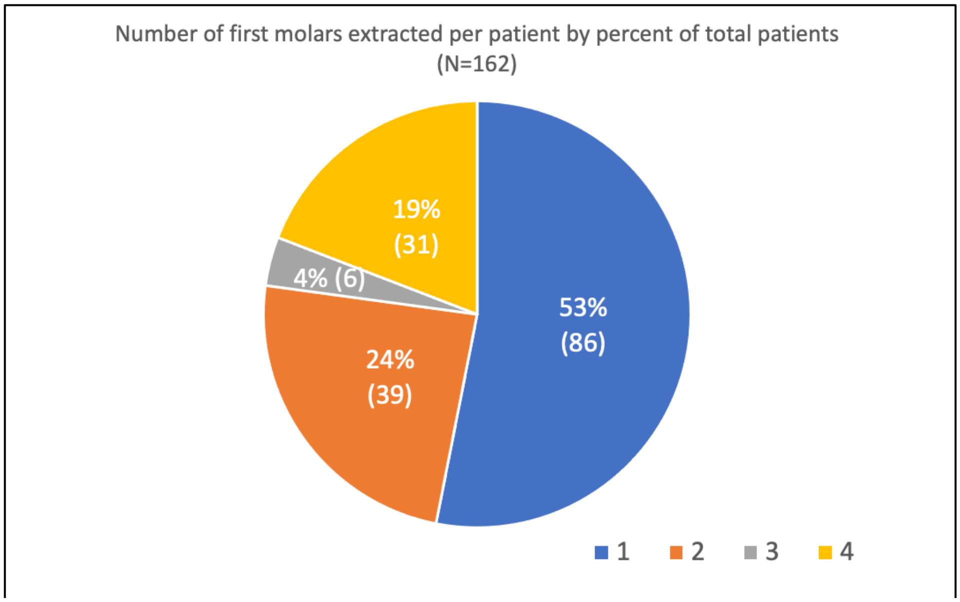


Figure 3. Number of first molars extracted per patient by percent of total patients.

The number of patients per location was significantly different and is as follows: 20 patients from UM, 46 patients from VCU, and 96 patients from UI (p<.0001). No difference was observed among locations with respect to gender (p=0.91). There were statistically significant differences between the locations with respect to outcome, therefore differences between locations were analyzed and reported. Data regarding ethnicity was recorded when available; of the 162 patients, 49 percent were White, 21 percent Black, 4 percent Hispanic/Latin American, and less than one percent each were American Indian or Asian/Pacific Islander. The remaining 25 percent of patients did not report their ethnicity data. To test for differences in ethnicity between locations, patients were categorized as White vs. non-White/unreported. The prevalence of White subjects at 15 percent for UM, 20 percent for VCU and 71 percent for UI (p<.001). See Appendix 2, tables 2 through 6.

The mean age at time of extraction (T2) for all study patients was 10.6 years, and the range 6.7 to 14.9 years (table 1). Thirty-three percent of all patients studied were between 8-10 years of age at the time of extraction, whereas 7 percent were younger than 8 years of age and 60 percent were older than 10 years of age. There were no differences among locations with respect to chronological age at T2 by category (8-10 years, <8 years or >10 years) or by mean chronological age (p=0.12, p=0.23); see Appendix 2, table 7. However, there were statistically significant differences between locations with respect to both Demirjian staging (A-H) and Demirjian category (early=A-D, ideal=E, late=F-H); UM and VCU both had more late-stage SPMs compared to UI, which had a relatively even distribution across all categories (p<.0001, p=0.0004). See Appendix 2, tables 8 and 9.

Descriptive data in relation to first molar extraction (*years*), all quadrants combined		
Descriptor	*Average*	*Range*
Chronological age at pre-ext pano	10.6	6.3-14.9
Chronological age at extraction	10.7	6.7-14.9
Time between pre-ext pano and extraction	0.2	0.0-2.1
Time between extraction and follow-up radiograph	4.1	0.5-12

Table 1. Descriptive data in relation to first molar extraction, all quadrants combined.

The presence of a TPM across all quadrants varied significantly among the locations, with UM and VCU reporting higher prevalence levels compared to UI (p=0.004). Overall, 64 percent of maxillary TPMs were observed (88/138), compared to 82 percent of mandibular TPMs (138/168). See Appendix 2, tables 10 and 11.

The mean time between the pre-extraction panoramic radiograph (T1) and extraction (T2) was 71 days, and the mean time between extraction and post-extraction radiograph (T3) was 1498 days. The mean time between T1 and T2 for maxillary quadrants was 94 days, and between T2 and T3 was 1470 days. For the mandibular arch, the mean time between T1 and T2 was 73.9 days, and the mean time between T2 and T3 was 1506 days (Appendix 2, table 12). The box and whisker plot demonstrates that the median values for the T1-T2 range is lower than the mean, with 42.5 days for the mandibular arch and 65 for the maxillary arch due to several outliers (figure 4).

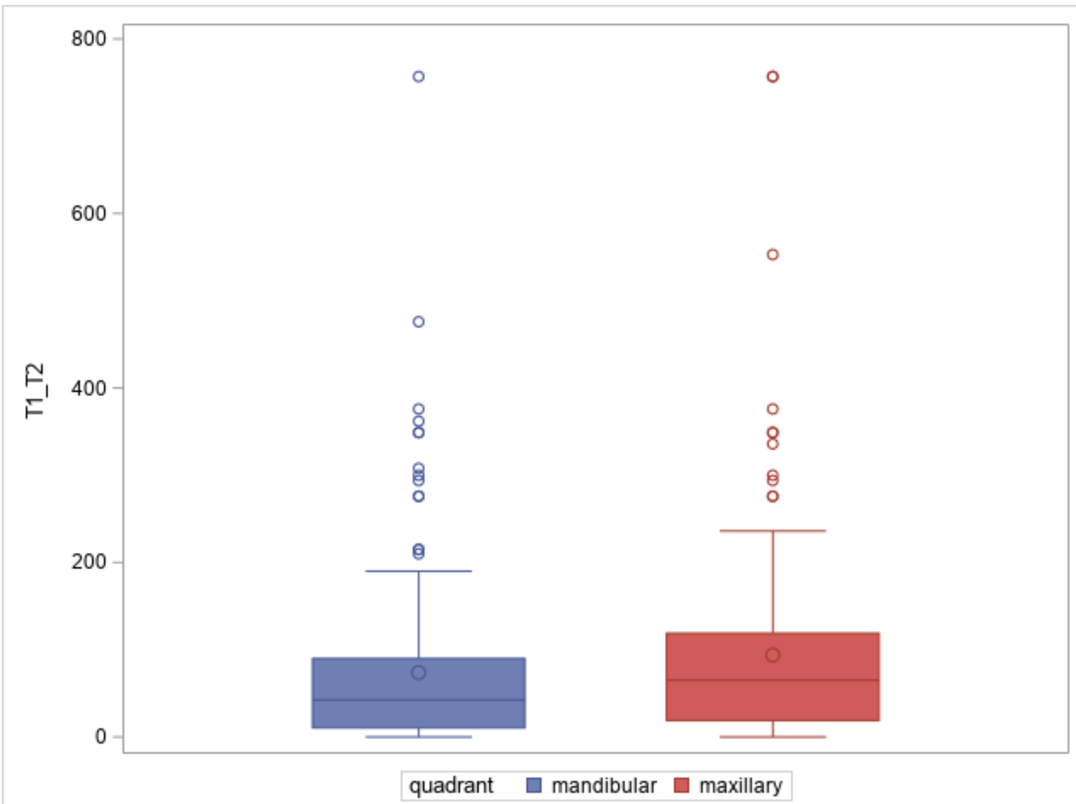


Figure 4. Time interval of T1-T2 (days) by maxillary and mandibular arches.

Three hundred and six quadrants were assessed in 162 patients, of which 168 were mandibular and 138 were maxillary. Within the arches, the right and left quadrants were evenly represented with 50 percent for each side (Appendix 2, Table 13).

Forty-five percent of the quadrants studied were maxillary (138/168) with a mean age at T2 of 10.2 years, and the most frequently observed SPM Demirjian stage of E, observed in 38 percent (52/138) of the pre-extraction radiographs (Appendix 2, Table 14). Stage D was the second most-frequent stage with 30 percent (41/138). By Demirjian category (early, ideal or late stage), 37 percent of maxillary SPMs were ideal, 30 percent were early, and 31 percent were late (Appendix 2, Table 15). Forty-one percent of maxillary FPMs were extracted between 8-10 years of age, while 52 percent were extracted after 10 years and just 7 percent extracted earlier than 8 years (Appendix 2, table 16). The TPM was present at T1 in 64 percent of the maxillary quadrants (Appendix 2, table 17). The type of radiograph used at T2 was predominantly bitewing radiographs (62 percent), followed by panoramic radiographs (37 percent), with PA radiograph used least often (1.5 percent), see Appendix 2, table 18.

For the mandibular quadrants, the mean age at time of extraction (T2) was 10.5 years (Appendix 2, table 12). The most frequently observed Demirjian stage for the mandibular SPM at T1 was stage E, with 25 percent; Stage F was the second most-observed stage with 22 percent (Appendix 2, table 19). By Demirjian category of early (stage A-D), ideal (stage E) or late (stage F-H), 56 percent of mandibular SPMs were classified as late stage, 26 percent were ideal, and 18 percent were early (Appendix 2, table 20). Demirjian stage A and B were not observed at T1 in any patients for either the maxillary or mandibular quadrants. The mean time between T1 and T2 for mandibular quadrants was 73.9 days and between T2 and T3 was 4.1 years (Appendix 2, table 12). Thirty-six percent of the mandibular FPMs were extracted between 8-10 years of age, whereas 57 percent were older than 10 years and 7 percent were younger than 8 years (Appendix 2, table 21). The TPM was present in 82 percent of the mandibular quadrants studied (Appendix 2, table 22). The SPM angulation category that was most observed was upright (50 percent), followed by mesial angulation (38 percent). Distal angulation of the SPM was relatively rare, occurring in just 11 percent of the mandibular quadrants (Appendix 2, table 23). SPM angulation demonstrated no significant difference among locations by sector or category (p=0.12, p=0.28), see Appendix 2, table 24. Intraoral bitewing radiographs were used to assess mandibular SPM eruption in 64 percent of patients, whereas panoramic radiography was used in 35 percent and intraoral periapical radiographs in less than one percent (Appendix 2, table 18).

The maxillary quadrants demonstrated an overall success rate of 82 percent (113/138), whereas the mandibular quadrants demonstrated an overall success rate of 51 percent (86/168). The explanatory variables (gender, chronological age category, SPM Demirjian stage category, Mandibular SPM angulation, and presence of TPM) were each analyzed on both a univariate level and on a multivariate level for statistical significance with respect to outcome. Location was also included with the explanatory variables in each model to test for differences.

Maxillary quadrants

On the **univariate level**, **chronological age category** at T2 demonstrated statistical significance with respect to outcome. Successful SPM eruption occurred in 91 percent of patients (52/57) with extraction between 8-10 years of age, whereas the success rate dropped to 74 percent (53/72) when the extraction occurred later than 10 years of age. In patients younger than 8 years, the success rate was 89 percent (8/9). The odds of success when the extraction occurred between 8-10 years of age were significantly higher than for an extraction later than 10 years of age (OR=3.3, 95% CI: 1.143-9.320, P=0.0271). Although the success rate for extractions completed earlier than

8 years of age was 89 percent (8/9), this was not statistically significant due to the low number of patients in this age group. Location was not significant when chronological age was adjusted in the maxillary arch (Appendix 3, table 1).

On the **univariate level**, **SPM Demirjian category (early, ideal, or late)** demonstrated statistical significance with respect to outcome (Appendix 3, table 2). The odds of successful eruption when the SPM is at an early stage is 7.2 times higher than when the SPM is at late stage (95% CI: 1.902-27.589, p=0.0037). Similarly, the odds of success when the SPM is at the ideal stage are 6.8 times higher compared to an SPM observed at a late stage (p=0.0068). Since there was only one patient with Demirjian stage C, logistic regression models did not converge when examining the effect of individual Demirjian stages on outcome. Location was not significant after adjusting for Demirjian category. Successful SPM eruption occurred in 93 percent (39/42) of quadrants when SPM development demonstrated early stage (stage C or D), and 92 percent (48/52) of quadrants when SPM was ideal stage (E). The success dropped to 59 percent (26/44) when the SPM was late stage (F-H), see Appendix 2, table 15.

On the **univariate level**, presence of the **TPM** had no statistically significant effect on outcome in the maxillary arch (p=0.2172). Location was not significant after adjusting for presence or absence of TPM (Appendix 3, table 3).

Gender did not significantly influence outcome in the maxillary arch although, when gender was adjusted for, VCU had lower odds for success (p=0.0418) and UM demonstrated a trend for lower odds when gender was adjusted, but this was not statistically significant (p=0.0640), see Appendix 3, table 4.

Multilevel modeling was then used to determine which variables in combination **(gender, Demirjian stage of SPM by category, chronological age category, presence of TPM and location)** resulted in a statistically significant correlation with a successful outcome (Appendix 3, table 5). After adjusting for nonsignificant variables in the multilevel model, Demirjian category (early, ideal or late) was the only variable remaining that correlated significantly with success (table 2). Maxillary SPMs at Demirjian developmental stage C or D (early) were 7.2 times likely to be more successful than SPMs at Demirjian stage F-H (late) (p=0.0037). Similarly, SPMs at the "ideal" Demirjian stage E were 6.8 times more likely to be successful than molars at late stage (F-H) (p=0.0068).

Multilevel analysis with nonsignificant variables removed, maxillary quadrants		
Variable	*Estimated Odds ratio (95% CI)*	*p value*
Early Demirjian category (A-D)	**7.2** (1.9-27.5)	0.0037
"Ideal" Demirjian category (E)	**6.8** (1.7-27)	0.0068
Late Demirjian category (F-H)	1.000	***

Table 2. Resulting model for maxillary quadrants after dropping non-significant variables.

Since the Demirjian stage by category was the only significant variable in the multilevel modeling, a univariate regression model was run by throwing out the patient with one SPM at stage C to demonstrate the relative odds ratio for success among the individual Demirjian stages relative to stage H (Appendix 3, table 6). Stages D,E,F demonstrated statistically significant odds favoring success, with a trend observed that the odds decrease with increasing SPM developmental stage. Stage G was not significantly better than stage H. Location was not significant when SPM stage was adjusted.

Mandibular quadrants

On the **univariate level**, the variable **chronological age category** demonstrated statistical significance with respect to outcome. When the FPM was extracted between 8-10 years of age, the odds of successful eruption were 3.9 times higher than when the FPM was extracted after 10 years of age (p=0.001). When the FPM was extracted younger than 8 years, the odds of success were 5.67 times higher compared to a quadrant with an FPM extracted after 10 years (p=0.01). After adjusting for age, location was significant, with VCU demonstrating lower odds for success (p=0.0040). See Appendix 3, table 7.

On the **univariate level**, **SPM Demirjian category** also demonstrated statistical significance with respect to outcome (Appendix 3, table 8). SPMs presenting with an early Demirjian stage (C-D) were 3.9 times more likely to erupt successfully than those SPMs presenting with late-stage development (F-H) (p=0.02). Similarly, Demirjian stage E, the ideal stage, was 3.3 times more likely to be successful than the SPMs with late stage (F-H) development (p=0.006). After adjusting for Demirjian stage, location was significant, with VCU demonstrating lower odds for success (p=0.0044).

Like the maxillary quadrants, regression modeling was not possible for the individual Demirjian stages due to lack of variance in the 3 subjects with stage C development. Stage C patients were removed, and the regression model for mandibular outcome by Demirjian stage was run. Similar to the maxillary arch, stages D,E, and F had significantly higher odds for success compared to stage H, and a trend was observed that the odds for success decrease with increasing SPM maturity (Appendix 3, table 9). Stage

G, like the maxillary arch, did not demonstrate significantly better odds compared to H. Location was significant after adjusting for Demirjian stage, with VCU having significantly lower odds for success than UI (p=0.0456).

On the **univariate level**, presence of the **TPM** was not significantly correlated with success (p=0.63). After adjusting for presence of the TPM, VCU was less likely to be successful compared to UI, and UM demonstrated a trend for lower success (p=0.0031, p=0.0653). See Appendix 3, table 10.

On the **univariate level**, the **SPM angulation** by sector (1-18) and by category (mesial, upright or distal) did not yield statistically significant results with respect to outcome (Appendix 3, tables 11 and 12). When angulation was adjusted by both sector and category, VCU demonstrated lower odds for success (p=0.00025).

Gender did not influence outcome on the **univariate level** in the mandibular quadrants studied (Appendix 3, table 13). When gender is adjusted, location was significant, again with VCU demonstrating lower odds for success (p=0.0025).

On the **multivariate level**, the variables were analyzed for combinations that resulted in statistically significant levels of success in the mandibular arch. **Chronological age category, gender, Demirjian category of the SPM, presence of TPM, angulation of the SPM by category, and location** were evaluated in the multilevel model (Appendix 3, table 14). After removing non-significant variables from the model, the only variable that remained was chronological age at time of extraction and location. As demonstrated in table 3, extraction of the mandibular FPM between 8-10 years of age demonstrated 3.9 times higher odds ratio for success when compared to extraction after 10 years of age (p=0.0011). Similarly, extraction of the FPM younger than 8 years of age was 5.7 times more likely to have a successful outcome than extraction occurring after 10 years of age (p=0.0116). When adjusting for the other variables in the multilevel model, VCU demonstrated a lower odds ratio for success compared to UI (p=0.0040) and UM demonstrated a trend for a lower odds ratio for success compared to UI (p=0.0570). See Appendix 3, table 15.

Multilevel analysis with nonsignificant variables removed, mandibular quadrants		
Variable	*Estimated Odds ratio (95% CI)*	*p value*
<8 years at extraction	**5.664** (1.5-21.8)	0.0116
8-10 years at extraction	**3.892** (1.7-8.8)	0.0011
>10 years at extraction	1.000	***

Table 3. Resulting model for mandibular quadrants after dropping non-significant variables except for clinic location.

<u>Toolkit testing</u>

To test the toolkit from Patel 2017 (figure 1) for prediction of SPM success in the mandibular arch, both variables of TPM and angulation of the SPM were assessed in combination (Table 4). For those patients with both a mesial-angulated SPM and presence of TPM, the predicted probability of success was 63 percent (95% CI: 57-69%), whereas the predicted probability of success for a mesially-angulated SPM without a TPM was 71 percent (95% CI: 62-81%).

Predicted probabilities of space closure in mandibular arch Based on toolkit parameters			
	Angulation of the second molar		
Presence/absence Of third molar	*Distal*	*Upright*	*Mesial*
Present (95% CI)	**40.6% (30.9-50.4%)**	**38.2% (33-43.3%)**	**63% (57.7-68.9%)**
Absent (95% CI)	**44.4%***	**45.4% (33.8-57%)**	**71% (61.5-80.5%)**

**N of 1, did not reach significance*

Table 4. Predicted probability of space closure in mandibular arch based on Patel et al toolkit parameters (1).

The toolkit model was rerun with the Demirjian stage H quadrants eliminated, as it was unclear in the Patel study how they defined their upper limit for the pre-extraction SPM developmental stage. The toolkit results without stage H SPMs (Appendix 3, table 16) were similar when compared to the toolkit model which included stage H SPMs (Table 4). When stage H SPMs are eliminated, the predicted probability for success of mesially-angulated SPMs with presence of a TPM had a predicted probability of 72 percent (95% CI: 67-77%) and the mesial-angulated SPMs without the TPM had a predicted probability of 73 percent (95% CI: 65-82%).

Since chronological age category was the only significant variable in the multilevel modeling for the mandibular arch (table 3), its predicted probability for success was calculated for comparison to the predicted probability of the toolkit. Predicted probability is 70 percent (67-73%, 95%CI) for the 8-10 year age group, and 66 percent (59-74%, 95%CI) for the <8 year group (Table 5). Comparatively, frequency data demonstrates 78 percent success among mandibular SPMs at stage D, followed by 70 percent for SPMs at both stages E and F (Appendix 2, table 19).

Predicted probability of space closure in mandibular arch based on chronological age category	
Variable	*Predicted probability of success (95% CI)*
<8 years at extraction	66.4% (58.6-74.3%)
8-10 years at extraction	**70.2% (67.2-73.1%)**
>10 years at extraction	**34.5% (31.9-37.0%)**

Table 5. Predicted probability of space closure in mandibular arch by chronological age category.

Kappa statistics were used for reliability testing for both intra-rater and inter-rater measurements. For intra-rater reliability testing, forty quadrants were selected at random and the explanatory and outcome variables re-examined by the primary researcher (K.N.) after a four-week washout period (Appendix 3, table 17). Almost perfect agreement was found for the Demirjian stage (C-H) and outcome. Substantial agreement was observed for the angulation of the SPM by sector (1-18) and presence of TPM, and almost perfect agreement was found for angulation by category (mesial, upright, distal). A second researcher (A.R.) examined the same explanatory and outcome variables for all 306 quadrants (Appendix 3, table 18). The inter-rater agreement was almost perfect for both the Demirjian dental stage (C-H) and presence of TPM. Moderate agreement was observed for both angulation of SPM by sector (1-18) and by category (mesial, upright, distal). Substantial agreement was observed with respect to outcome. Interpretation of Kappa values is found in Appendix 3, table 19.

DISCUSSION

The results of this study do not validate the toolkit parameters of Patel et al (figure 1), as the combination of an observed TPM and mesial angulation of the SPM did not result in the highest predicted probability for success in the mandibular arch (table 4). This combination resulted in a predicted probability of 63 percent, however the combination of mesial angulation of the SPM without the TPM resulted in the highest probability of 71 percent. In this study, the results of the multilevel modeling in the mandibular arch show the primary importance of chronological age for predicting successful outcome (Appendix 3, table 14). The predictive probability for success based solely on chronological age in the mandibular arch was 70 percent (table 5), which is comparable to the best-performing toolkit parameters, mesial angulation of the SPM without presence of the TPM, which had a predicted probability of 71 percent (table 4).

In the maxillary arch, the results of the multilevel modeling demonstrated that Demirjian SPM stage by category alone was significant, with the early (A-D) and ideal (E) stage categories both demonstrating 93 percent predictive probability of success, compared to just 64 percent in the late stage (F-H) Demirjian category (Appendix 3, table 20).

Although it is well-established that chronological age and dental developmental stage are correlated, significant variation is observed in dental development at various chronological ages, and understandably a clinician would not base the irreversible treatment decision of FPM extraction on chronological age alone (44,46,47). Fortunately, it would be expected that a patient requiring extraction of an FPM would have a panoramic radiograph, and therefore SPM developmental stage information would be readily available in combination with chronological age. For this reason, additional statistical analysis is warranted to investigate in greater detail the relationship between chronological age and outcome, as well as the relationship between chronological age and Demirjian dental stage of the SPM in the present study population. Preliminary frequency data relating outcome in each arch by chronological age at T2, rounded to the nearest whole integer year, is reported in Appendix 4, figures 1 and 2. Additionally, frequency data relating chronological age at T2 (rounded to the nearest whole integer year) and Demirjian stage observed is also reported (Appendix 4, figures 3 and 4).

There were several limitations in this study which may have affected the toolkit findings. Due to the multi-site nature of the sample, the panoramic images were taken on multiple devices by multiple operators resulting in unknown radiographic variability, which could have introduced error in toolkit angulation measurements. Larheim and Svanaes demonstrated that vertical and angular measurements are reproducible on panoramic images provided that the same device and settings are used, while horizontal measurements are not (48). Furthermore, Hardy et al assessed the effect of vertical head-positioning changes during panoramic radiograph exposure on the mesial-distal inclination of all teeth in dried skulls, and demonstrated that the mesial-distal angulation measurements of maxillary and mandibular posterior teeth are more sensitive to vertical head-positioning error than anterior teeth. The observed changes in molar angulation measurements were approximately equal to the change in vertical head positioning, with a superior head-tilt resulting in the appearance of a mesial root position of the mandibular molar and an inferior head-tilt resulting in a more distal root position. Hardy et al concluded that significant change in root tip assessment would be possible with a 5 degree superior head-tilt or a 7 degree inferior head-tilt (49). The variation in vertical head-positioning affected mandibular premolars similarly, although it was less exaggerated compared to the molars. Hardy et al used Frankfort horizontal as a reference line for tooth angulation measurement, whereas the present study used the occlusal plane as a reference line. It is possible that the discrepancy in root angulation with vertical head-positioning variation would all be relative, and the subsequent angulation errors negligible with respect to the occlusal plane. However, because the errors in vertical head positioning do not equally affect the angulation of mandibular molars and premolars, it is possible that head positioning errors also affect the occlusal plane (49). Nevertheless, Patel et al obtained all panoramic images at one location, and therefore likely had less variability in images and possibly more reliable angular measurements compared to this study (1).

Identifying the line of best fit for the occlusal plane in the toolkit may have been another source of error in this study. Patel et al did not explicitly define the landmarks for the occlusal plane reference line, but instead simply demonstrated the occlusal plane in one sample panoramic radiograph (Appendix 1, figure 3) and referenced a modification to the technique described by Shiller to assess angulation of the TPM (Appendix 1, figure 6) (1,50). The intra-operator reliability testing performed by the primary investigator (KN) demonstrated almost perfect agreement by SPM toolkit angulation category (mesial, upright, distal), with a kappa value of 0.90 (Appendix 3, table 17). Likewise, Patel et al reported almost perfect intra-rater agreement for the toolkit SPM angulation category, with a kappa value of 0.857. However, inter-rater reliability for SPM angulation category in the present study demonstrated a kappa value of 0.59, indicating only moderate agreement (Appendix 3, table 18). Patel et al reported higher inter-rater reliability values for SPM angulation category, with kappa values between 0.680-0.857, indicating good to very good agreement. Although the second examiner was trained to use the toolkit as described by Patel et al, the lack of a defined occlusal plane may leave the SPM angulation measurement prone to error. It is likely that Patel et al did not explicitly describe the occlusal plane in the instructions for the toolkit due to the inherent ambiguity in defining an occlusal plane for mixed dentition patients. Additional instruction from Patel et al regarding the use of the toolkit and definition of the occlusal plane may reduce any possible error in the SPM angulation measurement of the toolkit. Conversely, among studies using similar angulation measurements with a well-defined occlusal plane on panoramic radiographs of patients with all permanent teeth erupted, intra-rater reliability is near-perfect to perfect (51,52).

As stated previously, Patel et al reported that their methodology in assessment of SPM angulation was based on a modification to Shiller's method (Appendix 1, figure 6). Shiller's method refers to the instrument created to assess the angulation of the mandibular TPM relative to the occlusal plane of just the SPM instead of the entire posterior occlusal plane, which seems like it would reduce error in angulation measurement (50). Unfortunately, neither intra- nor inter-rater reliability testing were performed in Shiller's study. In another retrospective study on mandibular SPM substitution, Teo et al investigated SPM angulation but used the long axis of the FPM as the reference plane instead of the occlusal plane (45). SPM inclination was reported as a binary variable, mesial or not mesial. Unfortunately, no description or systematic way of assessing angulation was described in their study. Nevertheless, SPM angulation was found to be statistically significant with respect to a successful mandibular outcome. Utilizing the long axis of the FPM may be less prone to error than the occlusal plane, although clarification is needed with respect to the method described by Teo et al. Alternatively, measuring angulation of the SPM by more closely following Shiller's method in limiting the length of the occlusal reference plane to one posterior tooth may result in less error and better intra- and inter-rater reliability (50).

Fortunately, the Demirjian staging system (Appendix 1, figure 1) is based on shape and relative length criteria rather than angulation measurements or absolute lengths, and therefore is less sensitive to errors resulting from variability in panoramic machines and patient-positioning techniques (44). Not surprisingly, almost perfect agreement was observed regarding the Demirjian dental stage (C-H) of the SPM for both the intra- and inter-rater reliability testing, with kappa values of 0.86 and 0.81 respectively (Appendix 3, tables 17 and 18). The TPM variable was similarly unaffected, as its presence or absence relies on evidence of at least crypt formation or later stages of development. The kappa value for inter-rater reliability for presence or absence of the TPM demonstrated almost perfect agreement (0.85), whereas substantial agreement for intra-rater reliability was observed, with a kappa value of 0.79 (Appendix 3, tables 17 and 18). Similarly, in the Patel study, the intra and inter-rater reliability for both the TPM and Demirjian staging were reported as almost perfect to perfect agreement, with kappa values between 0.8337-1.000 (1).

The TPM can be difficult to detect in its earliest stages on a panoramic radiograph due to limited calcification compared to the other teeth. The TPM begins forming, on average, around 9.81 years± 2.35 years in girls and 9.79 ± 1.63 years in boys (53). The mean age at time of the panoramic radiograph in this study was 10.6 ± 2 years, therefore many patients in this study sample were in the early phase of TPM development, therefore making it difficult to detect. Furthermore, TPMs in the earliest stages of development may be more difficult to detect in the maxilla compared to the mandible with increased superimposition of anatomic structures including the zygomatic process of the maxilla, pterygomaxillary fissure and posterior wall of the maxillary sinus (54).

The dependent variable, outcome, had a narrow definition in the present study, but consistent with that of Patel et al: "success" defined as "complete space closure between the SPM and second premolar as well lack of significant vertical marginal ridge discrepancy" (1). This definition was feasible to determine in this study with radiographs only. Almost perfect agreement was observed from the intra-rater reliability testing, and substantial agreement for inter-rater reliability, with kappa values of 0.91 and 0.78 respectively (Appendix 3, tables 17 and 18). As noted by Patel et al, the binary nature of this outcome definition excluded some patients who had SPM eruption that was very close to ideal. On the other hand, the outcome criteria did not evaluate for open contact points anterior to the second premolar following FPM extraction. Teo et al accounted for distal movement of the second premolar in their outcome criteria in their first study, with success defined as: "complete space closure between the SPM and second premolar, no angulations or rotations and no distal movement of the second premolar" (39). The authors observed success in 61 percent of mandibular quadrants studied, which is higher than the overall success reported in both this study (51 percent) and in Patel et al (49 percent) despite the more stringent definition of success. Teo et al reported distal movement of the second premolar in just six percent of all mandibular quadrants studied, while none was reported in the maxillary arch (39). In their follow-up study re-assessing the mandibular quadrants, Teo et al assessed all contact points distal to the canine and defined “optimal success” as only extremely minor contact displacements and malocclusion of less than 1mm (45). Using this definition, their optimal success rate was 51 percent. The similarity among the studies with respect to rate of success in the mandibular arch suggests that successful outcomes in both Patel et al and this study are not over reported in spite of the relatively narrow definition of outcome used compared to the definition used by Teo et al (1,45).

The overall results for successful outcome by arch are similar to the results from previous retrospective studies. The overall success in the maxillary arch was 82 percent, whereas 51 percent success was observed in the mandibular arch. Patel et al observed 89.9 percent success in the maxillary arch and 49.0 percent in the mandibular arch (1). Similarly, Teo et al observed 92 percent success in the maxillary arch and 61 percent success in the mandibular arch (39). These studies, in addition to the present study, had similar inclusion criteria with respect to age range at time of extraction, number of quadrants evaluated, and time interval between extraction and follow-up, therefore comparisons can be made among the findings.

The findings of the present study contradict the findings of Teo et al regarding the effect of Demirjian developmental stage on outcome (39). Teo et al investigated the effect of SPM Demirjian stages D-G on outcome in 236 SPMs among 63 patients with extraction between 7-13 years. Although their results failed to reach statistical significance when comparing the various stages on outcome, they reported frequency data and concluded that the ideal Demirjian stage E did not result in the highest frequency of successful outcomes. They reported a success rate of 92 percent in the maxillary arch among all stages (D-G), with stage F resulting in 100 percent success. In this study, among stages D-G in the maxillary arch, the overall success was 85 percent, with stages D and E resulting in the highest frequency of success (92 and 93 percent respectively), and stage F having 80 percent success (Appendix 2, table 14). In the mandibular arch, Teo et al found 66 percent success among subjects with FPMs extracted at the ideal stage E, compared to 76 percent success at stage F, and stages D and G resulting in the lowest rates of success at 44 percent. The findings of this present study found contradictory results in the mandibular arch with stage E and F both resulting in 70 percent success, while stage D resulted in the highest success at 78 percent, whereas stage G had just 27 percent success (Appendix 2, table 19). While the present study did find success at both earlier and later stages than the guidelines' ideal stage E, there was a significant trend observed with extraction at earlier SPM stages being more favorable compared to later stages in both arches (Appendix 3, tables 6 and 9).

As stated previously, Teo et al then re-examined 127 mandibular quadrants in 66 patients from their 2013 study by assessing various pre-extraction variables suggested in the literature to have an influence on the outcome of spontaneous SPM eruption: position of the second premolar within the bifurcation of the primary second molar, mesial angulation of the developing SPM in relation to the FPM, presence of TPM, as well as their interaction with the ideal time as recommended by the guidelines (7,38,45,51,55). They found the most favorable outcomes resulted from a combination of the following variables: an SPM at stage D, E or F (not G), in combination with the mesial angulation of the SPM relative to the FPM, and presence of the TPM (45). For the mandibular quadrants with all of these parameters being met, successful outcome was 85 percent (45). Thus, their findings supported the importance of the TPM, the mesial angulation of the SPM in addition to the SPM Demirjian developmental stage on successful outcomes in the mandibular arch.

Patel et al examined similar radiographic parameters on the success of mandibular SPM eruption and came to similar conclusions as Teo et al (1). Angulation of the developing SPM and second premolar relative to the occlusal plane, Demirjian developmental stage of the SPM categorized as early (A-D), ideal (E) or late (F-H), and presence of TPM were evaluated with respect to successful outcome. Overall, or composite, dental age was also evaluated on each patient by recording the Demirjian stage of every tooth on the left side of the panoramic radiograph, and an established data set was then referenced to determine a mean chronological age for each tooth based on its stage of development. From this data, the authors were able to use statistical analysis to determine a mean dental age for each study patient to evaluate with respect to outcome. Patients ranged from 6-14.5 years at time of extraction, with a mean chronological age of 9.6 years. From multilevel analysis, the only variable that was correlated with statistical success in the maxillary quadrants was mean dental age; however, this was not clinically significant according to Patel et al due to the generally high levels of success in the maxillary arch (90 percent), and the predicted probability for success only decreased by 0.83 percent for each increase in dental age by one year (1). In the mandibular arch, however, the multilevel analysis demonstrated that the only variables correlated with success were presence of TPM and mesial angulation of the SPM. When the mandibular quadrants were run for predicted probability, the presence of a TPM combined with mesial angulation of the SPM resulted in 89.4 percent predicted probability of space closure (78.2-97.1, 95% CI), which was a significant improvement from the overall success rate of 49 percent in the mandibular quadrants studied (Appendix 1, figure 7). Since SPM Demirjian developmental stage category was not correlated with success in the mandibular arch, Patel et al concluded that the guidelines' recommendation to extract at Demirjian stage E are not supported by the findings in their study, but rather the presence of the TPM and mesial angulation of the SPM are most predictive of success (1).

In contrast, this study found that neither the presence of the TPM nor mesial angulation of the SPM significantly influenced mandibular arch success on either the unilevel or multilevel modeling, thus refuting the findings of both Teo et al and Patel et al and failing to validate the toolkit (Appendix 3, tables 10-12 and 14). However, as stated, the optimal pre-extraction parameters reported by Teo et al 2016 also required an SPM developmental stage of D,E or F in addition to the mesial angulation and presence of the TPM, whereas Patel et al only found mesial angulation and TPM to be significant (1,45). One possible explanation for the discrepancy in statistical significance with respect to SPM stage is that Patel et al reported SPM Demirjian stage by category, grouping stages A-D as early, E as ideal, and F-H as late (1). The grouping of SPM stages likely affected the significance of the variable in the multilevel modeling in Patel et al, given that Teo et al found that stages D-F were associated with success in combination with the mesial angulation and TPM, but stage G was not (1,45). Interestingly, the same discrepancy in significance of Demirjian stage versus Demirjian category was observed in this study. To closely follow the methodology of the Patel et al study design, the SPM developmental stage in this study was analyzed by category in the multilevel modeling. Like the findings of Patel et al, mandibular Demirjian SPM stage by category was not a significant variable on outcome in the multilevel modeling analysis (Appendix 3, table 14). However, on a univariate level, the influence of Demirjian stage by category on outcome demonstrated that both early and ideal SPMs had significantly higher odds for success compared to the late-stage SPMs (Appendix 3, table 8). Additional statistical analysis demonstrated on a univariate level that Demirjian stages D-F were significantly associated with higher likelihood of mandibular SPM success compared to stage H, whereas stage G was not (Appendix 3, table 9), which is consistent with the findings reported by Teo et al (45). Since there is evidence that stage F behaves differently than stage G or H, the Demirjian categories described by Patel et al and used in this study do not reflect the success observed by individual Demirjian stages.

Another possible explanation for failing to validate the toolkit may be due to the difference in mean chronological age of the populations studied. The mean chronological age at T1 for the present study is 10.6 years, whereas the mean age of study patients at T1 for both Patel et al was 9.2 years (1). The mean age for crypt formation of the TPM is reportedly 9.8 years, and therefore the population in the Patel et al study encompassed more patients in whom TPM development was not initiated (1,53). In this study, 64 percent of the maxillary and 82 percent of the mandibular quadrants demonstrated evidence of TPM formation (Appendix 2, table 11). By contrast, Patel et al reported evidence of the TPM in 62 percent of maxillary quadrants and just 75 percent of mandibular quadrants. Patel et al acknowledged that the influence of the TPM in their study population may be attributed to early TPM development rather than its absence, thus reducing the applicability of the toolkit in older children. The findings from this study support their suspicion (1).

TPM aside, the other toolkit parameter, SPM angulation, also failed to demonstrate statistical significance on either the univariate or multivariate level, although there was a trend observed at the univariate level that mesially-angulated mandibular SPMs had increased odds for success compared to distally angulated SPMs (Appendix 3, table 11, 12 and 14). No studies have yet investigated the physiologic changes in angulation of the mandibular SPM during maturation prior to eruption, therefore it is unknown what angulation changes may naturally occur over time prior to eruption as a result of typical growth and development (1). Therefore, the difference between mean chronological age at time of extraction for this study population and that of Patel et al cannot explain the lack of significance of SPM angulation on outcome (1). Furthermore, the fact that minor sagittal head positioning errors during panoramic radiograph exposure can lead to significant angulation measurement errors in the maxillary and mandibular posterior teeth further calls into question the clinical usefulness of the toolkit (49).

Although no direct comparisons can be made on the outcome of spontaneous TPM substitution following the extraction of SPMs in conjunction with orthodontic treatment, the orthodontic specialty literature is replete with case reports retrospective studies, and reviews on spontaneous TPM substitution (52,56,57). In 1986, Bishara and Burkey published an exhaustive review of the available literature on the controversial orthodontic treatment modality of SPM extraction, summarizing its proposed advantages and disadvantages (56). Per Bishara and Burkey, proposed benefits included relief of crowding, less lip retrusion and reduced impaction of the TPM. Opponents argue the

TPM can remain impacted, and/or fail to spontaneously erupt successfully, resulting in open contacts and excessive mesial tipping. The general consensus in the literature is that maxillary TPMs typically substituted successfully following extraction of the SPM, however lower rates of success were observed in the mandibular arch, with both arches demonstrating very similar success rates to those reported for SPM substitution following FPM extraction (52,58–60). Similar pre-extraction parameters were assessed in the orthodontic literature for the potential of predicting successful TPM substitution, including TPM root development and angulation. Gooris et al tested the predictive value of mandibular TPM angulation on the outcome of its spontaneous eruption following SPM extraction with orthodontic treatment by implementing a study design with striking similarities to that of Patel et al (1,52). Using pre-extraction panoramic radiographs in subjects between 9-19 years at time of extraction, Gooris et al assessed the angulation of the mandibular TPM, SPM, FPM and second premolar relative to both the occlusal plane and mandibular plane (Appendix 1, figure 8). Outcome was assessed on a post-extraction panoramic radiograph after eruption of the TPM to the level of the occlusal plane. Success was determined if the contact was closed and without a vertical discrepancy between the FPM and TPM. Gooris et al found only 46 percent (65/140) of the mandibular quadrants had satisfactory contact relationships between the FPM and TPM and that angulation measurements were not predictive of successful, spontaneous eruption of the TPM, consistent with findings from a previous study by Lawlor (52,61). De-la-Rosa-Gay et al assessed the predictive value of TPM dental development and chronological age at time of SPM extraction, and reported 96 percent of maxillary TPMs and 66 percent of mandibular TPMs successfully replaced the extracted SPMs with spontaneous eruption following orthodontic treatment (57). De-la-Rosa-Gay et al found a statistically significant relationship in both arches between unsuccessfully erupted TPMs and older patients with greater than 2/3 root formation of the TPM at time of SPM extraction, in agreement with the findings of several other authors (57,62–64).

Although the findings from this study cannot be compared directly to the orthodontic literature regarding spontaneous TPM substitution, similarities between SPM and TPM substitution patterns with respect to their outcome are indicative of general tendencies. Their success rates are similar in the literature with respect to each dental arch, as well as the negative sequelae often observed in the mandible: lack of proximal contact and excessive mesial tipping of the substituting molar. The similarities between the two types of molar substitution with respect to arch differences supports the general concept that the maxillary molars are more successful because their roots are positioned mesial relative to the crown during development, and spontaneous substitution requires primarily mesial crown movement/tipping to achieve an upright position, while the mandibular molars tend to have distal root position relative to the crown, and thus require greater mesial root movement to achieve an upright position. It is also of interest that the literature on TPM substitution demonstrates that pre-extraction angulation of the mandibular TPM has no effect on its successful substitution, while developmental stage of the TPM at time of SPM extraction in both arches has proven to be significantly associated with outcome (57,61–64). Both observations are consistent with the findings of this study regarding SPM substitution (Appendix 3, tables 6,9, and 12). Finally, given the similarities between the SPM and TPM substitution with respect to success rates by arch, negative sequelae, and variables predictive of success, it is worth noting that the

TPM is the most terminal tooth, and therefore success cannot be influenced by the development of a tooth posterior to it. Coincidentally or not, the findings of this study demonstrated that the presence of the TPM had no significant effect on outcome in either arch, resulting in further lack of support for the toolkit's usefulness (Appendix 3, tables 3,5, 10 and 14).

Like the Demirjian staging categories, the variable of chronological age at T2 was categorized for the multilevel analysis according to the age categories described by the guidelines: early: <8 years, ideal: 8-10 years, and late >10 years of age. The multilevel modeling in this study found that chronological age at T2 was the only variable significantly associated with outcome for the mandibular arch (Appendix 3, table 14). For the maxillary arch, chronological age category was significant on the univariate level (Appendix 3, table 1). However, it would be more clinically relevant to know in greater detail the effect of chronological age beyond the categories, as well as better-defined upper and lower age limits. Additionally, the relationships between chronological age, Demirjian developmental stage, and outcome need to be investigated in more detail and without their current, seemingly arbitrary categories.

The fact that the current guidelines present two simultaneous recommendations regarding extraction timing for the mandibular FPM suggests that the ideal Demirjian stage E also occurs at the ideal chronological age of 8-10 years (65). However, in this study, the mean chronological age at T1 for the various Demirjian stage categories for the mandibular quadrants are: early stage: 8.4±1.2 years; ideal stage: 9.1±1.7 years; late stage 11.5±2.1 years (Appendix 2, table 25). Since there are overlaps between the chronological age categories and Demirjian stage categories, the two guidelines regarding mandibular FPM extraction timing are unclear and may contradict each other in certain cases. Furthermore, because this study found that success in both arches was significantly associated with growth and development variables, chronological age and SPM Demirjian dental stage, additional analysis on the sample data in this study is warranted to narrow the window of optimal extraction timing.

This study found a clear trend that FPM extractions completed at younger ages and earlier SPM developmental stages are significantly associated with higher rates of success compared to older ages and later SPM stages (tables 2,3 and Appendix 3, tables 6,9). Currently, the guidelines advise deferring a mandibular FPM extraction until the "ideal" time, which may mean temporizing a hypoplastic and/or carious FPM in a young child until stage E is observed, and/or the 8-10 year age window(65). Given that enamel hypoplasia and caries occur early and often in young children soon after eruption of the FPM, the potential burdens to temporarily restore these teeth must be considered when deferring their extractions to the advised "ideal" time. The data in this study suggests there is no benefit to deferring their extraction until stage E is observed in the mandibular arch, however additional analysis is warranted within the age categories and Demirjian stages to assist clinicians in identifying an optimal time for extraction.

The results of this study can also be compared to two meta-analyses. Saber et al conducted a meta-analysis to review available literature on outcome of extraction of compromised FPMs completed between 5-15 years of age and concluded to extract based on Demirjian stage rather than chronological age, and found that stage E results in the fewest undesirable consequences in both arches (66). The results of this study support the recommendation to extract by Demirjian stage, but do not support deferring the extraction until stage E in the mandibular arch given stage D resulted in the highest frequency of success at 78 percent (Appendix 2, table 19). In the maxillary arch, stage D and E both resulted in 92 percent success (Appendix 2, table 14).

Eichenberger et al also conducted a similar meta-analysis with respect to extraction timing based on chronological age and outcome, analyzing maxillary and mandibular quadrants separately (67). By meta-analysis, Eichenberger et al observed in the maxilla, the overall spontaneous space closure was 72 percent, with the best results in the 8-10.5 year age range at time of extraction, achieving 80 percent success, although this did not differ significantly from the older (>10.5 years) and younger (<8 years) age categories studied. The maxillary arch results of this study agree with Eichenberger et al, with the odds for success in the maxillary arch highest in the 8-10 year age group compared to >10 years (Appendix 3, table 1). However, the <8 years group in this study had 89 percent success, but there were only 9 patients in this age group and therefore did not reach statistical significance. In contrast, the meta-analysis by Eichenberger et al for the mandibular arch resulted in a pooled success rate of 48 percent, with the 8-11.5 year age group having significantly higher likelihood of success compared to both the patients <8 years of age and those >11.5 years of age (67). When the 8-11.5 year age group was subdivided into 8-10.5 and 10.5-11.5 year age groups, the probability for success was 50 percent and 59 percent respectfully. In this study, regarding the mandibular arch, the 8-10 year category was 70 percent successful while the >10 year category was only 38 percent successful (Appendix 2, table 26). Additionally, the <8 year category in this study was almost as successful as the 8-10 year category, with 67 percent success in the mandibular arch. Essentially, the results of this study with respect to chronological age at time of extraction in the mandible contradict the results found in the meta-analysis by Eichenberger et al (67). These contradictory findings call into question the usefulness of the arbitrary, but often-used, chronological age categories on the study of SPM substitution.

The origin of the ideal, 8-10 year chronological age window for optimal timing of the mandibular FPM extraction as stated in the guidelines is still based on the findings and recommendations of Thunold in an observational, retrospective study from 1970 (38,43). Thunold reported on trends with respect to age at time of extraction and observed more tipping and rotation of the SPM when the extraction was performed in the later age group (12-14 years) compared to the earlier age groups (8-9 years and 10-11 years). Ten percent of all three age groups demonstrated distal tipping of the second premolar, although the 8-9 year age group demonstrated a very mild increase compared to the other two age groups. Thunold reported that patients with extractions between 8-10 years of age had the highest frequency of success in the mandibular arch. The optimal treatment timing (8-10 years) for mandibular FPM extraction, as advised by the guidelines and per Thunold's recommendation, were supported by this study's findings: the 8-10 year age category was 4 times more likely to have a successful outcome compared to late extraction, >10 years (Appendix 3, table 15). However, the odds for success in the youngest category (<8 years) is the best in this study, with 5.7 times the odds for success compared to the late extraction group. The current guidelines cites several reasons for avoiding extraction before 8 years of age: the TPM may not be visible, the second premolar can drift distally into the extraction space, tip and rotate, and the labial segments can retrocline with an increase in overbite (38). Interestingly, Thunold's study is cited in the guidelines as one of the primary sources of the potential negative sequelae following the extraction of the mandibular FPM prior to 8 years of age, although their data does not support this rationale. First, Thunold's study did not include any patients younger than 8 years of age at time of extraction. Second, Thunold did not find any evidence of an increase in overbite in her subjects, nor did she demonstrate a meaningful increase in distal tipping of the mandibular second premolar in the patients in her youngest category at time of extraction (8-9 years). Lastly, Thunold found that presence or absence of the TPM had no influence on outcome in the mandibular arch (43).

Early extraction of the FPM is reported to cause unwanted side effects in the developing dentition from a broader perspective than just the interproximal contact issues addressed in the present study. Unfortunately, the present study is limited to a relatively narrow definition for success due its longitudinal, retrospective, and multi-site design investigating the charts of pediatric dental patients; therefore, the orthodontic records required to investigate the broader effects of FPM extraction in a growing patient were unavailable. The older, observational studies first warned of the possible negative side effects of FPM extractions in growing patients, including upright incisors, deepening of the overbite, increased overjet and, in cases with asymmetric extractions, supraeruption of an unopposed upper FPM and/or shifting of the dental midline, and the questionable success of TPM euption (33,34,40,43). Some of the possible negative side effects of FPM extraction first published in the observational studies have since been subjected to statistical analysis, including effect on overbite/overjet, dental midline, and eruption of the TPM.

Balancing and compensating extractions are commonly discussed with respect to early extraction of FPMs and are discussed in the guidelines. Compensating extractions refers to the extraction of an otherwise sound upper FPM when an extraction of a lower FPM is required due to caries and/or enamel hypoplasia to prevent its supraeruption. Balancing extractions refers to the extraction of an otherwise sound FPM to prevent midline shift following the extraction of the contralateral FPM. The guidelines currently recommend compensating extractions as a rule, while less emphasis is placed on balancing extractions (38).

The cohort study published by Holm in 1970 is the main source for the recommendation of compensating extraction (34). Holm analyzed 9,000 treated orthodontic cases from the Public Health Orthodontic Institute of Hamburg, noting that 33 percent involved extractions and of those extraction cases, almost 40 percent involved first molar extractions (1,119 cases). He reported the number of cases involving the compensated bilateral (all four FPMs) and unilateral extractions (upper and lower FPMS on right or left sides) increased with time during the treatment period analyzed (1960-1970), as compared to cases with asymmetric or uncompensated extractions. Holm noted the trend in successful case outcomes mirrored the trend observed in the type of extraction patterns and inferred that the increase in compensated extractions accounted for the increase in successful orthodontic outcomes following FPM extractions. Unfortunately, Holm did not publish any additional details regarding the specifics of pre-extraction variables nor post-extraction outcomes. Instead, five cases were presented in the paper, each with a different FPM extraction pattern, along with their treatment outcomes using casts, photos, and pre-extraction radiographs. Each of the five cases were treated with removable functional appliances and extractions, and no additional data were published with respect to the type of orthodontic treatment received by the other subjects. Holm concluded that, in his opinion, the best orthodontic treatment results included compensated bilateral or unilateral FPM extractions, and the worst outcomes involved an uncompensated lower FPM extraction or asymmetric extraction patterns. Holm's study is still the source cited in the FDSRCS guidelines, although very little information can be extrapolated from the publication due to the lack of data presented in the article (34).

Two additional studies with relatively low numbers of subjects made observations about uncompensated upper FPMs following extraction of a compromised lower FPM. Jalevik and Moller evaluated the spontaneous space closure in 27 children with a mean age of 8.2 years (range 5.6-12.7 years) at time of extraction of one or more FPMs due to molar hypomineralization (68). No compensating extractions were performed in any of the study patients, resulting in uncompensated upper FPMs in four of the 27 patients following extraction of a lower FPM. Jalevik and Moller noted that none of the four cases resulted in supraeruption of the unopposed upper FPM. Unbalanced extractions were also observed in two patients, neither of whom experienced a shift of the midline (68). Similarly, Mejare et al evaluated the outcome of 76 patients with severe FPM hypomineralization treated with extraction compared to non-extraction (29). Thirty-two patients were treated with extraction of one or more FPMs at mean age of 10.5 years, and for whom no compensating or balancing extractions were performed. Mejare et al observed no supraeruption of unopposed maxillary SPMs, and no statistically significant difference was observed in midline deviation between the patients treated with extraction compared to those treated with restorations (29).

Although these two studies refuting the current guidelines' recommendations on compensating and balancing extractions are small, retrospective cohort studies with small sub-samples of patients with uncompensated or unbalanced FPMs, the decision to extract one versus two FPMs in a pediatric patient is significant for the clinician and can tip the balance from local anesthesia to general anesthesia for behavior management. General anesthesia carries an inherently higher burden in terms of financial cost, increased health risks for the patient, possible delay in receiving care for an emergent dental need, and difficulty finding a provider with the proper credentialing for the treatment under general anesthesia (69).

To further investigate the guideline on compensating extractions, Innes et al registered a prospective, randomized controlled clinical trial to evaluate the long-term outcome of uncompensated extractions in patients requiring a mandibular FPM extraction but have a maxillary FPM of good prognosis (70). The two-arm parallel groups were to include a control group, patients receiving a compensating extraction of the maxillary FPM in addition to the mandibular FPM extraction in accordance with the current guidelines, and a case group, patients who would not receive a compensating extraction. Unfortunately, this prospective study was terminated early due to poor recruitment. (70)

The guidelines on balancing extractions is less firm than for compensating extractions based on the quality of evidence (65). As stated, Jalevik and Moller as well as Mejare et al reported no dental midline shift in their very small subsample of patients with unbalanced FPM extractions. Caglaroglu et al investigated retrospectively the effects of early unilateral first maxillary or mandibular molar extraction, prior to age 12 years, on skeletal and dental asymmetry using posteroanterior radiographs taken between

17-19 years of age and compared to a control group with a complete dentition, class 1 relationship, and only slight or moderate anterior crowding (71). The authors found that unilateral first molar extractions caused dental midline deviations in both arches to the extraction side, but this was more prominent in the mandibular arch. For study patients with unilateral extractions, the mean dental midline deviation was 1.11mm in the mandible and 0.69mm in the maxilla, whereas the control group had just 0.20mm of midline deviation. The difference in deviation was statistically significant when comparing the midline of patients with a mandibular extraction to the control group, although that difference was less than 1mm. Furthermore, for the extraction groups, the authors did not describe the pre- or post-extraction characteristics of the patients' occlusion, with the only inclusion criteria being the extraction of one upper or one lower FPM prior to age 12. However, the control group was selected from patients with ideal class 1 relationships, no missing teeth, and mild-moderate anterior crowding. Although the patients in this study with a unilateral extraction of a mandibular FPM had a statistically significant midline deviation, causation cannot be proven based on the study design. Furthermore, the clinical significance of this midline deviation is questionable; as stated, the maxillary extraction group had a mean midline deviation of 0.69mm, and the mandibular extraction group had a mean midline deviation of 1.11mm. These measurements were comparing the upper and lower dental midlines to each other, and no measurement captured if either midline was on with the sagittal skeletal midline. Dental midline discrepancy can be the result of multiple occlusal factors and determining cause and effect from extraction of a unilateral FPM would require more information regarding the pre-treatment occlusal characteristics of the extraction group, much like was described for the control group (71). Not surprisingly, the recommendation for balancing extractions is equivocal (65).

The potential unwanted side effect of mandibular FPM extractions on overbite, overjet, and inclination of the mandibular incisors was described by Thilander and Skagius; they observed a general increase in overbite and overjet following the extraction of mandibular FPMs associated with retroclination of the mandibular incisors (40). Similarly, Thunold observed that extraction of all 4 FPMs did result in an increased interincisal angle but no corresponding change in the vertical dimension was observed, and the overbite remained stable (43). Richardson evaluated the overbite, overjet, and incisor angulations over a 12-month period of 43 patients who underwent extraction of both lower FPMs between 8-14 years at time of extraction using lateral cephalometric radiographs (31). Richardson observed that the range of change for overbite, overjet and incisor inclination was large and included both an increase and decrease in all variables studied. Although no data of statistical significance could be drawn, Richardson concluded that during the first year following extractions, the overbite increased in just over half of patients studied, seemingly due to proclination of upper incisors and retroclination of lower incisors, while overjet remained stable. Additionally, pre-treatment overbite seemed to be less predictive of increased overbite following extractions compared to the pre-treatment observations of proclined upper and lower incisors and increased overjet (31). Abu Aihaija et al performed a study very similar to that of Richardson's and assessed the pre and post-extraction lateral cephalometric radiographs of 28 patients with extraction of both lower molars between 8-14 years, with approximately 18 months between radiographs (72). A control group matched for age and sex from a published growth study was used to control for growth change. Statistical analysis was used to assess for differences before and after extractions. Abu Aihaija et al concluded that extraction of the lower molars resulted in, on average, an increase in overbite over the 18-month review period when compared to the control group but had no effect on anterior facial height or any other vertical measurement. The increased overbite and overjet were associated with lingual positioning and retroclination of the lower incisors. The mean change in overbite observed in the extraction group was an increase of 0.32mm, whereas the control group decreased by -0.48mm (72). Although these measurements are statistically significant, the change in overbite between the two groups differ by less than 1 mm, suggesting the potential side effects of mandibular FPM extractions reported in the study with respect to on overbite and overjet may be less significant clinically.

Several authors have evaluated the effect of first molar extraction on the development and eruption of the TPM, when it is present (51,73,74). Halicioglu et al evaluated the development of the TPM following extraction of the FPM in 294 patients between 13-20 years of age who had a unilateral extraction of a maxillary or mandibular FPM, using panoramic radiographs taken before and after extraction (73). The TPM on the side with the extracted FPM demonstrated significantly accelerated development when compared to the contralateral non-extraction side, with no difference between the maxillary and mandibular TPMs (73). Ay et al evaluated the effect of FPM extraction on the spontaneous angular and positional changes of the mandibular TPMs in 107 patients who had unilateral mandibular FPM extraction prior to 16 years of age using a post-extraction panoramic radiograph (74). Ay et al compared impaction parameters of the

TPM on the non-extraction and extraction side, as well as the angulation of the TPM relative to the occlusal plane using a modification of Shiller's method, like that used in this study. The authors found a statistically significant difference in positioning of the TPM between the extraction and non-extraction side and concluded that the FPM extraction increases space available for TPM eruption and improves angulation. The authors were careful to note however that only TPM position was evaluated, and that the unwanted side effects of mandibular FPM extraction were observed but not studied in this investigation. This would be expected considering the broad range in age at time of extraction (<16 years) and without any investigation of pre-extraction parameters (74). Bayram et al investigated the effect on the TPM eruption space and angulation when all four FPMs were extracted in conjunction with orthodontic treatment, compared to patients with non-extraction treatment, prior to eruption of the TPMs using pre-treatment panoramic radiographs and another panoramic radiograph at the end of a 2.5-3.5 year observation period (51). The authors found a statistically significant increase in available eruption space in both arches in the extraction group compared to the non-extraction group due to the mesial movement of the second molars, whereas non-extraction orthodontic treatment showed little to no effect on available space for the TPM. Bayram et al recalled the extraction patients to evaluate the TPM eruption status clinically and radiographically and observed that TPM angulation in the extraction group improved more significantly in the maxillary arch compared to the mandibular arch, with 96 percent of maxillary TPMs in excellent positions compared to 83 percent of mandibular TPMs. No impacted molars were observed in the extraction group, compared to 53 percent in the non-extraction group. Additionally, Bayram et al compared their results to the numerous existing studies investigating the outcome of spontaneous TPM eruption following extraction of the second molar and found that their success rates were equal to or better than similar studies investigating the spontaneous TPM eruption following extraction of SPMs in conjunction with orthodontic treatment (51).

While the extraction of an FPM in a pediatric dental patient should never be taken lightly, the available evidence suggests that the negative side effects on the developing dentition may not be as deleterious as Thilander and Skagius, Thunold, and others had warned (33–35,40,43). Additional research investigating the effect of FPM extraction on orthodontic variables in the developing dentition is warranted, as FPM extraction is still an essential treatment modality for pediatric dental patients considering the current prevalence of caries and enamel hypomineralization.

CONCLUSIONS

- In the maxillary arch, the Demirjian stage category of the SPM was statistically significant with respect to outcome, with the best odds ratio for success associated with the earliest Demirjian stage category (C-D), followed by ideal (E), and with late stage (F-H) having the lowest relative odds for success (table 2).
- In the mandibular arch, the chronological age of the patient at time of extraction was statistically significant with respect to outcome, with the youngest age category (<8 years) demonstrating the best odds for success, followed by the ideal age category (8-10 years), and with the oldest age category (>10 years) having the lowest odds for success (table 3).

- The Patel et al toolkit parameters, presence of a TPM in combination with a mesially-angulated SPM did not result in the highest probability for success, and therefore the toolkit was not validated in this study population (table 4) (1).
- Additional analysis is warranted regarding the statistically significant variables associated with success in this study to ultimately provide the clinician with more detailed, predictive information beyond the relatively broad categories used in this study for Demirjian staging and chronological age at time of extraction (Appendix 4, figures 1-4).

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APPENDIX 1: BACKGROUND/METHODS

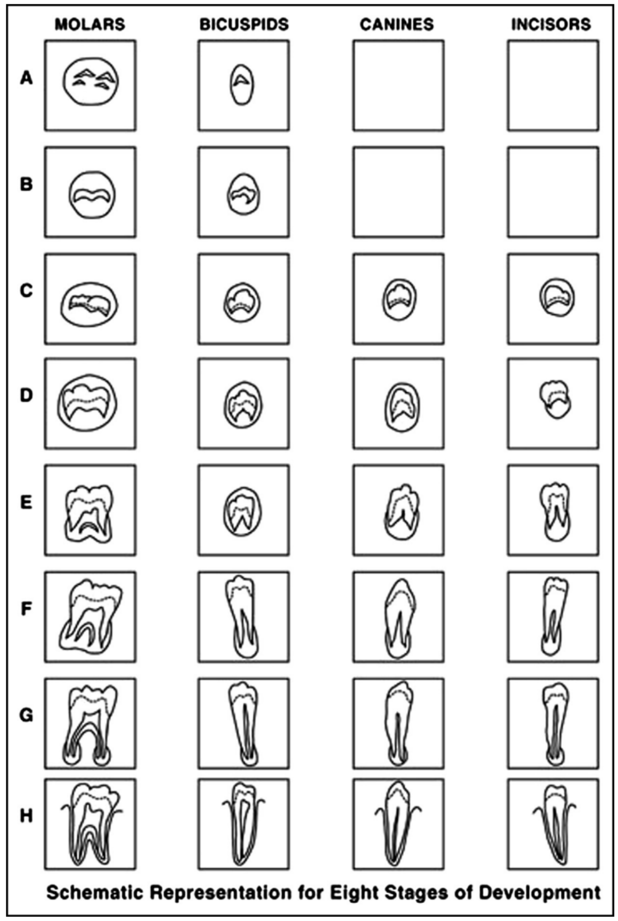

Figure 1. Demirjian staging of dental development (44).

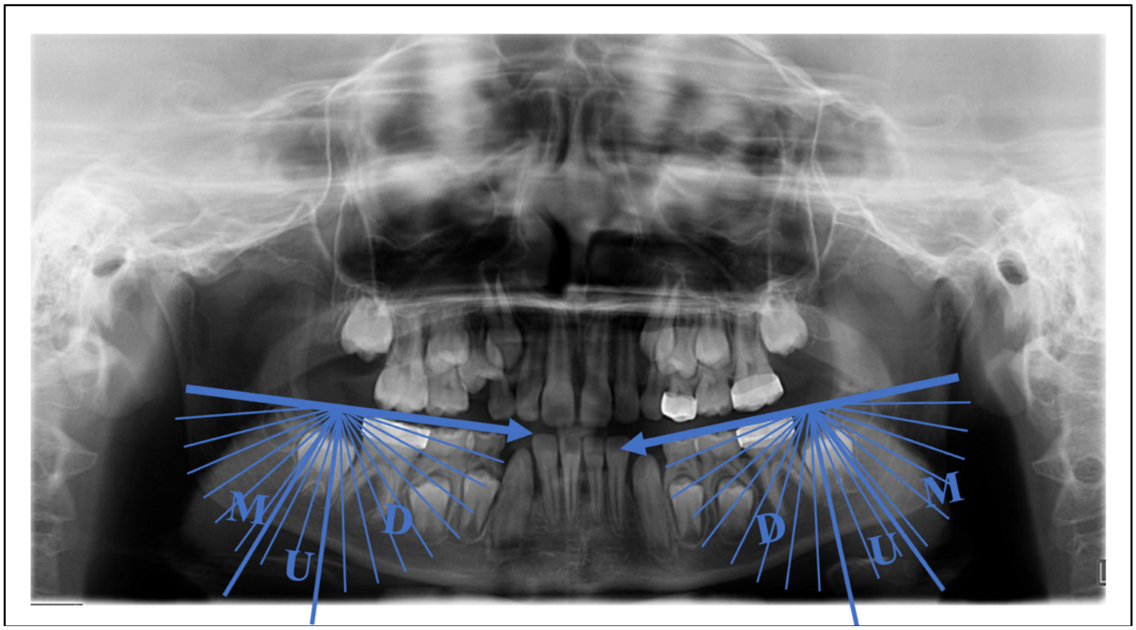

Figure 2. Demonstration of the Patel et al toolkit applied in this study (1).

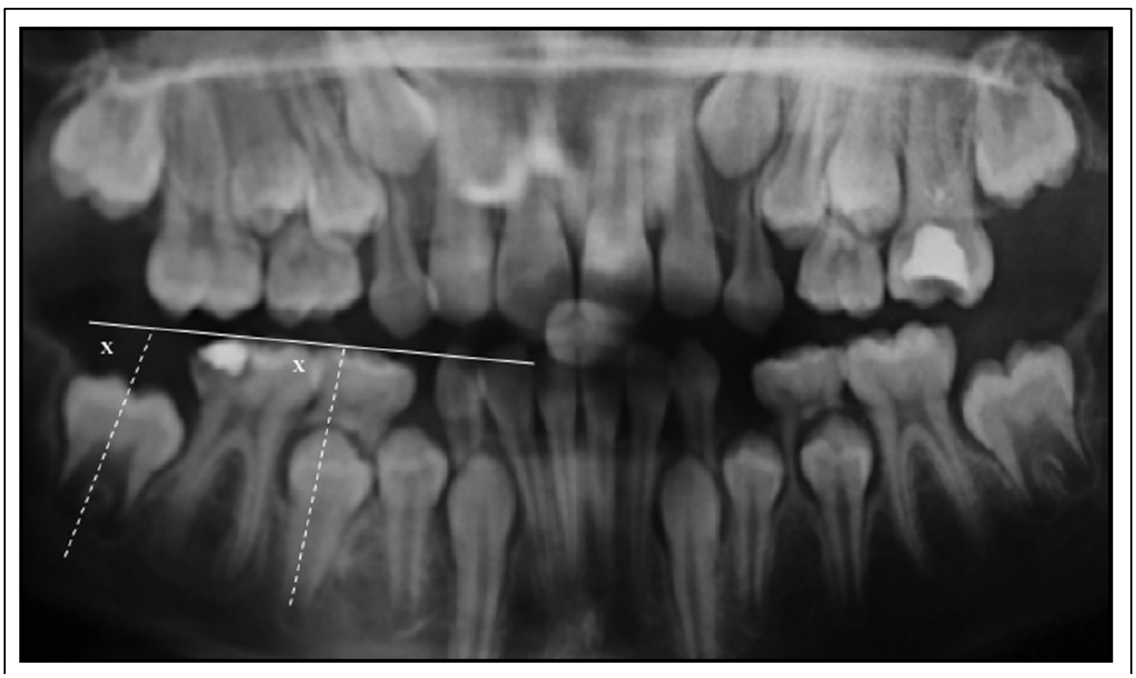

Figure 3. Method for angular measurements demonstrated in Patel et al (1).

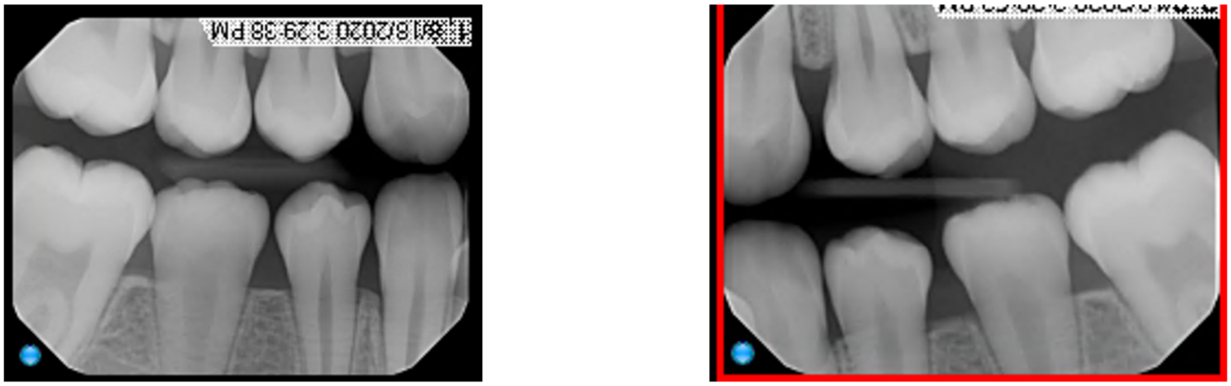

Figure 4. Example of successful outcome in this study (all four quadrants evaluated).

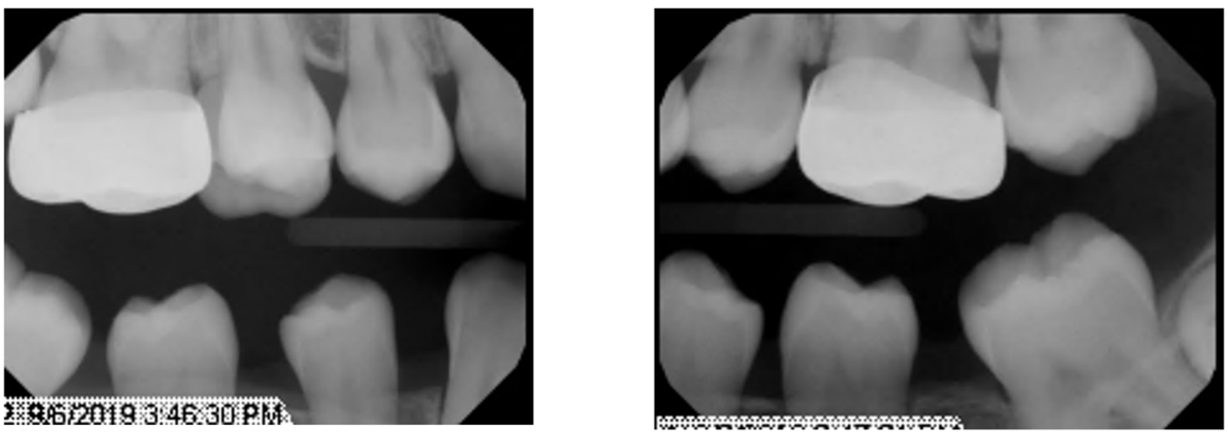

Figure 5. Example of unsuccessful outcome in this study (both mandibular quadrants evaluated).

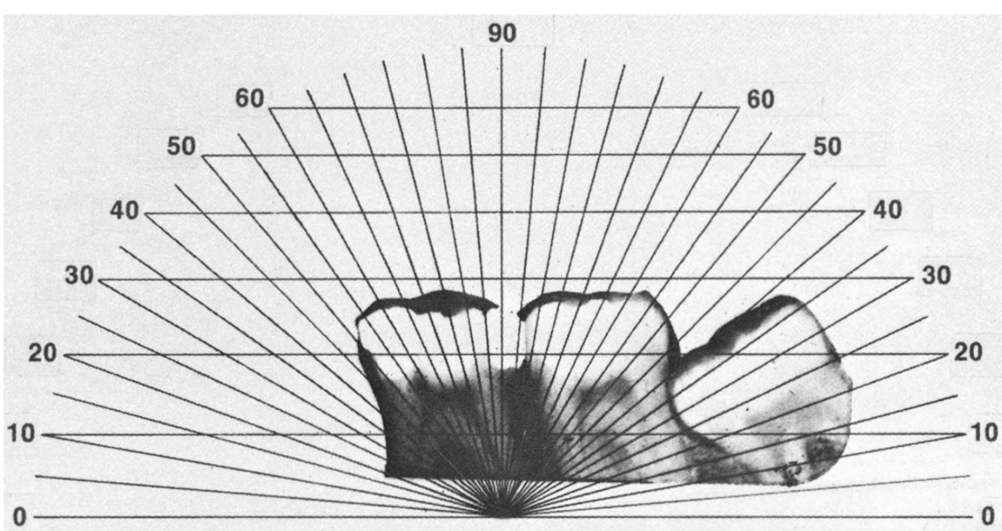

Figure 6. Shiller's method for measurement of angulation of TPM in relation to SPM (50).

Presence/absence of third molar	Angulation of second molar		
	Distal	Upright	Mesial
Present (95% CI)	28.7% (14.7-39.1)	56.5% (43.3-66.5)	89.4% (78.2-97.1)
Absent (95% CI)	7.8% (1.8-12.4)	21.3% (14.0-41.1)	63.7% (51.8-75.3)

Figure 7. Predicted probabilities of space closure in mandibular arch in relation to toolkit variables: angulation of the SPM and presence or absence of TPM, Patel et al (1).

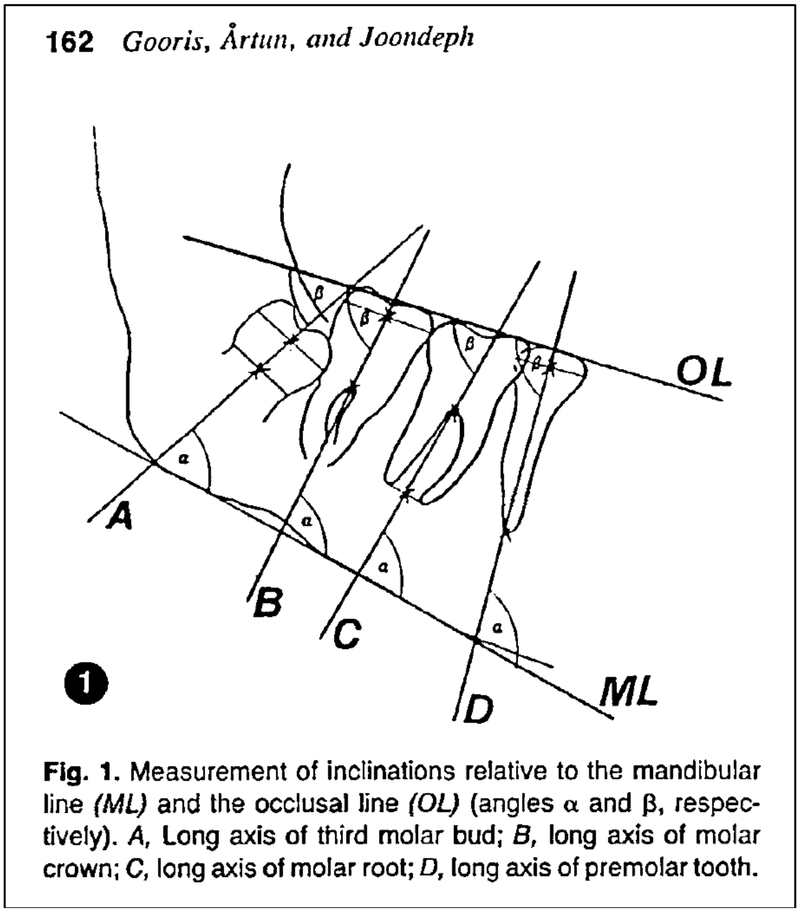
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Fig. 1. Measurement of inclinations relative to the mandibular line *(ML)* and the occlusal line *(OL)* (angles α and β, respectively). *A*, Long axis of third molar bud; *B*, long axis of molar crown; *C*, long axis of molar root; *D*, long axis of premolar tooth.

Figure 8. Demonstration of angular measurements prior to extraction of mandibular SPM for TPM substitution, Gooris et al (52).

APPENDIX 2: RESULTS

Table of gender by location				
gender	location			
Frequency Column Percent	UM	VCU	UI	Total
female	11 55.00	25 54.35	49 51.04	85
male	9 45.00	21 45.65	47 48.96	77
Total	20	46	96	162

(P=0.91 from Chi-square test)

Table 1. Gender by location.

location		
location	Frequency	Percent
UM	20	12.35
VCU	46	28.40
UI	96	59.26

(P<.0001 from Chi-square test)

Table 2. Number of patients per location.

Table of ethnicity by location				
ethnicity	location			
Frequency Column Percent	UM	VCU	UI	Total
White	3 15.00	9 19.57	68 70.83	80
Black or African American	7 35.00	13 28.26	14 14.58	34
Hispanic or Latino	3 15.00	3 6.52	0 0.00	6
American Indian or Alaska Native	1 5.00	0 0.00	0 0.00	1
Unreported	6 30.00	20 43.48	14 14.58	40
Asian/Pacific Islander	0 0.00	1 2.17	0 0.00	1
Total	20	46	96	162

Table 3. Ethnicity by location.

Table of ethnicity by location				
ethnicity	location			
Frequency Column Percent	UM	VCU	UI	Total
Non-white or unreported	17 85.00	37 80.43	28 29.17	82
white	3 15.00	9 19.57	68 70.83	80
Total	20	46	96	162

(P<.0001 from Fisher's exact test)

Table 4. Ethnicity by location (white vs. non-white or unreported).

Parameter	Level	Estimated OR	Lower limit 95% CI	Upper limit 95% CI	P value
location	UM	0.267	0.067	1.061	0.0606
location	VCU	0.317	0.106	0.948	0.0398
location	UI	1.000	1.000	1.000	.

Table 5. Outcome by location, maxillary quadrants.

Parameter	Level	Estimated OR	Lower limit 95% CI	Upper limit 95% CI	P value
location	UM	0.398	0.153	1.032	0.0580
location	VCU	0.272	0.119	0.625	0.0021
location	UI	1.000	1.000	1.000	.

Table 6. Outcome by location, mandibular quadrants.

Table of age category at time of extraction (T2) by location				
age category at extraction (T2)	location			
Frequency Column Percent	UM	VCU	UI	Total
8-10 years	6 30.00	9 19.57	38 39.58	53
< 8	2 10.00	5 10.87	5 5.21	12
> 10	12 60.00	32 69.57	53 55.21	97
Total	20	46	96	162

(P=0.12 from Fisher's exact test)

Table 7. Age at time of extraction by location.

Table of Demirjian stage category by location				
Demirjian stage category	location			
Frequency Column Percent	UM	VCU	UI	Total
Early (A-D)	7 20.59	13 15.85	52 27.37	72
Ideal (E)	5 14.71	19 23.17	71 37.37	95
Late (F-H)	22 64.71	50 60.98	67 35.26	139
Total	34	82	190	306

(P=0.0004 from Fisher's exact test)

Table 8. SPM Demirjian category by location.

Table of Demirjian stage by location				
Demirjian stage	location			
Frequency Column Percent	UM	VCU	UI	Total
C	0 0.00	2 2.44	2 1.05	4
D	7 20.59	11 13.41	50 26.32	68
E	5 14.71	19 23.17	71 37.37	95
F	11 32.35	14 17.07	32 16.84	57
G	8 23.53	19 23.17	15 7.89	42
H	3 8.82	17 20.73	20 10.53	40
Total	34	82	190	306

(P<.0001 from Fisher's exact test)

Table 9. SPM Demirjian stage by location.

Table of TPM by location				
TPM	location			
Frequency Column Percent	UM	VCU	UI	Total
absent	6 17.65	12 14.63	62 32.63	80
present	28 82.35	70 85.37	128 67.37	226
Total	34	82	190	306

P=0.004 from Chi-square test

Table 10. Presence/absence of TPM by location.

Table of TPM by quadrant			
TPM	quadrant		
Frequency Column Percent	mandibular	maxillary	Total
absent	30 17.86	50 36.23	80
present	138 82.14	88 63.77	226
Total	168	138	306

Table 11. Frequency of presence/absence of TPM by arch.

quadrant	(N)	Variable	Mean	Std Dev	Minimum	Lower Quartile	Median	Upper Quartile	Maximum
mandibular	168	T1-T2 (d)	73.9	100.2	0.0	10.5	42.5	90.0	757.0
		T2-T3 (d)	1506.9	939.2	155.0	753.0	1193.0	2239.0	4492.0
		T1 age (y)	10.3	2.3	-1.5	8.8	10.1	11.9	14.9
		T2 age (y)	10.5	2.3	-1.4	9.0	10.3	12.1	14.9
maxillary	138	T1-T2 (d)	94.0	122.4	0.0	19.0	65.0	119.0	757.0
		T2-T3 (d)	1470.3	870.9	251.0	753.0	1129.5	2068.0	3481.0
		T1 age (y)	10.0	1.9	-0.5	8.8	9.8	11.3	14.6
		T2 age (y)	10.2	1.8	-0.5	9.0	10.1	11.4	14.7

Table 12. Descriptive data regarding time between T1-T2 and T2-T3, and chronological age at T1 and T2.

Teeth ID	Frequency	Percent
1	70	22.88
2	68	22.22
3	84	27.45
4	84	27.45

Table 13. Frequency of quadrants (1,2,3,4) among all subjects.

Table of outcome by Demirjian stage							
Outcome	Demirjian stage						
Frequency Column Percent	C	D	E	F	G	H	Total
unsuccessful	0 0.00	3 7.32	4 7.69	4 20.00	9 56.25	5 62.50	25
successful	1 100.00	38 92.68	48 92.31	16 80.00	7 43.75	3 37.50	113
Total	1	41	52	20	16	8	138

Table 14. Outcome by SPM Demirjian stage, maxillary quadrants.

Table of outcome by Demirjian category				
Outcome	Demirjian category			
Frequency Column Percent	Early (A-D)	Ideal (E)	Late (F-H)	Total
unsuccessful	3 7.14	4 7.69	18 40.91	25
successful	39 92.86	48 92.31	26 59.09	113
Total	42	52	44	138

Table 15. Outcome by SPM Demirjian category, maxillary quadrants.

Table of outcome by age at extraction (T2)				
Outcome	Age at extraction by category			
Frequency Column Percent	8-10 y	< 8 y	> 10 y	Total
unsuccessful	5 8.77	1 11.11	19 26.39	25
successful	52 91.23	8 88.89	53 73.61	113
Total	57	9	72	138

Table 16. Outcome by chronological age category at T2, maxillary quadrants.

Table of Outcome by TPM			
Outcome	TPM		
Frequency Column Percent	absent	present	Total
unsuccessful	5 10.00	20 22.73	25
successful	45 90.00	68 77.27	113
Total	50	88	138

Table 17. Outcome by presence/absence of TPM, maxillary quadrants.

Table of radiograph evaluated at T3 by arch			
T3 radiograph	arch		
Frequency Column Percent	mandibular	maxillary	Total
panoramic	59 35.12	51 36.96	110
intraoral bitewing	108 64.29	85 61.59	193
intraoral periapical	1 0.60	2 1.45	3
Total	168	138	306

Table 18. Type of radiograph evaluated at T3, maxillary and mandibular quadrants.

Table of outcome by Demirjian stage							
Outcome	Demirjian stage						
Frequency Column Percent	C	D	E	F	G	H	Total
unsuccessful	3 100.00	6 22.22	13 30.23	11 29.73	19 73.08	30 93.75	82
successful	0 0.00	21 77.78	30 69.77	26 70.27	7 26.92	2 6.25	86
Total	3	27	43	37	26	32	168

Table 19. Outcome by SPM Demirjian stage, mandibular quadrants.

Table of outcome by Demirjian category				
Outcome	Demirjian category			
Frequency Column Percent	Early (A-D)	Ideal (E)	Late (F-H)	Total
unsuccessful	9 30.00	13 30.23	60 63.16	82
successful	21 70.00	30 69.77	35 36.84	86
Total	30	43	95	168

Table 20. Outcome by SPM Demirjian category, mandibular quadrants.

Table of outcome by age at extraction (T2)				
Outcome	Age at extraction by category			
Frequency Column Percent	8-10 y	< 8 y	> 10 y	Total
unsuccessful	18 30.00	4 33.33	60 62.50	82
successful	42 70.00	8 66.67	36 37.50	86
Total	60	12	96	168

Table 21. Outcome by chronological age at T2, mandibular quadrants.

Table of outcome by TPM			
Outcome	TPM		
Frequency Column Percent	absent	present	Total
unsuccessful	12 40.00	70 50.72	82
successful	18 60.00	68 49.28	86
Total	30	138	168

Table 22. Outcome by presence/absence of TPM, mandibular quadrants.

Table of outcome by SPM angle category				
Outcome	SPM angle category			
Frequency Column Percent	mesial	upright	distal	Total
unsuccessful	22 34.38	49 57.65	11 57.89	82
successful	42 65.63	36 42.35	8 42.11	86
Total	64	85	19	168

Table 23. Outcome by SPM angulation category, mandibular quadrants.

Table of SPM angle category by location				
SPM angle category	location			
Frequency Column Percent	UM	VCU	UI	Total
mesial	4 20.00	17 35.42	43 43.00	64
upright	13 65.00	27 56.25	45 45.00	85
distal	3 15.00	4 8.33	12 12.00	19
Total	20	48	100	168

(P=0.28 from Fisher's exact test)

Table 24. SPM angulation category by location, mandibular quadrants.

Chronological age data (y) at T1 by Demirjian stage category								
Demirjian category	N	Mean	Std Dev	Minimum	Lower Quartile	Median	Upper Quartile	Maximum
Early (A-D)	30	8.4	1.2	6.3	7.5	8.2	8.7	11.6
Ideal (E)	43	9.1	1.7	-0.5	8.6	9.2	9.9	10.8
Late (F-H)	95	11.5	2.1	-1.5	10.3	11.7	12.8	14.9

Table 25. Chronological age data by Demirjian stage category at T1.

Table of outcome by age at extraction (T2)				
Outcome	age at extraction by category			
Frequency Column Percent	8-10 (y)	< 8 (y)	> 10 (y)	Total
unsuccessful	18 30.00	4 33.33	60 62.50	82
successful	42 70.00	8 66.67	36 37.50	86
Total	60	12	96	168

Table 26. Outcome by chronological age category, mandibular quadrants.

APPENDIX 3: REGRESSION ANALYSIS

Parameter	Level	Estimated OR	Lower limit 95% CI	Upper limit 95% CI	P value
Age category	8-10 (y)	3.264	1.143	9.320	0.0271
Age category	< 8 (y)	2.953	0.250	34.865	0.3899
Age category	> 10 (y)	1.000	1.000	1.000	.
Location	UM	0.289	0.078	1.078	0.0646
Location	VCU	0.339	0.112	1.031	0.0567
Location	UI	1.000	1.000	1.000	.

Table 1. Odds ratio for successful outcome by chronological age category at T2, maxillary quadrants.

Parameter	Level	Estimated OR	Lower limit 95% CI	Upper limit 95% CI	P value
Demirjian category	early	7.243	1.902	27.589	0.0037
Demirjian category	ideal	6.811	1.698	27.324	0.0068
Demirjian category	late	1.000	1.000	1.000	.
location	UM	0.431	0.084	2.205	0.3124
location	VCU	0.572	0.189	1.731	0.3227
location	UI	1.000	1.000	1.000	.

Table 2. Odds ratio for successful outcome by Demirjian stage category, maxillary quadrants.

Parameter	Level	Estimated OR	Lower limit 95% CI	Upper limit 95% CI	P value
TPM	present	0.513	0.178	1.480	0.2172
TPM	absent	1.000	1.000	1.000	.
location	UM	0.294	0.072	1.208	0.0896
location	VCU	0.350	0.121	1.012	0.0525
location	UI	1.000	1.000	1.000	.

Table 3. Odds ratio for successful outcome by presence/absence of TPM, maxillary quadrants.

Parameter	Level	Estimated OR	Lower limit 95% CI	Upper limit 95% CI	P value
gender	female	1.027	0.377	2.800	0.9588
gender	male	1.000	1.000	1.000	.
location	UM	0.267	0.066	1.080	0.0640
location	VCU	0.316	0.105	0.958	0.0418
location	UI	1.000	1.000	1.000	.

Table 4. Odds ratio for successful outcome by gender, maxillary quadrants.

Parameter	Level	Estimated OR	Lower limit 95% CI	Upper limit 95% CI	P value
gender	male	1.284	0.438	3.766	0.6492
gender	female	1.000	1.000	1.000	.
age category	8-10 y	1.600	0.502	5.092	0.4266
age category	< 8 y	0.792	0.067	9.336	0.8532
age category	> 10 y	1.000	1.000	1.000	.
Demirjian category	early	6.479	1.597	26.288	0.0089
Demirjian category	ideal	5.880	1.282	26.976	0.0227
Demirjian category	late	1.000	1.000	1.000	.
TPM	present	0.917	0.332	2.529	0.8666
TPM	absent	1.000	1.000	1.000	.
location	UM	0.446	0.087	2.281	0.3321
location	VCU	0.612	0.195	1.922	0.4004
location	UI	1.000	1.000	1.000	.

Table 5. Multilevel regression analysis with all variables, maxillary quadrants.

Parameter	Level	Estimated OR	Lower limit 95% CI	Upper limit 95% CI	P value
Demirjian stage	D	21.184	2.905	154.47	0.0026
Demirjian stage	E	18.315	2.961	113.29	0.0018
Demirjian stage	F	9.037	1.364	59.864	0.0225
Demirjian stage	G	1.496	0.250	8.947	0.6586
Demirjian stage	H	1.000	1.000	1.000	.
location	UM	0.272	0.048	1.558	0.1438
location	VCU	0.581	0.184	1.841	0.3563
location	UI	1.000	1.000	1.000	.

Table 6. Odds Ratio for success by Demirjian stage, maxillary quadrants.

Parameter	Level	Estimated OR	Lower limit 95% CI	Upper limit 95% CI	P value
age category	8-10 y	3.892	1.725	8.779	0.0011
age category	< 8 y	5.664	1.473	21.780	0.0116
age category	> 10 y	1.000	1.000	1.000	.
location	UM	0.396	0.152	1.028	0.0570
location	VCU	0.276	0.115	0.662	0.0040
location	UI	1.000	1.000	1.000	.

Table 7. Odds ratio for success by chronological age category, mandibular quadrants.

Parameter	Level	Estimated OR	Lower limit 95% CI	Upper limit 95% CI	P value
Demirjian category	Early	3.884	1.262	11.956	0.0180
Demirjian category	Ideal	3.318	1.410	7.808	0.0060
Demirjian category	late	1.000	1.000	1.000	.
location	UM	0.451	0.169	1.204	0.1121
location	VCU	0.303	0.133	0.689	0.0044
location	UI	1.000	1.000	1.000	.

Table 8. Odds ratio for success by Demirjian stage category, mandibular quadrants.

Parameter	Level	Estimated OR	Lower limit 95% CI	Upper limit 95% CI	P value
Demirjian_stage	D	51.500	7.267	364.95	<.0001
Demirjian_stage	E	33.396	5.916	188.51	<.0001
Demirjian_stage	F	38.087	6.714	216.06	<.0001
Demirjian_stage	G	6.557	0.953	45.133	0.0561
Demirjian_stage	H	1.000	1.000	1.000	.
location	UM	0.367	0.116	1.160	0.0879
location	VCU	0.369	0.139	0.981	0.0456
location	UI	1.000	1.000	1.000	.

Table 9. Odds ratio for success by Demirjian stage, mandibular quadrants.

Parameter	Level	Estimated OR	Lower limit 95% CI	Upper limit 95% CI	P value
TPM	Present	0.798	0.313	2.038	0.6376
TPM	Absent	1.000	1.000	1.000	.
location	UM	0.404	0.154	1.059	0.0653
location	VCU	0.281	0.121	0.651	0.0031
location	UI	1.000	1.000	1.000	.

Table 10. Odds ratio for success by presence of TPM, mandibular quadrants.

Parameter	Level	Estimated OR	Lower limit 95% CI	Upper limit 95% CI	P value
SPM sector	4	0.936	0.081	10.765	0.9575
SPM sector	5	1.668	0.226	12.314	0.6159
SPM sector	6	3.083	0.521	18.243	0.2144
SPM sector	7	2.507	0.656	9.583	0.1792
SPM sector	8	0.567	0.146	2.207	0.4132
SPM sector	9	2.329	0.681	7.961	0.1778
SPM sector	10	1.000	1.000	1.000	.
location	UM	0.516	0.186	1.426	0.2018
location	VCU	0.289	0.119	0.703	0.0062
location	UI	1.000	1.000	1.000	.

Table 11. Odds ratio for success by mandibular SPM angulation, individual sectors.

Parameter	Level	Estimated OR	Lower limit 95% CI	Upper limit 95% CI	P value
SPM angle category	mesial	2.819	0.811	9.807	0.1031
SPM angle category	upright	1.045	0.319	3.419	0.9426
SPM angle category	distal	1.000	1.000	1.000	.
location	UM	0.468	0.171	1.285	0.1406
location	VCU	0.279	0.122	0.638	0.0025
location	UI	1.000	1.000	1.000	.

Table 12. Odds ratio for success by mandibular SPM angulation category.

Parameter	Level	Estimated OR	Lower limit 95% CI	Upper limit 95% CI	P value
gender	female	0.742	0.373	1.474	0.3938
gender	male	1.000	1.000	1.000	.
location	UM	0.405	0.152	1.077	0.0700
location	VCU	0.272	0.117	0.632	0.0025
location	UI	1.000	1.000	1.000	.

Table 13. Odds ratio for success by gender, mandibular quadrants.

Parameter	Level	Estimated OR	Lower limit 95% CI	Upper limit 95% CI	P value
gender	male	1.736	0.749	4.024	0.1988
gender	female	1.000	1.000	1.000	.
age category	8-10 y	3.657	1.323	10.110	0.0125
age category	< 8 y	6.018	1.317	27.490	0.0206
age category	> 10 y	1.000	1.000	1.000	.
Demirjian category	early	1.541	0.336	7.061	0.5775
Demirjian category	ideal	1.630	0.608	4.369	0.3318
Demirjian category	late	1.000	1.000	1.000	.
TPM	present	1.587	0.477	5.276	0.4516
TPM	absent	1.000	1.000	1.000	.
SPM angle category	mesial	1.675	0.443	6.339	0.4473
SPM angle category	upright	0.670	0.184	2.433	0.5425
SPM angle category	distal	1.000	1.000	1.000	.
location	UM	0.495	0.180	1.359	0.1721
location	VCU	0.264	0.099	0.701	0.0075
location	UI	1.000	1.000	1.000	.

Table 14. Multilevel regression analysis with all variables, mandibular quadrants.

Parameter	Level	Estimated OR	Lower limit 95% CI	Upper limit 95% CI	P value
age category	8-10 y	3.892	1.725	8.779	0.0011
age category	< 8 y	5.664	1.473	21.780	0.0116
age category	> 10 y	1.000	1.000	1.000	.
location	UM	0.396	0.152	1.028	0.0570
location	VCU	0.276	0.115	0.662	0.0040
location	UI	1.000	1.000	1.000	.

Table 15. Multilevel regression analysis with nonsignificant variables removed, mandibular quadrants.

TPM	SPM angle category	N	Predicted probability of success	Lower 95% CI	Upper 95% CI
absent	mesial	14	0.731	0.645	0.818
	upright	14	0.507	0.411	0.603
	distal	1	0.433	.	.
present	mesial	44	0.720	0.669	0.771
	upright	47	0.552	0.494	0.609
	distal	16	0.450	0.348	0.553

Table 16. Predicted probability of space closure in mandibular arch based on toolkit parameters, stage H SPMs eliminated.

	Kappa statistics	95% CI	Agreement
Angulation of SPM by sector (1-18)	0.72	0.52 – 0.92	Substantial agreement
Angle category (mesial, upright, distal)	0.90	0.71 - 1	Almost perfect agreement
Demirjian stage (C,D, E, F, G, H)	0.86	0.75 – 0.96	Almost perfect agreement
TPM (present, absent)	0.79	0.57 - 1	Substantial agreement
Outcome (successful, unsuccessful)	0.91	0.73 - 1	Almost perfect agreement

Table 17. Intra-rater reliability, 40 quadrants reassessed.

	Kappa statistics	95% CI	Agreement
Angulation of SPM by sector (1-18)	0.42	0.34 – 0.51	Moderate agreement
Angle category (mesial, upright, distal)	0.59	0.48-0.70	Moderate agreement
Demirjian stage (C, D, E, F, G, H)	0.81	0.77 – 0.85	Almost perfect agreement
TPM (present, absent)	0.85	0.78 – 0.91	Almost perfect agreement
Outcome (successful, unsuccessful)	0.78	0.71 – 0.85	Substantial agreement

Table 18. Inter-rater reliability, all quadrants reassessed.

Value of Kappa	Strength of agreement
< 0	Poor
0.01 - 0.20	Slight
0.21-0.40	Fair
0.41-0.60	Moderate
0.61-0.80	Substantial
0.81 - 1.00	Almost perfect

Table 19. Interpretation of kappa.

Demirjian category	N	Predicted Probability of outcome=1	Lower 95% CI	Upper 95% CI
early (A-D)	42	0.923	0.914	0.933
ideal (E)	52	0.924	0.918	0.929
late (F-H)	36	0.643	0.612	0.674

Table 20. Predicted probability for success by Demirjian stage category, maxillary quadrants.

APPENDIX 4: FUTURE ANALYSIS

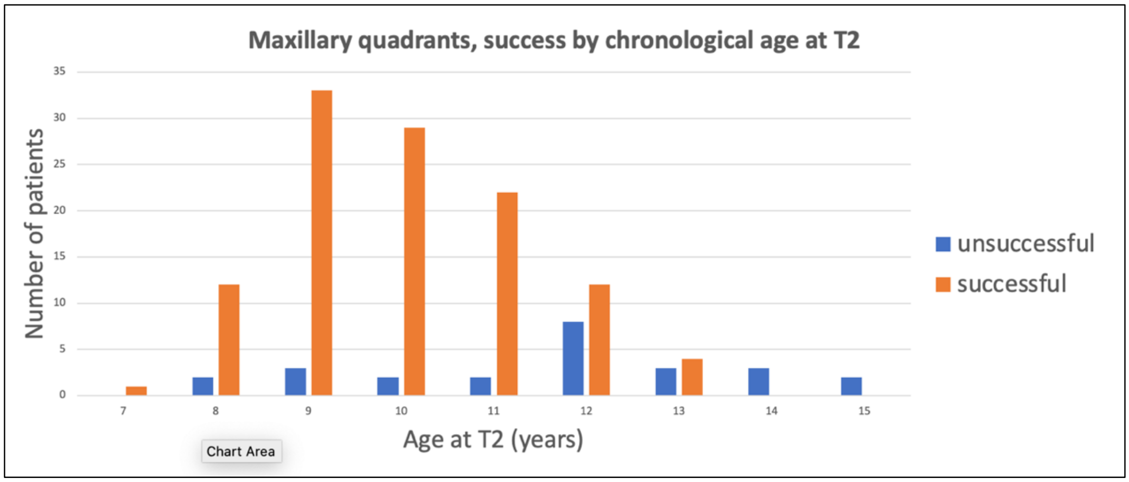

Figure 1. Outcome by chronological age (rounded to nearest whole integer year) at T2, maxillary quadrants.

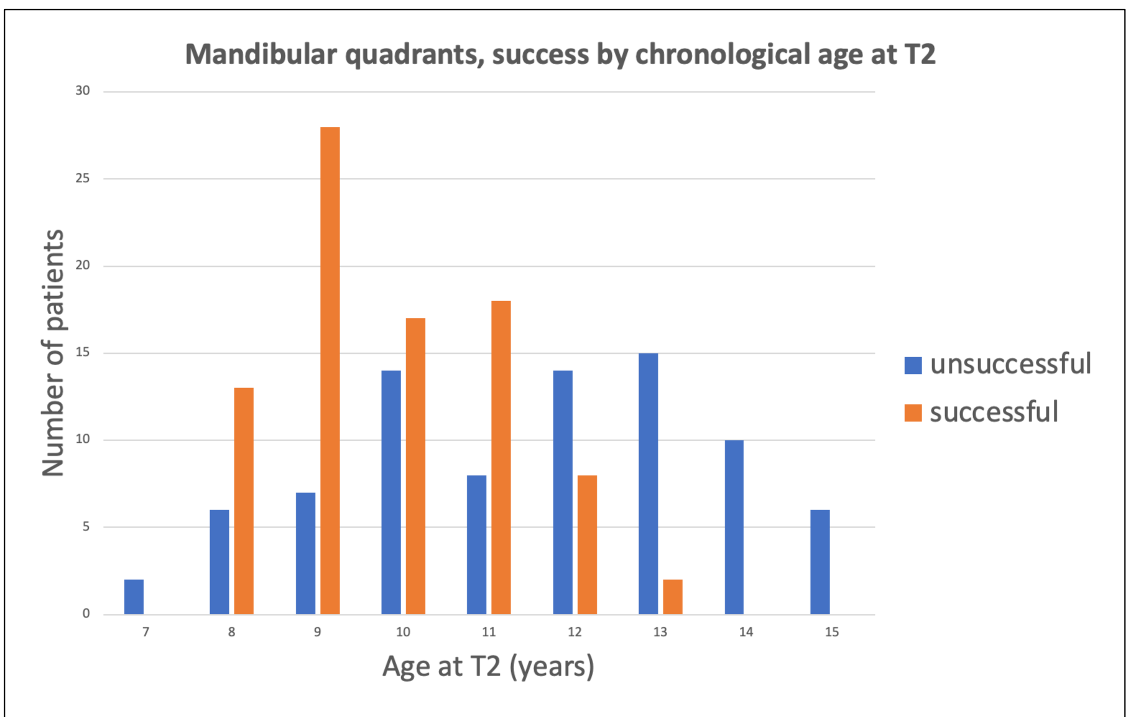

Figure 2. Outcome by chronological age (rounded to nearest whole integer year) at T2, mandibular quadrants.

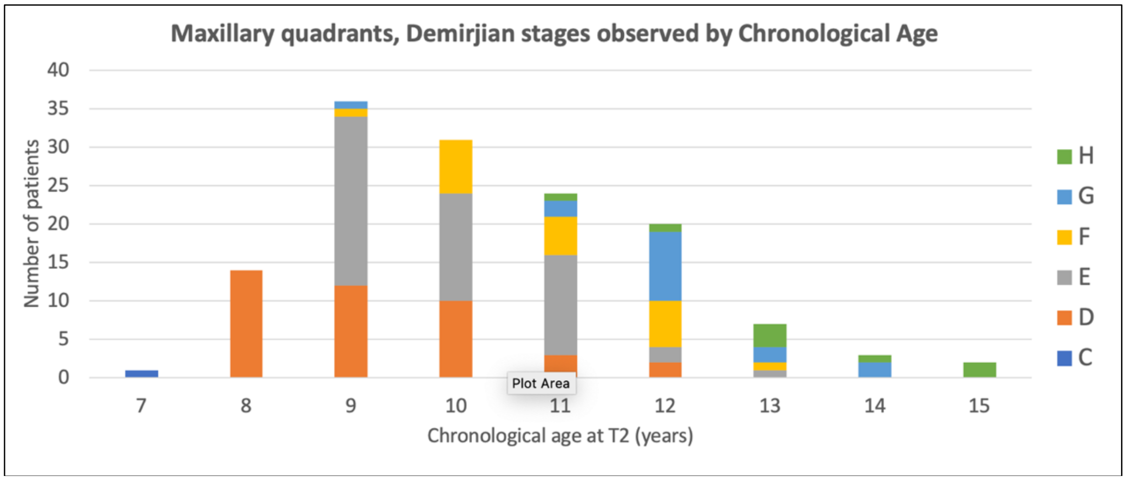

Figure 3. Demirjian stage distribution at each chronological age (rounded to nearest whole integer year), maxillary quadrants.

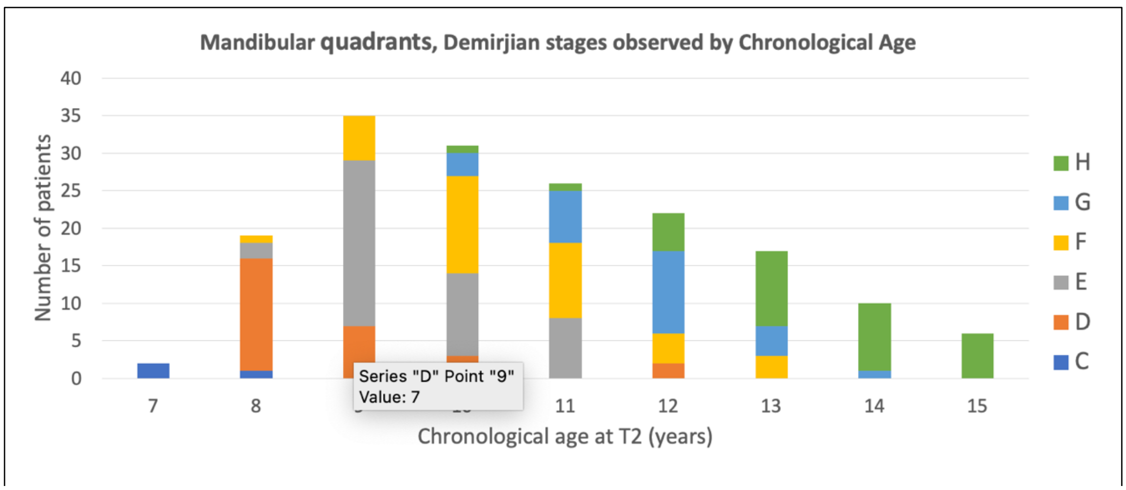

Figure 4. Demirjian stage distribution at each chronological age (rounded to nearest whole integer year), mandibular quadrants.