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Systematic Review

Disc Displacement of the Temporomandibular Joint and Facial Asymmetry in Children and Adolescents: A Systematic Review and Meta-Analysis

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Abstract: Subjects with facial skeletal asymmetries have a higher incidence of anterior temporomandibular joint disc displacement. The objective of the study was to consolidate existing evidence on the connection between temporomandibular joint disc displacement and mandibular asymmetry in youngsters and adolescents. A thorough examination was undertaken in the following databases: PubMed, Scopus, EMBASE, Web of Science, and Cochrane. To judge the publications' methodological quality Newcastle Ottawa Scale was used. From the 1011 identified records, eight were selected for the qualitative synthesis and five for the quantitative synthesis, amounting to 692 subjects. Fifteen cephalometric variables were meta-analyzed. The distance from menton (Me) to midline (lateral mandibular asymmetry) was significantly shorter [−1.75 (95% CI −2.43–−1.07), $p \leq 0.001$] in subjects with disc displacement compared to those without disc displacement. The distance from articulare (Ar) to gonion (Go) was significantly longer [3.74 (95% CI 1.04–6.44), $p = 0.007$] in subjects with disc displacement compared to those without disc displacement. The relationship between distance from articulare (Ar) to gonion (Go) or sella (S) to gonion (Go) and disc displacement was shown to be close to statistical significance level, but not for other cephalometric data. Disc displacement was associated with several cephalometric measurement variations in children and adolescents.

Keywords: jaw asymmetry; temporomandibular disorder; mandible; youths; minors

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1. Introduction

Unilateral condylar bone changes were found to be linked with frontal craniofacial morphology [1]. Subjects with facial skeletal asymmetries have a higher incidence of temporomandibular disorders (TMDs) [2]. The menton shift was found to be significantly related to temporomandibular joint (TMJ) disc position on magnetic resonance imaging, with more deviation to the side with disc displacement [3]. It has been shown that unilateral anterior DD of the TMJ in adolescents can lead to mandibular asymmetry (MA), especially on the same side [4].

MA has been described as a contributing factor to temporomandibular disorders (TMDs) [5,6]. In young patients, mandible deviation and condylar bone changes have been associated with DD, with unilateral condylar bone changes causing mandible deviation on the same side [7]. Asymmetries in condylar movement and mandibular volume have been encountered in patients with MA, highlighting the close relationship between morphology and function [8]. A unilateral asymmetrically positioned mandible may result in asymmetrical condyles, especially on the affected side, due to the functional displacement of the mandible [9]. The development of MA may be connected to DD without reduction and changes in the mandibular condylar bone, with condylar modifications being more frequent on the deviated side [10]. In addition, it has been stated that on the side with the deviated mandible there was a higher probability of experiencing anterior DD [11]. The difference in condylar height between the unaffected and affected sides may increase the risk of MA, with the disc on the affected side shifting anteriorly [12]. It has been reported that jaw movements may be associated with craniofacial morphology, with the non-deviated side having a wider range of jaw movements than the deviated side [13]. It has been shown that TMD, unusual condyle modeling and craniofacial asymmetry are frequent and associated factors, with lengthened or wider condyles being observed on the shorter mandibular ramus side [14].

In subjects with juvenile idiopathic arthritis as a result of unilateral or asymmetrical TMJ involvement, limited mandibular movements have been encountered, mandibular deviation being associated with the affected side, which displayed the most severe facial asymmetry [15]. In patients with juvenile idiopathic arthritis, the asymmetry of the face, particularly around the chin, seemed to have been connected to asymmetrical TMJ destruction, however, the association between facial asymmetry and impacted TMJ is modest and underpowered [16].

As far as we are aware, there are currently no extensive studies to check the hypothesis that facial asymmetry or lateral mandible shift occurrence is similar in children and adolescents with and without TMJ disc displacements. Consequently, the study aimed at conducting a comprehensive review with a meta-analysis of existing studies on the relationship between TMJ DD and mandibular asymmetry in youths.

2. Materials and Methods

2.1. Procedure and Enrollment

The systematic review was undertaken in accordance with the guidelines of the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA) Statement" [17].

The Open Science Framework platform was used to register the study protocol prospectively on 25 July 2022 which can be found at the following location: https://osf.io/ax683 (accessed on 25 July 2022).

2.2. Standards for Selection

Original publications that explored the study goals, with a focus on the presence of facial asymmetry or lateral mandible shift in children or adolescents with TMJ DD, were the inclusion criteria. Subjects who had orthodontic or orthognathic therapy were excluded, as were systematic reviews, meta-analyses, scoping reviews, opinion pieces, comments, communications, cases, conference proceedings, editorials, and papers written in languages other than English.

2.3. Resources of Knowledge

In July 2022, an untimed organized electronic search was undertaken in the following databases: PubMed, Scopus, EMBASE, Web of Science, and Cochrane. Terms from MeSH and Emtree were utilized when suitable. On 20 July 2022, the final automated search of all databases was completed. Additionally, appropriate study reference lists were individually examined. On the Rayyan internet website, all citations were retrieved and sorted [18].

2.4. Methodology for Selection

There were no search filters or restrictions, nor was there a time limit on searches. The PECO framework served as the basis for the study design: Patient (P)-children or adolescents; Exposure (E)-with TMJ DD; Comparison (C)-without TMJ DD; Outcome (O)-facial anthropometric measurements or occurrence of facial asymmetry. A single search strategy was performed, that included the following terms: ("temporomandibular joint" OR "TMJ") AND ("disk displacement" OR "disc displacement") AND ("facial asymmetry" OR "lateral mandible shift" OR "lateral mandibular shift" OR "lateral mandible deviation" OR "lateral mandibular deviation") AND "child".

The complete search strategy adapted for the PubMed database is presented in Supplementary Table S1.

2.5. Recruitment Procedure

Rayyan was used to eliminate redundancies from the output lists of results from all databases. The papers were organized, and an objective, blind assessment of the included papers was conducted. The "blind on" mode was used to decrease selection bias. The residual findings were exported to an Excel spreadsheet which was provided as a digital format for screening, retrieval, and quality evaluation. (Microsoft Office 365, MS, Redmond, WA, USA). Zotero software version 6.0.6 was used to handle all citations [19]. Two researchers (O.A., D.C.L.) separately examined the eligible studies and corroborated if the item should be included. The chosen publications were acquired in full text and individually appraised, with disagreements addressed through negotiation. The rationale for each excluded item was documented.

2.6. Technique for Data Gathering

In the uniform Microsoft Excel sheet file, two researchers retrieved data from the publications, following parameters were recorded: author names and publishing year, name of publication, summary, keywords, study objective, study population, DD classification, asymmetry, radiographic evaluation, findings (facial anthropometric measurements—Figures 1 and 2), conclusions.

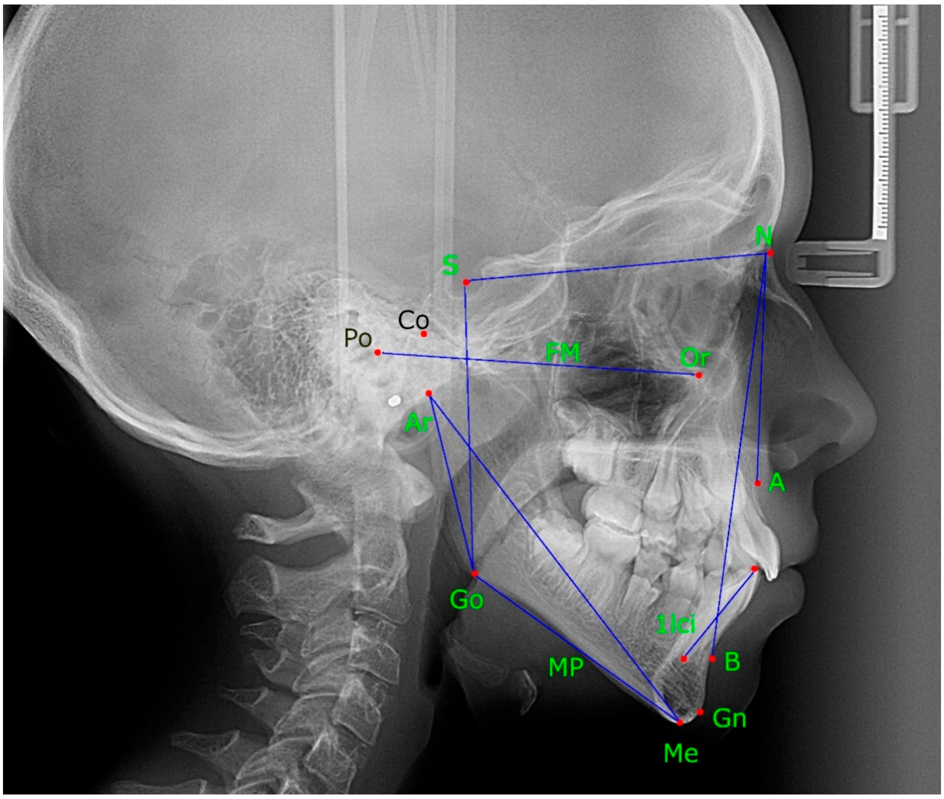

Figure 1. Lateral cephalogram–anthropometric landmarks and lines. S, sella; N, nasion; SNA, the angle between sella, nasion and point A; SNB, the angle between sella, nasion and point B; ANB, the angle between point A, and point B; Go, gonion; Co, condylion; Ar, articulare; Gn, gnathion; Po, porion; Me, menton; 1lci, 1 lower central incisor; NB, nasion point B line; FM, Frankfurt plane; MP, mandibular plane.

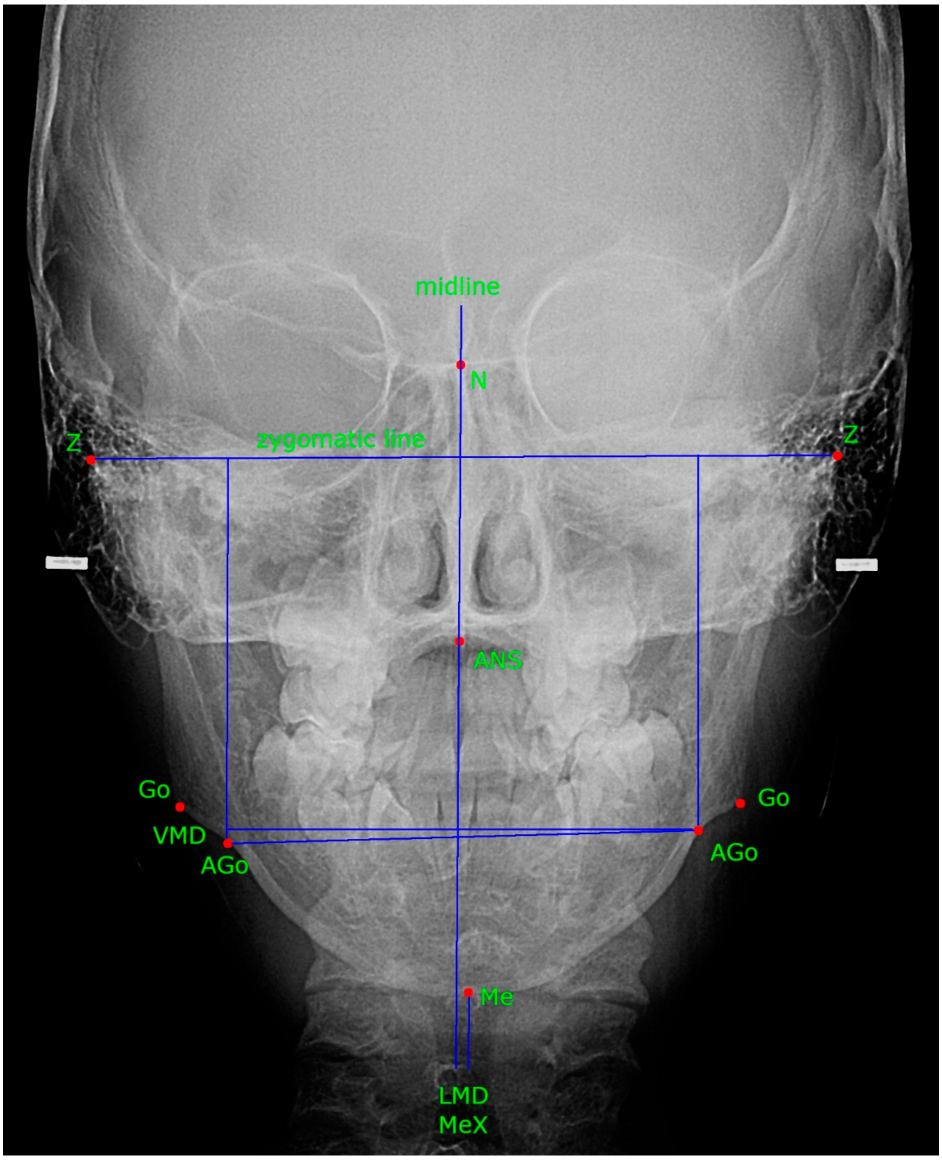

Figure 2. Posteroanterior cephalogram–anthropometric landmarks and lines. Go, gonion; AGo, antegonion; N, nasion; Z, zygomatic point; ANS, anterior nasal spine; Me, menton, VMD, vertical mandibular displacement; LMD, lateral mandibular displacement; MeX, menton to the midline.

2.7. Critical Evaluation of Each Study

The quality of evidence of the qualifying papers included in our research was assessed using the Newcastle Ottawa Scale: checklist for observational case-control publications [20]. We considered the presence of DD as defining the case group and the absence of otherwise or similar groupings regarding DD presence in unilateral or bilateral situations. The cephalometric variables were considered as the exposure.

2.8. Synthesis Methods

Since the results of different articles in the meta-analysis offered either the statistics of two compared groups or the difference between the two groups, we chose to compute the effect size as the difference between the DD and normal disc (ND) position groups, along with the standard error (SE). Where the standard deviation (SD) remained unavailable, it was determined by employing confidence intervals (CIs) or *p*-values, according to the Cochrane Handbook criteria [21]. On the computed mean differences and SE, meta-analyses were conducted using the meta program [22]. Because of variability among investigations, the random effects model was employed to calculate the conventional difference between the means and ninety-five percent confidence interval (CI) for each variable. To examine statistical variance between trials, the chi-square Q-test and I2 were implemented. An analysis with one variable removed was performed to see how reliable the results were. The assumption of statistical significance was made if the *p*-value was less than 0.05. The R environment for statistical computation and visualization (R Foundation for Statistical Computing, Vienna, Austria) version 4.1.2 was used to perform the calculations [23].

2.9. Identification of Bias

The risk of bias could not be established due to the small number of papers. Therefore, we chose the Egger test to investigate articles' bias.

3. Results

3.1. Selection of Sources of Evidence

A total of 1011 were enrolled after applying the search strategy (229 via PubMed; 373 of Scopus; 153 of EMBASE; 104 of Web of Science and 152 via Cochrane). Following the removal of similar documents, a number of 749 papers were screened. The included studies were chosen during the initial phase based on their title, abstract, and relation to the research question. The remaining 29 articles' full texts were obtained and reviewed for eligibility. After reading all the publications that were considered for eligibility, eight have been included in the review, of which five were employed in the meta-analysis. A PRISMA flowchart serves to illustrate the recruiting and screening process (Figure 3).

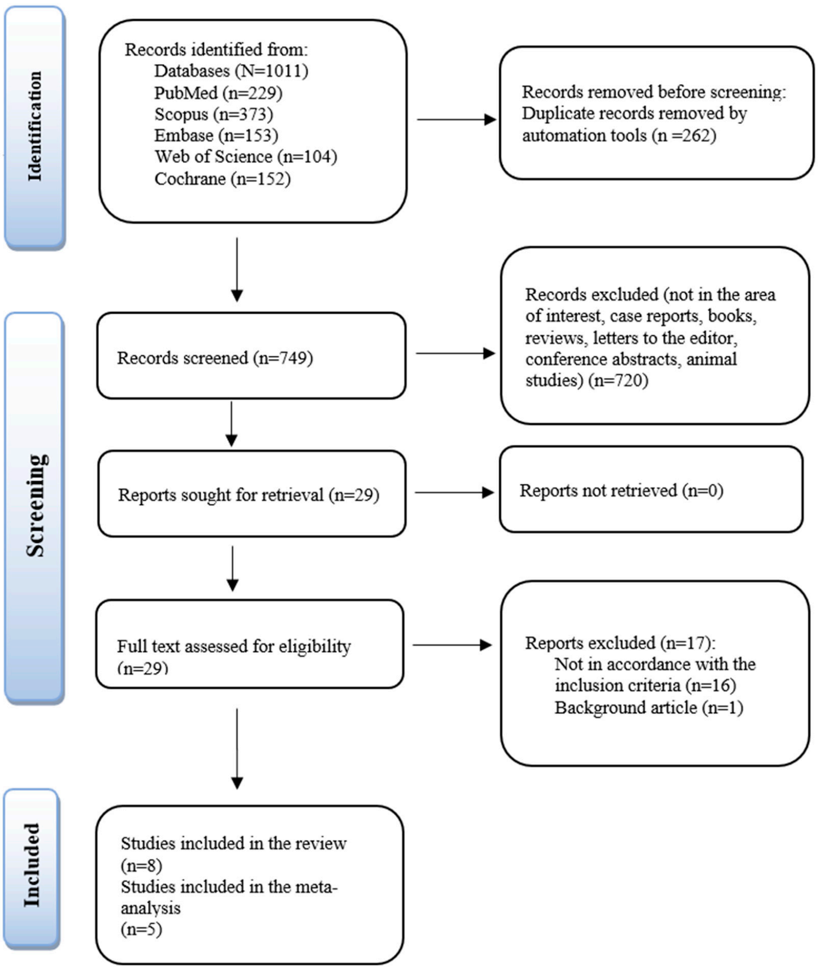

Figure 3. PRISMA illustration of the chosen studies.

3.2. Features of Research

Table 1 summarizes the features of the selected investigations, as well as the (1) authorship and date, (2) study aim, (3) study population, (4) disc displacement classification, (5) asymmetry, (6) radiographic evaluation, (7) author's findings, and (8) author's conclusion. In the eight studies included in the qualitative synthesis, there were 692 subjects involved. In the five studies from the quantitative synthesis, a total number of 515 subjects were included. Seven studies used the MRI method for disc position classification, whereas just one study used temporomandibular disorders investigation criteria for a diagnosis (RDC/TMD) [24]. Radiographic evaluation used lateral cephalogram in four studies [24–27], and posteroanterior cephalogram in five studies [3,4,26,28,29], Trpkova et al. [26] used both methods. Bilateral DD was reported in four studies [3,25,26,28], unilateral DD was reported in [3,4,26,28,29], while two studies did not report the presence of either unilateral or bilateral DD [24,27].

3.3. Results of Syntheses

3.3.1. Distance from Menton to Midline (Mandibular Lateral Asymmetry, or Displacement)

The distance from menton to midline (in mm) on the posteroanterior cephalogram was significantly lower [−1.75 (95% CI −2.43–−1.07), $p \leq 0.001$] in subjects with disc displacement compared to those without disc displacement in the random-effects meta-analysis model (Figure 4). The heterogeneity was low (I2 = 0%) and not statistically significant. Both studies had statistically significant results, pointing in the same direction. The results are robust to leave-one-out sensitivity analyses.

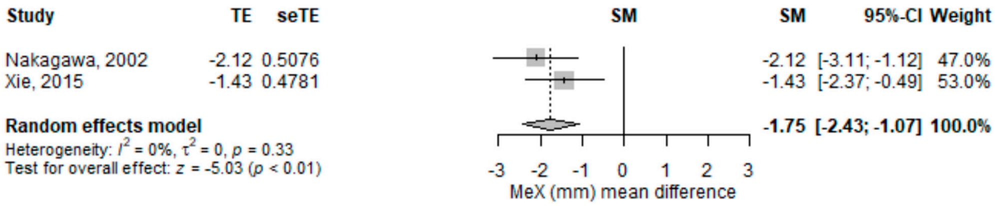

Figure 4. Forest plot for (mm) standardized mean change difference. MeX−distance from menton to midline; TE−effect; seTE—effect's standard error; SM−the average discrepancy; CI-interval of confidence.

3.3.2. Distance from Articulare to Gonion (Mandible Ramus Height)

The distance from articulare to gonion, (in mm) on the lateral cephalogram was higher [1.98 (95% CI −0.11–4.08), $p = 0.063$] in subjects with disc displacement compared to those without disc displacement in the random-effects meta-analysis model (Figure 5), but it did not reach the significance threshold. The heterogeneity was moderate (I2 = 42.3%), albeit not statistically significant. Only one study out of the three included had a statistically significant result pointing in the same direction. Omitting Bastos study [24] in the leave-one-out sensitivity analyses modified the pooled result to be significant, but the exclusion of any of the other studies did not have the same effect (Supplementary Figure S8).

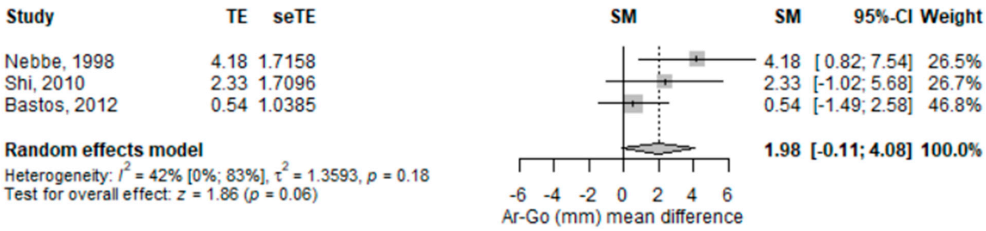

Figure 5. Forest plot for distance from articulare to gonion (mm) standardized mean change difference. Ar-Go—distance from articulare to gonion; TE—effect; seTE—effect's standard error the effect; SM—the average discrepancy; CI—confidence interval.

Table 1. Study characteristics.

Author, Year	Aim	Study Population	DD Classification	Asymmetry	Radiographic Evaluation	Findings	Conclusions
Nebbe, 1998 [25]	to test the hypothesis of no difference in facial cephalometric measurements in adolescents with DD	study group: bilateral DD 17 teenage girls, 13.65 years on average Control group: ND position 17 teenage girls, 13.53 years on average	MRI	study group: lower overall posterior height (S-Go) reduced mandibular ramus length (Co-Go, Ar-Go) shortened posterior facial height (S-Ar) increase in the distance from S-N to the palatal plane increase in the distance from S-N to a line tangent to the inferior border of the mandible's body posterior displacement of Gn related to anterior structures of the face posterior rotation of the mandible Control group: higher mandibular lateral displacement inclined frontal occlusal plane	lateral cephalogram	mean differences (95% CI): Ar-Go (mm) 4.18 (0.69–7.68); Ar-Me 4.33 (mm) (−0.01–8.68); Ar-Go-Me (degrees) 0.46 (−4.18–3.27); FH/MP 3.80 (degrees) (−8.02–0.42); S-Go (mm) 5.57 (1.96–9.18); N-Me (mm) 1.07 (−5.54–3.40)	bilateral DD: posterior vertical facial height diminished; Juvenile disc position aberrations are not within the range of typical physiologic diversity.
Trpkova, 2000 [26]	if TMJ ID (DD) is associated with craniofacial asymmetry	80 females (average age, 13.20 ± 1.7) bilateral normal TMJ: 42 unilateral right TMJ ID: 13 unilateral left TMJ ID: 10 bilateral TMJ ID: 15	MRI TMJ ID: disc displacement and disc length	the longitudinal imbalance in the area of AGo differed substantially	posteroanterior cephalograms lateral cephalograms	increased asymmetry of the AGo with a shorter mandible ramus in bilateral TMJ ID	women with symmetrical TMJ ID experienced higher vertical mandible asymmetry

Table 1. *Cont.*

Author, Year	Aim	Study Population	DD Classification	Asymmetry	Radiographic Evaluation	Findings	Conclusions
Nakagawa, 2002 [28]	to determine the relationship between LMD, VMD, DD, and mandible growth	54 female adolescents (average age: 15.7 ± 3.0) Group 1: bilateral ND position: 23 subjects (average age: 14.9 ± 3.4); Group 2: unilateral /bilateral DD (=partial DD): 12 subjects (average age: 15.9 ± 2.9) Group 3: unilateral /bilateral disc dislocation (=complete DD): 19 subjects (mean age: 16.4 ± 2.4 years)	MRI	right and left mandibular height (VMD) LMD	posteroanterior cephalograms	mandible deviation is linked to DD and disc dislocation Group 1: VMD (AGo-zygomatic line): mean 0.89 ± 0.74 mm LMD (MeX) mean 1.33 ± 1.23 mm Group 2: VMD mean 3.2 ± 1.51 mm LMD mean 3.01 ± 2.51 mm Group 3: VMD mean 3.13 ± 2.3 mm LMD mean 3.72 ± 2.42 mm	DD disturbs normal mandible growth VMD was not related to age LMD was related to age DD was related to LMD and VMD
Shi, 2010 [27]	to evaluate the relationship between partial DD and mandibular dysplasia	46 female adolescents aged 10.1–12.8 years. DD group (n = 26), ND group (n = 20)	MRI	the displaced group exhibited a reduced length of the mandible (Go-Po), sharper mandible plane (MP/FH), and steep mandible inclination (Ar-Go-Me)	lateral cephalograms	DD vs. ND: SNA(°) 79.31 ± 3.40 vs. 80.15 ± 4.79, p = 0.489; SNB(°) 74.31 3.06 vs. 75.25 5.09, p = 0.440; ANB(°) 6 ± 1.45 vs. 6 ± 1.02, p = 1; Ar-Go(mm) 45.42 ± 4.59 vs. 47.75 ± 6.50, p = 0.162; Ar-Me(mm) 95.73 ± 4.68 vs. 99.05 ± 6.95, p = 0.060; Go-Po(mm) 69.00 ± 3.96 vs. 72.00 ± 3.54, p = 0.011 *; Ar-Go-Me (°) 118.77 ± 5.03 vs. 115.75 ± 2.78, p = 0.020 *; MP/FH (°) 31.23 ± 3.85 vs. 26.80 ± 5.54, p = 0.003; S-Go(mm) 74.50 ± 3.26 vs. 76.50 ± 5.57, p = 0.134; N-Me(mm) 116.12 ± 4.22 vs. 116.30 ± 4.96, p = 0.892	partial DD may be related to horizontal jaw impairments but not longitudinal abnormalities

Table 1. *Cont.*

Author, Year	Aim	Study Population	DD Classification	Asymmetry	Radiographic Evaluation	Findings	Conclusions
Bastos, 2012 [24]	to evaluate differences between the cephalometric variables for facial growth patterns in children and adolescents with articular TMD and control group	Experimental group 30 patients with articular TMD. Control group: 30 volunteers without TMD, matched	RDC/TMD	the analysis of the post-peak of pubertal growth spurt showed that the experimental group had mean values for SNA and SNB angles decreased, and the facial axis angle (SN.Gn) and lower incisor inclination (1-NB) increased with the mean values found in the control group, revealing statistically significant differences	lateral cephalograms	DD vs. ND:Pre-peak: S.N.A (°) 82.05 ± 3.03 vs. 81.39 ± 4.34, $p = 0.611$; S.N.B (°) 4.30 ± 1.91 vs. 3.98 ± 4.63, $p = 0.799$; A.N.B (°) 4.3 ± 1.91 vs. 3.98 ± 4.63, $p = 0.799$; Ar-Go (mm) 39.22 ± 3.86 vs. 39.46 ± 3.50, $p = 0.853$; Ar.Go.Me (°) 129.66 ± 6.75 vs. 126.15 ± 5.37, $p = 0.104$; S-Go (mm) 68.25 ± 6.10 vs. 67.23 ± 5.68, $p = 0.619$; N-Me (mm) 110.40 ± 7.96 vs. 110.24 ± 7.69, $p = 0.952$; post-peak: S.N.A (°) 78.25 ± 3.55 vs. 82.90 ± 4.53, $p = 0.008$; S.N.B (°) 74.69 ± 3.63 vs. 79.26 ± 4.75, $p = 0.011$; A.N.B (°) 3.55 ± 2.98 vs. 3.71 ± 2.89, $p = 0.891$; Ar-Go (mm) 42.18 ± 3.53 vs. 43.12 ± 3.99, $p = 0.532$; Ar.Go.Me (°) 125.76 ± 5.59 vs. 128.02 ± 4.42, $p = 0.265$; S-Go (mm) 73.42 ± 6.42 vs. 72.99 ± 4.36, $p = 0.842$; N-Me (mm) 121.26 ± 9.21 vs. 115.37 ± 7.58, $p = 0.088$	changes in morphometric parameters were detected in youngsters with joint TMD
Xie, 2015 [29]	to determine the amount of MA in asymmetric ADD individuals	study group: average age 16.74 years vs. average age 16.21 years in the control group (165 patients with ADD (101 left, 64 right), 156 controls without ADD	MRI	of 119 MA patients in ADD group, 73 with left ADD, 46 with right ADD,	posteroanterior cephalograms	in the ADD group, category 27.88% had no MA, mean MeX: 5.62 mm in the control group, 25.64% had MA, mean MeX: 4.19 mm	MA is more unilateral ADD teenagers The greater the DD, the shorter the condyle and higher the jaw irregularity

Table 1. *Cont.*

Author, Year	Aim	Study Population	DD Classification	Asymmetry	Radiographic Evaluation	Findings	Conclusions
Xie, 2016 [4]	to observe the influence of ADD and to analyze its effect on the symmetry of the mandible	average age 16.31 28 females, 16 males The average follow-up period was 12.22 months	MRI	first evaluation 86.36% MA follow-up: 93.18% MA	posteroanterior cephalograms	the correlation coefficient between condyle height disparity and MeX (CC = 0.681, $p < 0.05$) the increase of menton deviation was significantly related to the age of patients at the initial visit (correlation coefficient = −0.760, $p < 0.05$). the average MeX was 5.58 mm at the initial visit, while it was 7.74 mm after follow-up	in adolescents, MA was secondary or fostered by UJADD
Guercio-Monaco, 2020 [3]	to analyze the association between TMJ disc position evaluated by MRI and the mandible deviation evaluated by PA in adolescents	53 adolescents (37 females and 16 males, mean age 14.28 ± 2.46 years; 11–18) and 106 TMJs group I Same disc position bilateral (n = 23); group II DD is more severe ipsilateral (n = 17); group III DD more severe contralateral (n = 13)	MRI	significant differences between the mean of group II (4.4 ± 2.2) with groups I and III (p = 0.016 and p = 0.036 respectively), with a greater menton deviation concerning the rest of the groups a statistical association between DD and gender was observed (p = 0.002), with more frequent DD in females	posteroanterior cephalograms	MeX menton deviation: Same disc position bilateral 2.17 ± 1.93; DD more severe ipsilateral 4.40 ± 2.26; DD more severe contralateral 2.10 ± 1.70	the menton deviation was related to unilateral or bilateral cases TMJ DD the menton tended to exhibit more deflection to the side more affected

DD, disc displacement; ND, normal position of the articular disc; ADD, disc displacement towards the anterior; UJADD, unilateral juvenile anterior disc displacement; S, Sella; SNA, the angle between sella, nasion and point A; SNB, the angle between sella, nasion and point B; ANB, the angle between point A, nasion and point B; Go, gonion; Co, condylion; Ar, articulare; N, nasion; Gn, gnathion; AGo, antegonion; Po, porion; Me, menton; 1, lower central incisor; NB, nasion point B line; FM, Frankfurt plane; MP, mandibular plane; MA, mandibular asymmetry; TMJ, temporomandibular joint; TMD, temporomandibular joint disorder; RDC, research diagnostic criteria; ID, internal derangement; MRI, magnetic resonance images; LMD, lateral mandibular displacement; VMD, vertical mandibular displacement; MA, mandibular asymmetry; MeX, menton to midline. *, statistically significant.

3.3.3. Distance from Articulare to Menton (Total Mandibular Length)

The distance from articulare to menton (in mm) on the lateral cephalogram was significantly higher [3.74 (95% CI 1.04–6.44), p = 0.007] in subjects with disc displacement compared to those without disc displacement in the random-effects meta-analysis model (Figure 6). The heterogeneity was low (I2 = 0%), and not statistically significant. Only one study out of the two included had a statistically significant result, and both pointed in the same direction. The other study, Shi was close to statistical significance [27].

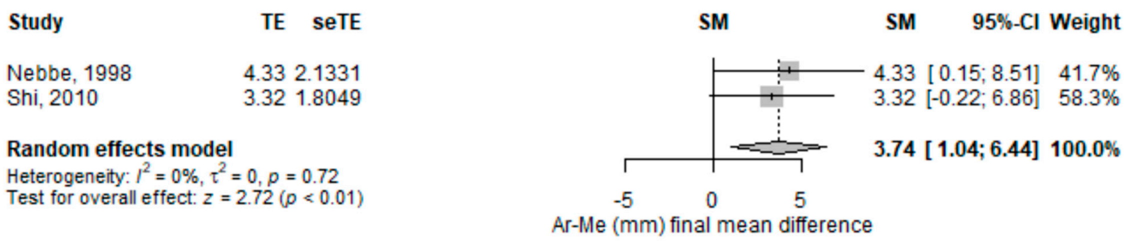

Figure 6. Forest plot for distance from articulare to menton (mm) standardized mean change difference. Ar-Me—distance from articulare to menton; TE—effect; seTE—effect's standard error of the effect; SM—the average discrepancy; CI—confidence interval.

3.3.4. Distance from Sella to Gonion (Overall Posterior Jawline Dimension)

The length between sella to gonion (in mm) on the lateral cephalogram was significantly higher [4.15 (95% CI −0.32–8.63), p = 0.069] in subjects with disc displacement compared to those without disc displacement in the random-effects meta-analysis model (Figure 7). The heterogeneity was substantial (I2 = 76%), and statistically significant. Only one study out of the two included had a statistically significant result, and both pointed in the same direction.

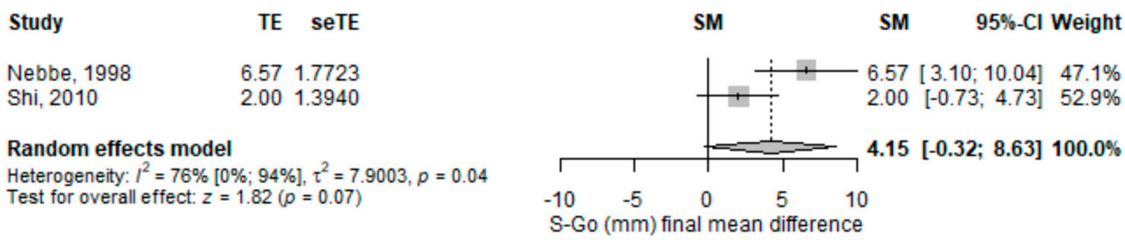

Figure 7. Forest plot for distance from sella to gonion (mm) standardized mean change difference. S-Go—distance from sella to gonion; TE TE—effect; seTE—effect's standard error; SM—the average discrepancy; CI—confidence interval.

3.3.5. Other Cephalogram Measurements

The other cephalogram measurements were not statistically significant (Table 2, Supplementary Figures S1–S7).

3.4. Investigation's Potential Bias

The Newcastle Ottawa Scale (NOS) was engaged to evaluate the scientific research (Table 3). The case and control definitions were adequately followed in the majority of the studies since they used MRI to diagnose the disc position, except for one study that used research diagnostic criteria for temporomandibular disorders [24]. The case representativeness was reported in only two studies that either used a consecutive sample [4] or all the subjects in their database [3]. But all the other studies did not specify if all the subjects were selected from the same source. The comparability of the groups was partially assured by five studies since they studied only female subjects [25–29]. Only one study matched the groups by gender, Angle's categorization of misaligned teeth, and the cervical vertebra development score [24]. All the studies can be considered to have an appropriate exposure ascertainment by using cephalometric measurements.

Table 2. Meta-analyses results.

Characteristic, Effect Size Type	Number of Studies	Effect Size (95% CI)	*p*-Value	I2 (95% CI)	*p*-Value	Egger Test	Studies	Leave One Out
MeX (mm) mean difference	2	−1.75 (−2.43–−1.07)	<0.001	NC		NC	Nakagawa, 2002 [28]; Xie, 2015 [29]	-Nakagawa, 2002: −1.43 (−2.37–−0.49), $p = 0.003$, I2 = NA%; -Xie, 2015: −2.12 (−3.11–−1.12), $p \leq 0.001$, I2 = NA%
Ar-Go (mm) mean difference	3	1.98 (−0.11–4.08)	0.063	42.3 (0–82.6)	0.177	0.265	Nebbe, 1998 [25]; Shi, 2010 [27]; Bastos, 2012 [24]	-Nebbe, 1998: 1.02 (−0.71–2.76), $p = 0.248$, I2 = 0%; -Shi, 2010: 2.11 (−1.42–5.63), $p = 0.242$, I2 = 70%; -Bastos, 201: 3.25 (0.88–5.63), $p = 0.007$, I2 = 0%
Go-Po (mm) mean difference	2	1.3 (−2.37–4.97)	0.487	NC		NC	Shi, 2010 [27]; Bastos, 2012 [24]	-Shi, 2010: −0.76 (−3.93–2.41), $p = 0.636$, I2 = NA%; -Bastos, 2: 3 (0.83–5.17), $p = 0.007$, I2 = NA%
Ar-Me (mm) mean difference	2	3.74 (1.04–6.44)	0.007	NC		NC	Nebbe, 1998 [25]; Shi, 2010 [27]	-Nebbe, 1998: 3.32 (−0.22–6.86), $p = 0.066$, I2 = NA%; -Shi, 2010: 4.33 (0.15–8.51), $p = 0.042$, I2 = NA%
S-Go (mm) mean difference	2	4.15 (−0.32–8.63)	0.069	NC		NC	Nebbe, 1998 [25]; Shi, 2010 [27]	-Nebbe, 1998: 2 (−0.73–4.73), $p = 0.151$, I2 = NA%; -Shi, 2010: 6.57 (3.1–10.04), $p \leq 0.001$, I2 = NA%
N-Me (mm) mean difference	3	−0.19 (−2.24–1.86)	0.859	0 (0–89.6)	0.471	0.721	Nebbe, 1998 [25]; Shi, 2010 [27]; Bastos, 2012 [24]	-Nebbe, 1998: −0.61 (−3.09–1.87), $p = 0.631$, I2 = 8%; -Shi, 2010: −0.7 (−4.34–2.93), $p = 0.705$, I2 = 26%; -Bastos, 201: 0.43 (−1.86–2.73), $p = 0.711$, I2 = 0% Supplementary Figure S10
SNA (deg) mean difference	2	1.31 (−0.28–2.9)	0.105	NC		NC	Shi, 2010 [27]; Bastos, 2012 [24]	-Shi, 2010: 1.64 (−0.43–3.71), $p = 0.12$, I2 = NA%; -Bastos, 2: 0.84 (−1.63–3.31), $p = 0.506$, I2 = NA%
SNB (deg) mean difference	2	2.82 (−0.74–6.37)	0.12	NC		NC	Shi, 2010 [27]; Bastos, 2012 [24]	-Shi, 2010: 4.57 (2.43–6.71), $p \leq 0.001$, I2 = NA%; -Bastos, 2: 0.94 (−1.58–3.46), $p = 0.465$, I2 = NA%
ANB (deg) mean difference	2	−0.02 (−0.67–0.64)	0.958	NC		NC	Shi, 2010 [27]; Bastos, 2012 [24]	-Shi, 2010: −0.11 (−1.76–1.53), $p = 0.894$, I2 = NA%; -Bastos, 2: 0 (−0.71–0.71), $p = 1$, I2 = NA%
MP/FH (deg) mean difference	2	−0.45 (−8.51–7.61)	0.913	NC		NC	Nebbe, 1998 [25]; Shi, 2010 [27]	-Nebbe, 1998: −4.43 (−7.27–−1.59), $p = 0.002$, I2 = NA%; -Shi, 2010: 3.8 (−0.26–7.86), $p = 0.067$, I2 = NA%
Ar-Go-Me (deg) mean difference	3	−1.55 (−3.52–0.41)	0.121	30.8 (0–92.8)	0.236	0.06	Nebbe, 1998 [25]; Shi, 2010 [27]; Bastos, 2012 [24]	-Nebbe, 1998: −2.23 (−4.15–−0.31), $p = 0.023$, I2 = 11%; -Shi, 2010: −0.42 (−2.69–1.84), $p = 0.715$, I2 = 0%; -Bastos, 201: −1.57 (−4.93–1.8), $p = 0.362$, I2 = 61% Supplementary Figure S9

S, Sella; SNA, the angle between sella, nasion, and point A; SNB, the angle between sella, nasion, and point B; ANB, the angle between point A, nasion, and point B; Go, gonion; Co, condylion; Ar, articulare; N, nasion; Po, porion; Me, menton; MP, mandibular plane; FM, Frankfurt plane; MA, mandibular asymmetry; MeX, menton to midline; CI, confidence interval; NC—cannot be computed due to a low number of studies.

Table 3. Newcastle Ottawa Scale rating of the identified papers.

Researcher and Release Year	Case Definition Sustainability	Cases' Representativeness	Controls Selecting	Controls Defining	Cases and Controls Comparability	Exposure Assessment
Nebbe, 1998 [25]	*		*	*	*	*
Trpkova, 2000 [26]	*		*	*	*	*
Nakagawa, 2002 [28]	*		*	*	*	*
Shi, 2010 [27]	*		*	*	*	*
Bastos, 2012 [24]			*		**	*
Xie, 2015 [29]	*		*	*	*	*
Xie, 2016 [4]	*	*	*	*	NA	*
Guercio-Monaco, 2020 [3]	*	*	*	*		*

NA—not applicable.

4. Discussion

4.1. Scientific Proof Synopsis

The present study showed a significantly lower distance from menton to midline (mandibular lateral displacement), measured on posteroanterior cephalogram, and a higher distance from articulare to gonion (mandible ramus height) measured on the lateral cephalogram in subjects with disc displacement compared to those with normal disc position; furthermore, for the relation between the distance from articulare to gonion (the height of the mandibular ramus) or from sella to gonion (total posterior facial height) and disc displacement, the results were near the significance level, but not for other cephalometric measurements.

Mandibular asymmetry was evaluated on posteroanterior cephalograms by the distance of the menton to the midline (mandibular lateral displacement, or asymmetry) in [3,4,28,29]. Another way to indicate the mandibular asymmetry was the vertical mandibular displacement, as the distance between antegonion and the zygomatic arch line (mandibular height) [28]. Trpkova et al. [26] used a formula to calculate the asymmetry between the right and left side for different cephalometric measurements: (right − left)/(right + left)/200. Xie et al. [4], had no control group but used a longitudinal self-control design to assess whether unilateral anterior DD would lead to asymmetry of the mandible or of the mandible condyle, the mean follow-up being 12.2 months. The study observed that unilateral juvenile anterior DD leads in time to shorter condylar height on the same side and MA. Bastos [24] divided the study and the control group depending on the cervical spine development Bastos et al., identified a connection between the TMJ state and a hyperdivergent face growth pattern in youths [24]. The onset of the DD was found to be related to the mandibular DD, by Nakagawa [28]. The menton deviation was significantly correlated with the disc position, being more deviated to the more affected side, and related to the unilateral as well the bilateral DD [3]. Young girls with incomplete disc displacement and Class II, Division 1 dentition may show transverse but not longitudinal abnormalities in the jaw [27].

MA has also been reported to be much more widespread and extensive in young patients with unilateral DD, with the degree of asymmetry being linked with condyle height and disc morphology [29]. Patients with DD had a shorter jaw length as well as a backward jaw position, suggesting that DD is linked with abnormal structural architecture [30]. According to research, it has been shown that there is a clear relationship between severe DD and skeletal deformities in orthodontic patients [31]. DD affects facial morphology, the differences becoming more pronounced with the progress of the displacement, highlighting the significance of early DD diagnosis and treatment [32].

To encourage temporomandibular condyle natural growth and prevent facial deformity, DD in young individuals should be corrected as soon as feasible, especially if it is asymmetric [33]. In young patients with unilateral anterior DD, arthroscopic disc repositioning has been shown to improve facial growth [33].

4.2. Strengths and Weaknesses

The papers considered in this study had several drawbacks. The most frequently encountered issue was the representativeness of the cases that were not reported, as well as the diversity of clinical settings that generated the study cohorts. The other problems relating to the quality of the articles were the use of RDC/TMD instead of MRI for the DD diagnosis and the absence of measures to aid comparability–but luckily, only one study for each problem had this issue. Being cross-over studies, the causality between DD and facial asymmetry cannot be augmented. Nevertheless, a strong association was observed for several cephalometric variables. Furthermore, one study observed in a prospective cohort of children the increase of facial asymmetry with time and in relation to DD. For sure, the question of who the cause is will remain debatable.

In addition, our evaluation includes the following strengths: this is the first holistic research and meta-analysis of facial asymmetry in youths; both posteroanterior and lateral cephalogram measurements were assessed; a thorough search approach was employed; considerable representative databases were explored (PubMed, Scopus, EMBASE, Web of Science, and Cochrane); sensitivity analyses were usedand fifteen cephalometric variables were meta-analyzed.

5. Conclusions

In patients with disc displacement compared to those with normal disc position, the present study identified a significantly reduced distance from menton to midline on the posteroanterior cephalogram and a larger distance from articulare to gonion on the lateral cephalogram.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/children9091297/s1,Table S1: Search strategies for PubMed database. Figure S1: Forest plot for (deg) standardized mean change difference. SNA—sella nasion point A angle, TE—effect; seTE—the standard error of the effect; SM—mean difference; CI—confidence interval.; Figure S2: Forest plot for (deg) standardized mean change difference. SNB-sella nasion point B angle, TE—effect; seTE—the standard error of the effect; SM—mean difference; CI—confidence interval.; Figure S3: Forest plot for (deg) standardized mean change difference. ANB-point A—nasion-point B angle, TE—effect; seTE—the standard error of the effect; SM—mean difference; CI—confidence interval.; Figure S4: Forest plot for (deg) standardized mean change difference. MP—mandibular plane, FM-Frankfurt plane, TE—effect; seTE—the standard error of the effect; SM—mean difference; CI—confidence interval.; Figure S5: Forest plot for (deg) standardized mean change difference. Ar-articulare, Go-gonion, Me-menton, TE—effect; seTE—the standard error of the effect; SM—mean difference; CI—confidence interval.; Figure S6: Forest plot for (mm) standardized mean change difference. Go-gonion, Po = porion, TE—effect; seTE—the standard error of the effect; SM—mean difference; CI—confidence interval.; Figure S7: Forest plot for (mm) standardized mean change difference. TE—effect; seTE—the standard error of the effect; SM—mean difference; CI—confidence interval.; Figure S8: Leave-one-out sensitivity analysis for articulare to gonion distance $\hat{\Theta}$ = mean difference; Figure S9: Leave-one-out sensitivity analysis for Ar-Go-Me $\hat{\Theta}$ = mean difference, Ar-articulare, Go-gonion, Me-menton; Figure S10: Leave-one-out sensitivity analysis for N-Me $\hat{\Theta}$ = mean difference, N-nasion, Me-menton.

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References

1. Estomaguio, G.A.; Yamada, K.; Saito, I. Unilateral Condylar Bone Change, Inclination of the Posterior Slope of the Articular Eminence and Craniofacial Morphology. *Orthod. Waves* **2008**, *67*, 113–119. [CrossRef]
2. Khojastepour, L.; Omidi, M.; Vojdani, M.; Bagheri, K. Investigating Possible Correlation between Condylar Asymmetry and Clinical Dysfunction Indices in Patients with Temporomandibular Dysfunction Using Cone-Beam Computed Tomographic. *J. Cranio-Maxillofac. Surg.* **2019**, *47*, 438–442. [CrossRef] [PubMed]
3. Guercio-Monaco, E.; De Stefano, A.; Impellizzeri, A.; Galluccio, G. Association between the Temporomandibular Joint Disc Position on Magnetic Resonance Imaging and the Mandibular Deviation on Posteroanterior Cephalogram: A Cross-Sectional Study in Adolescents. *Clin. Ter.* **2020**, *171*, e509–e516. [CrossRef] [PubMed]
4. Xie, Q.; Yang, C.; He, D.; Cai, X.; Ma, Z.; Shen, Y.; Abdelrehem, A. Will Unilateral Temporomandibular Joint Anterior Disc Displacement in Teenagers Lead to Asymmetry of Condyle and Mandible? A Longitudinal Study. *J. Craniomaxillofac. Surg.* **2016**, *44*, 590–596. [CrossRef] [PubMed]
5. Santana-Mora, U.; López-Cedrún, J.; Suárez-Quintanilla, J.; Varela-Centelles, P.; Mora, M.J.; Da Silva, J.L.; Figueiredo-Costa, F.; Santana-Penín, U. Asymmetry of Dental or Joint Anatomy or Impaired Chewing Function Contribute to Chronic Temporomandibular Joint Disorders. *Ann. Anat. Anat. Anz.* **2021**, *238*, 151793. [CrossRef]
6. Toh, A.Q.J.; Chan, J.L.H.; Leung, Y.Y. Mandibular Asymmetry as a Possible Etiopathologic Factor in Temporomandibular Disorder: A Prospective Cohort of 134 Patients. *Clin. Oral. Investig.* **2021**, *25*, 4445–4450. [CrossRef]
7. Uy-Co, E.T.; Yamada, K.; Hanada, K.; Hayashi, T.; Ito, J. Condylar Bony Change and Mandibular Deviation in Orthodontic Patients—Using Helical CT and MRI. *Clin. Orthod. Res.* **2000**, *3*, 132–143. [CrossRef]
8. Ikeda, M.; Miyamoto, J.J.; Takada, J.; Moriyama, K. Association between 3-Dimensional Mandibular Morphology and Condylar Movement in Subjects with Mandibular Asymmetry. *Am. J. Orthod. Dentofac. Orthop.* **2017**, *151*, 324–334. [CrossRef]
9. Kilic, N.; Kiki, A.; Oktay, H. Condylar Asymmetry in Unilateral Posterior Crossbite Patients. *Am. J. Orthod. Dentofac. Orthop.* **2008**, *133*, 382–387. [CrossRef]
10. Ooi, K.; Inoue, N.; Matsushita, K.; Mikoya, T.; Minowa, K.; Kawashiri, S.; Tei, K. Relations between Anterior Disc Displacement and Maxillomandibular Morphology in Skeletal Anterior Open Bite with Changes to the Mandibular Condyle. *Br. J. Oral Maxillofac. Surg.* **2020**, *58*, 1084–1090. [CrossRef]
11. Zhang, Y.-L.; Song, J.-L.; Xu, X.-C.; Zheng, L.-L.; Wang, Q.-Y.; Fan, Y.-B.; Liu, Z. Morphologic Analysis of the Temporomandibular Joint Between Patients with Facial Asymmetry and Asymptomatic Subjects by 2D and 3D Evaluation: A Preliminary Study. *Medicine* **2016**, *95*, e3052. [CrossRef]
12. Zhuo, Z.; Cai, X.; Xie, Q. Is Anterior Disc Displacement Without Reduction Associated with Temporomandibular Joint Condylar Height in Juvenile Patients Younger Than 20 Years? *J. Oral Maxillofac. Surg.* **2015**, *73*, 843–849. [CrossRef]
13. Oguri, Y.; Yamada, K.; Fukui, T.; Hanada, K.; Kohno, S. Mandibular Movement and Frontal Craniofacial Morphology in Orthognathic Surgery Patients with Mandibular Deviation and Protrusion: Mandibular Movement in Patients with Mandibular Deviation and Protrusion. *J. Oral Rehabil.* **2003**, *30*, 392–400. [CrossRef]
14. Nicot, R.; Chung, K.; Vieira, A.R.; Raoul, G.; Ferri, J.; Sciote, J.J. Condyle Modeling Stability, Craniofacial Asymmetry and ACTN3 Genotypes: Contribution to TMD Prevalence in a Cohort of Dentofacial Deformities. *PLoS ONE* **2020**, *15*, e0236425. [CrossRef]
15. Pawlaczyk-Kamieńska, T.; Kulczyk, T.; Pawlaczyk-Wróblewska, E.; Borysewicz-Lewicka, M.; Niedziela, M. Limited Mandibular Movements as a Consequence of Unilateral or Asymmetrical Temporomandibular Joint Involvement in Juvenile Idiopathic Arthritis Patients. *J. Clin. Med.* **2020**, *9*, E2576. [CrossRef]
16. Bernini, J.M.; Kellenberger, C.J.; Eichenberger, M.; Eliades, T.; Papageorgiou, S.N.; Patcas, R. Quantitative Analysis of Facial Asymmetry Based on Three-Dimensional Photography: A Valuable Indicator for Asymmetrical Temporomandibular Joint Affection in Juvenile Idiopathic Arthritis Patients? *Pediatr. Rheumatol. Online J.* **2020**, *18*, 10. [CrossRef]
17. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews. *BMJ* **2021**, *372*, n71. [CrossRef]
18. Ouzzani, M.; Hammady, H.; Fedorowicz, Z.; Elmagarmid, A. Rayyan—A Web and Mobile App for Systematic Reviews. *Syst. Rev.* **2016**, *5*, 210. [CrossRef]
19. Corporation for Digital Scholarship Zotero 6.0.6. Available online: https://www.zotero.org/ (accessed on 25 July 2022).
20. Wells, G.; Shea, B.; O'Connell, D.; Peterson, J.; Welch, V.; Losos, M.; Tugwell, P. Ottawa Hospital Research Institute. Available online: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed on 29 April 2022).
21. Higgins, J.P.; Green, S. *Cochrane Handbook for Systematic Reviews of Interventions: Cochrane Book Series*; John Wiley & Sons: Chichester, UK, 2008.
22. Schwarzer, G. Meta: General Package for Meta-Analysis 2022. Available online: https://cran.r-project.org/web/packages/meta/meta.pdf (accessed on 25 July 2022).
23. R Core Team. *A Language and Environment for Statistical Computing*; R Foundation for Statistical Computing: Vienna, Austria, 2021.
24. Bastos, L.V.W.; Tesch, R.d.S.; Denardin, O.V.P. Cephalometric Deviations Present in Children and Adolescents with Temporomandibular Joint Disorders. *Dental Press J. Orthod.* **2012**, *17*, 74–84. [CrossRef]
25. Nebbe, B. Adolescent Female Craniofacial Morphology Associated with Advanced Bilateral TMJ Disc Displacement. *Eur. J. Orthod.* **1998**, *20*, 701–712. [CrossRef]

26. Trpkova, B.; Major, P.; Nebbe, B.; Prasad, N. Craniofacial Asymmetry and Temporomandibular Joint Internal Derangement in Female Adolescents: A Posteroanterior Cephalometric Study. *Angle Orthod.* **2000**, *70*, 81–88. [CrossRef]
27. Shi, J.-J.; Zhang, F.; Zhou, Y.-Q.; Gu, Z.-Y. The Relationship between Partial Disc Displacement and Mandibular Dysplasia in Female Adolescents. *Med. Sci. Monit.* **2010**, *16*, CR283-8.
28. Nakagawa, S.; Sakabe, J.; Nakajima, I.; Akasaka, M. Relationship between Functional Disc Position and Mandibular Displacement in Adolescent Females: Posteroanterior Cephalograms and Magnetic Resonance Imaging Retrospective Study. *J. Oral. Rehabil.* **2002**, *29*, 417–422. [CrossRef]
29. Xie, Q.; Yang, C.; He, D.; Cai, X.; Ma, Z. Is Mandibular Asymmetry More Frequent and Severe with Unilateral Disc Displacement? *J. Cranio-Maxillofac. Surg.* **2015**, *43*, 81–86. [CrossRef]
30. Jeon, D.-M.; Jung, W.-S.; Mah, S.-J.; Kim, T.-W.; Ahn, S.-J. The Effects of TMJ Symptoms on Skeletal Morphology in Orthodontic Patients with TMJ Disc Displacement. *Acta Odontol. Scand.* **2014**, *72*, 776–782. [CrossRef]
31. Jung, W.-S.; Kim, H.; Jeon, D.-M.; Mah, S.-J.; Ahn, S.-J. Magnetic Resonance Imaging-Verified Temporomandibular Joint Disk Displacement in Relation to Sagittal and Vertical Jaw Deformities. *Int. J. Oral Maxillofac. Surg.* **2013**, *42*, 1108–1115. [CrossRef]
32. Şakar, O.; Çalişir, F.; Marşan, G.; Öztaş, E. Evaluation of the Effects of Temporomandibular Joint Disc Displacement and Its Progression on Dentocraniofacial Morphology in Symptomatic Patients Using Posteroanterior Cephalometric Analysis. *CRANIO®* **2013**, *31*, 23–31. [CrossRef]
33. Liu, Z.; Xie, Q.; Yang, C.; Chen, M.; Bai, G.; Abdelrehem, A. The Effect of Arthroscopic Disc Repositioning on Facial Growth in Juvenile Patients with Unilateral Anterior Disc Displacement. *J. Craniomaxillofac. Surg.* **2020**, *48*, 765–771. [CrossRef]

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Article

Petrotympanic Fissure Architecture and Malleus Location in Temporomandibular Joint Disorders

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Abstract: The aim of this research was to assess possible relationships between petrotympanic fissure (PTF) characteristics, malleus position, and temporomandibular joint disorders (TMD). A retrospective study was performed, including patients with TMD. Magnetic resonance imaging (MRI) and cone-beam computed tomography (CBCT) examination were used to evaluate temporomandibular joint (TMJ) disc position and condylar bone changes. Fifty-eight TMJs from twenty-nine patients (23:6 females: males) were assessed. Erosive changes (DDR-disc displacement with a reduction of 6 (24%), DDwR-disc displacement without a reduction of 8 (61.5%) vs. normal disc position 3 (15%), $p = 0.012$) and condyle osteophytes production (DDR 6 (24%), DDwR 9 (69.2%) vs. normal condyle 7 (35%), $p = 0.012$) were more frequent in subjects with disc displacement compared to normal disc position; malleus was closer to PTF in cases with erosive changes (median 2.15 interquartile range: (1.85–2.75) vs. 2.75 (2.25–3.15), $p = 0.029$) as well as those with condylar osteophytosis (2.25 (1.91–2.75) vs. 2.75 (2.33–3.32), $p = 0.015$); the PTF length was higher in cases with condylar osteophytosis compared to those without (4.45 (3.50–4.77) vs. 3.67 (3.34–4.28), $p = 0.039$). The disc position and disc shape were not related to PTF or malleus position. Malleus position and PTF dimensions were not associated with the PTF type. In cases with erosive changes and condylar osteophytosis, malleus was closer to PTF.

Keywords: petrotympanic fissure; malleus position; temporomandibular disorder; disc displacement; condyle productive changes

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1. Introduction

Morphological studies showed a close relationship between the TMJ and structures of the middle ear, explained by the presence of the anterior mallear ligament (AML), the sphenomandibular ligament (SML), and the discomallear ligament (DML) [1]. The malleus is attached to the tympanic cavity by ligaments; however, the relationship between the DML and the temporomandibular articular disc (TMJ disc) has an exact undisclosed morphology. Previous reports suggested that the anatomical feature of the connection between malleus and TMJ disc gives rise to TMJ pain and dysfunction [2]. One of the clinical causes of hearing impairment and temporomandibular joint dysfunction (TMD) is an architectural association between the temporal bones and the DML [3–5]. Therefore, the conformation of these ligaments may be associated with TMJ pain and dysfunction, as well as hearing impairment. Several studies have linked otological disorders to ligamentous structures between the middle ear and the TMJ [6,7].

The presence of DML has been described in anatomic studies in human adult specimens and fetuses, being attached to the retrodiscal tissues of the TMJ [6]. It was suggested that the PTF, in combination with the DML, has a significant role in auditory functionality [8]. The excessive elongation of the condyle could be a possible cause of otological issues in patients with temporomandibular disorders (TMDs). Sencimen et al. have stated that ligaments connecting the tympanic ossicular chain and the TMJ could lead to auditory impairment in TMD patients [9,10] due to the tension of the DML and the movement of the malleus [11].

Clinical implications for the morphology of the tympanic cavity structures were noticed in TMJ disorders [12]. A recent ex vivo study demonstrated the movement of the malleus head caused by stretching on the DML with possible clinical implications on TMJ disc displacement (DD) [13].

It has also been suggested that the structure of the PTF could play an important role in the movement of the malleus in the middle ear and the TMJ articular disc [13]. CBCT can accurately characterize the anatomical type of PTF with a reduced radiation dose [14]. However, the CBCT does not allow the soft tissues to be analyzed, and neither the morphology of DML nor the TMJ articular disc is visible on CBCT. The CBCT assessment of malleus head position and TPF morphology and their correlation with TMJ disc position on MRI examination could better explain the DML involvement in otologic symptoms in TMD patients.

The study of the relationship between the TMJ disc and malleus position could be important for a better understanding of auditory symptoms in patients with TMD. Moreover, in patients with acoustic disturbances, the imaging evaluation of the TMD may be relevant.

As far as we know, no study has yet investigated the PTF types concerning the TMJ disc displacement (DD) on MRI and malleus position, and the results could be relevant for dental and ENT practitioners. Our hypothesis was that petrotympanic architecture and malleus location is connected to TMJ disc position. Therefore, the aim of this research was to assess possible relationships between petrotympanic fissure characteristics (length, diameter, and type—1, 2, 3), malleus position (malleus to tegmen tympani distance and malleus to PTF distance), and temporomandibular disorders (disc displacement with or without reduction, and normal disc position).

2. Materials and Methods

A retrospective study was designed to evaluate the TMJ disc displacement by magnetic resonance imaging (MRI) and the morphology of the PTF and malleus position by cone beam computed tomography (CBCT). Patients were selected from those admitted to our clinic for treatment of temporomandibular disorders (TMDs), with a median age of 30 (IQR 18–37), ranging from 18 to 59 years, who were clinically investigated according to the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) axis I protocol [15]. Only patients with clinical suspicion of TMD were included in the study. All patients underwent MRI and CBCT examination to evaluate disc displacement (DD) and condylar bone changes. The study did not include subjects aged less than 18 years with TMJ tumors, cleft, TMJ trauma, condylar resorption, inflammatory arthritis, and MRI joint effusion.

The procedures and protocol were approved by the institutional review board at the University and by the Ethics Committee, certificate number 173.010. Informed consent was obtained from each of the subjects before performing the study.

2.1. MRI Examination

All MRI images were obtained using a 1.5 T system (General Electric, Signa Excite HD, General Electric Healthcare, Helsinki, Finland) with a split head coil. All subjects were placed into the standard head coil with fixation devices on both sides. Disc position was evaluated on proton density fast spin echo sagittal oblique images with the closed and open mouth position (TR, 2000 ms; TE, 13 ms; FOV, 326 × 140 mm; matrix, 256/256) and

T2 fast spin echo sagittal oblique images with closed mouth position (TR, 2980 ms; TE, 77 ms; FOV, 196 × 84 mm; matrix, 256/256). Coronal oblique slices were placed parallel to the long axis of the mandibular condyles, whereas sagittal oblique slices were placed perpendicular to the long axis of the condyles. The disc shape (Figure 1) was assessed on sagittal oblique reconstruction oriented perpendicular to the longest diameter of the condylar head according to the shapes described by Orhan et al. [16]. The following disc shapes were encountered: folded (curved shape when not lying flat); lengthened (a disc with equal thickness); thickened posterior band; normal disc shape (biconcave shape, with narrowed intermediate zone and fully visible posterior and anterior bands).

Figure 1. Disc shape figures: (**a**) folded—curved shape when not lying flat; (**b**) lengthened—a disc with equal thickness; (**c**) thickened posterior band; (**d**) normal—biconcave shape, with narrowed intermediate zone and fully visible posterior and anterior bands.

The encountered disc positions on MRI were normal disc position (N), disc displacement with reduction (DDR), and disc displacement without reduction (DDwR), according to the examination protocol previously described [17].

2.2. CBCT Examination of the TMJ and the Temporal Bone

CBCT was used to determine the PTF type, condyle morphology, and the malleus position. Axial slices were obtained from a Planmeca ProMax 3DMid CBCT machine (Planmeca Oy, Helsinki, Finland), 80 × 80 mm FOV, voxel size 0.2 mm^3. On CBCT images, axial sections through the maximum diameter of the condyle were identified, and reconstructions were made in the oblique sagittal and coronal plane of the condyle axis. The sections with visible petrotympanic fissures were selected for assessing the PTF type, PTF dimensions, and malleus position. The multiplanar reconstruction and measurements were performed using the CBCT software (Romexis 6.1.1, Planmeca Oy, Helsinki, Finland).

The type of petrotympanic fissure was described according to Sato et al., [13]: type 1: wide tunnel-shaped structure; type 2: tunnel-shaped structure widely open in the entrance of the PF to the mandibular fossa and gradually thinning out in the tympanic cavity; type 3: tunnel-shaped structure widely open in the entrance of the mandibular fossa, the middle region with flat-shaped tunnel structure and narrow exit in the tympanic cavity and is shown in Figure 2. The PFT's length and maximal diameter were also recorded on oblique sagittal CBCT reconstructions (Figure 3).

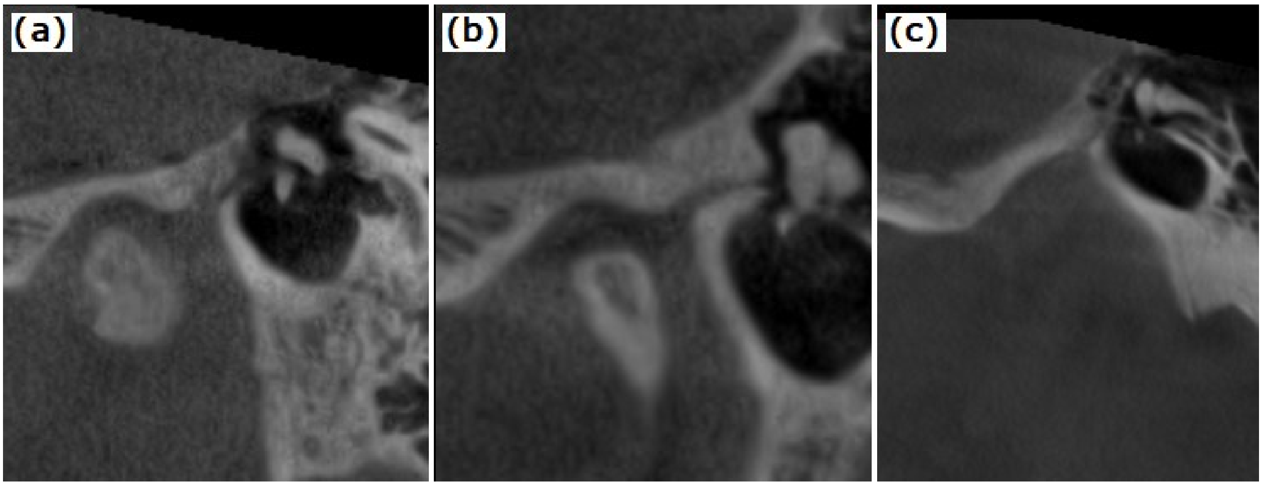

Figure 2. PTF types—(**a**) type 1: broad tunnel-shaped structure; (**b**) type 2: tunnel-shaped structure widely open in the entrance to the mandibular fossa and gradually thinning out in the tympanic cavity; (**c**) type 3: tunnel-shaped structure widely open in the entrance of the mandibular fossa and narrow egress in the tympanic cavity.

Malleus position was assessed related to the opening of PTF in the tympanic cavity on the oblique reconstructed sagittal images on the long condyle axis. The malleus position was quantified by measuring the shortest distance from the malleus head to the tegmen tympani and the petrotympanic fissure.

The normal type of condyle was considered in the absence of any shape or size changes. Bone degenerative changes such as modified articular condyle surface, bone productive changes, bone erosion, and subcortical cyst were noted.

All MRI and CBCT images were evaluated independently by two observers with over ten years of experience in maxillofacial diagnosis on the same monitor and under identical examining conditions after mutual calibration.

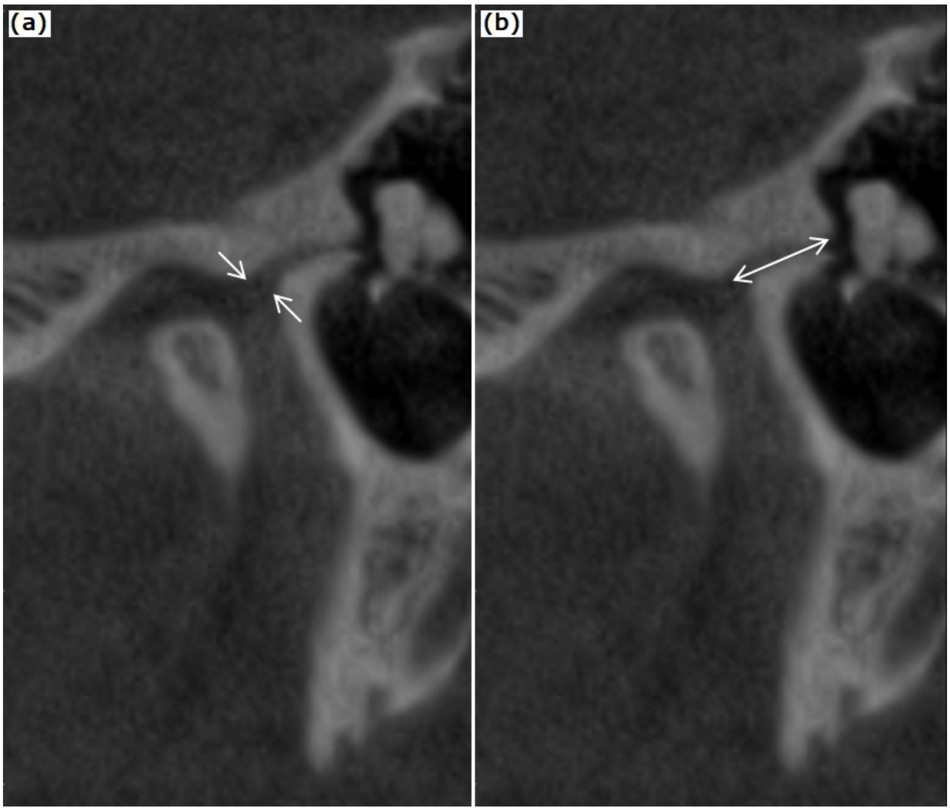

Figure 3. Measurements of petrotympanic fissure: (**a**) largest width (diameter); (**b**) length.

2.3. Statistical Analysis

For normally distributed data, the mean and standard deviation were used; otherwise, the median and interquartile range were computed. The data were assessed for normality using the quantile–quantile plot and the Shapiro–Wilk test. For nonnormally distributed data, the Wilcoxon rank-sum test or Kruskal–Wallis test were used to look for differences between two or more independent sets of quantitative data. Absolute and relative frequencies were used to describe qualitative data. The relationship between qualitative variables was assessed using the Fisher exact test if more than 20% of the predicted frequencies were less than 5 or the chi-squared test otherwise. The interclass correlation coefficient (ICC) and the accompanying test of significance were used to examine interrater reliability for the measurements of PTF dimensions and malleus position (ICC ranged between 0.61 and 0.76 $p < 0.0001$). The significance threshold alpha used for all statistical tests was 0.05, and the two-tailed p-value was obtained. The statistical analysis was performed using the R environment for statistical computing and graphics, version 4.1.2 [18]. The IRR package version 0.84.1 was used for interrater reliability [19].

3. Results

Fifty-eight TMJs from twenty-nine patients (23 females and 6 males) were assessed. The study group consisted of thirty-eight TMJs with disc displacements: twenty-five with reduction (DDR) and thirteen without reduction (DDwR). The control group comprised twenty TMJs with normal disc positions (N).

The PTF characteristics and malleus position are summarized in Tables 1 and 2. The analyzed cases were comparable regarding the PTF type. The most prevalent PTF type was type 1, followed by type 3 and type 2. The largest diameter was encountered in the type 1 fissure. The length of the fissure ranged from 1.8 to 5.55, being the shortest in type 2 PTF, with no statistical differences between types. The overall PTF diameter ranged between 0.6 and 3.45 mm. The malleus position, expressed by the distance to tegmen tympani and PTF, showed no statistical difference between the PTF types.

Table 1. PTF type in TMD patients according to disc position.

Disc Position	PTF Type 1 (n = 23)	PTF Type 2 (n = 14)	PTF Type 3 (n = 21)	*p*-Value
DDR, n (%)	10 (43.48)	7 (50)	8 (38.1)	0.56
DDwR, n (%)	7 (30.43)	3 (21.43)	3 (14.29)	
Normal, n (%)	6 (26.09)	4 (28.57)	10 (47.62)	

PTF, petrotympanic fissure; TMD, temporomandibular disorder; DDR, disc displacement with reduction; DDwR, disc displacement without reduction.

Table 2. CBCT evaluation of PTF characteristics and malleus position.

Characteristics	PTF Type 1 (n = 23)	PTF Type 2 (n = 14)	PTF Type 3 (n = 21)	*p*-Value
PTF characteristics				
PTF diameter (mm), median (IQR)	1.5 (1.25–1.77)	1.12 (0.86–2.09)	1.4 (1.1–2.3)	0.484
PTF length (mm), median (IQR)	3.90 (3.35–4.50)	3.65 (3.35–4.21)	4.35 (3.35–4.70)	0.483
Malleus position				
Malleus to tegmen tympani distance (mm), median (IQR)	2.60 (1.73–3.12)	2.35 (1.95–2.94)	2.55 (2.05–3.25)	0.708
Malleus to PTF distance (mm), median (IQR)	2.75 (2.22–3.45)	2.65 (2.09–2.75)	2.4 (2.05–2.9)	0.249

CBCT, cone beam computed tomography; PTF, petrotympanic fissure; IQR, interquartile range.

Comparisons between disc position related to PTF dimensions and malleus position are summarized in Table 3. There were no differences regarding PTF types and PTF dimensions related to disc position. The distance between the malleus head and tegmen tympani varied between 0.95–4.45 mm. The malleus position was not associated with significant changes in the distance from the malleus head to tegmen tympani or the PTF in subjects with disc displacement compared to those with normal disc positions.

Table 3. The PTF characteristics and malleus position according to MRI disc position.

MRI Disc Position	DDR (n = 25)	DDwR (n = 13)	Normal (n = 20)	*p*-Value
PTF characteristics				
PTF diameter (mm), median (IQR)	3.94 (0.76)	3.88 (0.91)	3.94 (0.97)	0.977
PTF length (mm), median (IQR)	4.00 (3.35–4.50)	4.10 (3.35–4.70)	3.85 (3.34–4.50)	0.993
Malleus position				
Malleus to tegmen tympani distance (mm), median (IQR)	2.40 (1.75–3.00)	2.60 (1.90–2.95)	2.42 (1.90–3.15)	0.969
Malleus to PTF distance (mm), median (IQR)	2.75 (2.15–3.1)	2.4 (2.1–3)	2.52 (2.16–2.92)	0.519

PTF, petrotympanic fissure; MRI, magnetic resonance imaging; TMD, temporomandibular disorder; DDR, disc displacement with reduction; DDwR, disc displacement without reduction; IQR, interquartile range.

Comparisons between disc shape related to malleus position and PTF dimensions are shown in Table 4. A modified disc shape was encountered in 31 subjects with DD (81.57%) and 11 subjects (55%) with normal disc positions. No significant associations were found between disc shape, PTF dimensions, and malleus position.

Table 4. PTF dimensions and malleus position related to disc shape.

Disc Shape	Folded (n = 6)	Lengthened (n = 16)	Thickened Posterior Band (n = 20)	Normal (n = 16)	*p*-Value
PTF diameter (mm), median (IQR)	1.32 (1.14–1.48)	1.25 (1.14–1.64)	1.40 (0.90–1.92)	1.68 (1.24–2.06)	0.424
PTF length (mm), median (IQR)	3.60 (3.31–4.22)	3.45 (3.00–4.50)	4.15 (3.44–4.53)	4.10 (3.50–4.74)	0.487
Malleus to tegmen tympani distance (mm), median (IQR)	2.7 (1.95–3.19)	2.67 (2.18–3.21)	2.3 (1.86–2.95)	2.3 (1.87–2.96)	0.624
Malleus to PTF distance (mm), median (IQR)	2.85 (2.1–3.56)	2.55 (2.11–3.29)	2.65 (2.09–3.1)	2.4 (2.19–2.75)	0.891

PTF, petrotympanic fissure; IQR, interquartile range.

Only a number of twenty-three TMJs (39.65%) were with normal condyle. Normal and disc displacement subjects encountered various bone productive changes, bone erosions, and condyle shape changes (Table 5). The erosive changes and condyle osteophytes production were more frequent in subjects with disc displacement compared to normal disc position. The condylar bone changes, meaning erosions, flat condyle, osteophytosis, or osteosclerosis, were identified in 21 cases (55.26%) of subjects with disc displacements (out of 38) and 14 subjects (70%) with normal disc position (out of 20).

Table 5. Condylar changes in TMD according to disc position.

Condylar Changes	DDR (n = 25)	DDwR (n = 13)	Normal (n = 20)	*p*-Value
Bone cysts, n (%)	0 (0)	0 (0)	1 (5)	0.569
Erosive changes, n (%)	6 (24)	8 (61.54)	3 (15)	0.012
Condylar osteosclerosis, n (%)	6 (24)	5 (38.46)	3 (15)	0.33
Condylar osteophytes, n (%)	6 (24)	9 (69.23)	7 (35)	0.023
Condyle shape changes, n (%)	9 (36)	8 (61.54)	10 (50)	0.303
Normal condyle, n (%)	14 (56)	3 (23.08)	6 (30)	0.08

TMD, temporomandibular disorder; MRI, magnetic resonance imaging; DDR, disc displacement with reduction; DDwR, disc displacement without reduction.

The PTF dimensions and malleus position related to condylar changes are shown in Table 6. We found that malleus was closer to PTF in cases with erosive changes as well as those with condylar osteophytosis. Moreover, the PTF length was higher in cases with condylar osteophytosis compared to those without.

Table 6. PTF dimensions and malleus position related to condylar changes.

Characteristics	PTF Diameter (mm)	PTF Length (mm)	Malleus to Tegmen Tympani Distance (mm)	Malleus to PTF Distance (mm)
Bone cysts				
no (n = 57)	1.40 (1.15–1.95)	4.00 (3.35–4.50)	2.50 (1.90–3.10)	2.55 (2.15–3.10)
yes (n = 1)	0.80 (0.80–0.80)	1.80 (1.80–1.80)	2.05 (2.05–2.05)	1.50 (1.50–1.50)
p-value	0.12	0.088	0.57	0.12
Erosive changes				
no (n = 41)	1.50 (1.20–1.95)	3.95 (3.35–4.50)	2.55 (1.90–3.25)	2.75 (2.25–3.15)
yes (n = 17)	1.25 (1.10–1.95)	4.00 (3.00–4.70)	2.50 (2.00–2.90)	2.15 (1.85–2.75)
p-value	0.338	0.584	0.351	0.029
Condyle shape changes				
no (n = 31)	1.55 (1.15–2.05)	3.95 (3.40–4.50)	2.60 (1.90–3.25)	2.75 (2.30–3.00)
yes (n = 27)	1.35 (1.12–1.73)	4.00 (3.17–4.65)	2.30 (1.90–2.95)	2.40 (1.92–3.12)
p-value	0.31	0.749	0.382	0.221

Table 6. *Cont.*

Characteristics	PTF Diameter (mm)	PTF Length (mm)	Malleus to Tegmen Tympani Distance (mm)	Malleus to PTF Distance (mm)
Condylar osteosclerosis				
no (n = 44)	1.30 (1.05–1.91)	3.83 (3.34–4.41)	2.52 (1.90–3.25)	2.60 (2.15–3.11)
yes (n = 14)	1.68 (1.40–1.99)	4.65 (3.51–4.91)	2.40 (1.52–2.94)	2.42 (2.10–2.94)
p-value	0.113	0.055	0.331	0.501
Condylar osteophytes				
no (n = 36)	1.40 (0.90–1.83)	3.67 (3.34–4.28)	2.50 (1.87–3.35)	2.75 (2.33–3.32)
yes (n = 22)	1.55 (1.17–2.02)	4.45 (3.50–4.77)	2.50 (1.90–2.86)	2.25 (1.91–2.75)
p-value	0.208	0.039	0.199	0.015
Nomal condyle				
no (n = 35)	1.40 (1.15–1.95)	4.05 (3.33–4.72)	2.30 (1.90–2.92)	2.50 (2.00–3.00)
yes (n = 23)	1.40 (0.90–1.97)	3.90 (3.42–4.30)	2.90 (1.85–3.35)	2.75 (2.30–3.20)
p-value	0.644	0.622	0.184	0.169

Results are presented as medians and interquartile ranges. PTF, petrotympanic fissure.

4. Discussion

The discomallear ligament has been identified as a band of connective tissue located laterally relative to the sphenomandibular ligament. DML runs through the petrotympanic fissure (PTF) from the anterior part of the malleus towards the posteromedial side of the TMJ disc inside the PTF [6]. According to some authors, DML is an independent ligament structure being a vestige of the primitive lateral pterygoid muscle, which crosses the petrotympanic fissure, whereas other reports sustain that discomallear ligament is a component of the anterior mallear ligament (AML) [20].

The relationship between TMJ disc and malleus was described mainly in ex vivo studies. In trying to clarify the ligaments' involvement in malleus movement, traction and tension experiments were performed on fifteen skulls, showing that excessive inferior movement of the condyle can unpredictably mobilize the ossicles of the middle ear [9]. However, there is controversy related to the influence of the DML on the malleus movement. Some authors point out the influence of AML stretch on malleus position, while other studies showed that DML and AML are intrinsic ligamentous structures of the TMJ with no important function. [3,10] In this debate, our study tried to bring more evidence related to the PTF morphology and malleus position measured on CBCT images concerning DDR and DDwR evaluated on MRI. The correlation of these imaging aspects could provide more concrete evidence for the relationship between TMJ disc and the middle ear in clinical TMD cases.

In our retrospective study, we found that the malleus position was not significantly different in patients with DD compared to TMD's normal disc position. However, the distance between the malleus head and PTF was decreased in subjects with DD compared to those with normal disc positions. In addition, the PTF length and diameter were not correlated with DD or malleus position. Only in patients with TMD and condylar erosive changes, as well as those with condylar osteophytosis a closer position of the malleus to PTF was noted. Condylar erosion is a symptom of ongoing osteoarthritic alterations that may be linked to altered dentofacial morphology [21]; thus, bone erosions may be associated with disc displacement. Moreover, condylar erosion was found to be a major contributor to a painful disc displacement without reduction [22].

In contrast to our findings, Anastasi et al. [23] discovered that, depending on the clinical aspects, TMJ can determine variations in tension passed on the tympanic membrane responsible that could explain a higher prevalence of tinnitus in TMD patients [24]. More authors suggested that connections between the middle ear and TMJ play a significant clinical role in the occurrence of auditory symptoms [23,25,26]. Our study did not take into consideration the otological symptoms in TMD included subjects which could explain the differences between our results and the previously reported ones. However, Kijac et al. explained the presence of tinnitus by vascular modifications and alterations in cochlear microcirculation, due to the tension of the masticatory muscles. In addition, they have shown that tinnitus is highly associated with the form and location of the petrotympanic fissure and was reported by patients with TMJ disc displacement [27].

PTF is a fine structure and is better highlighted on high-resolution images, such as CBCT. We found a lower incidence of type 2 PTF, which is consistent with other research findings [5,13]. No significant differences in PTF type were found connected to DD. In the literature, the prevalence of the reported PTF type is variable. Some authors evidence no link between age and gender, and PTF type was reported [5], whereas others found a higher prevalence of type 3 in male patients [20].

Villalba et al. reported a higher prevalence of Type 2 PTF (46.7%) compared to other studies [28]. However, the reported prevalence of PTF type is variable and depends on the applied methods for PTF evidence and the examination conditions. Cakur et al. suggested that the difference in reported PTF types could be related to the fact that type 3 is easier to diagnose than types 1 and 2, and because type 2 gradually thins out, diagnosing it would be difficult [5]. In our study, we encountered 39.65% type 1—a wide tunnel-shaped tunnel, 24.13% type 2—large and gradually narrows to the tympanic cavity, and 36.20% type 3 PTF—wide at the mandibular fossa's entrance. Although no significant differences were encountered in TMD patients, type 3 was more frequent in TMD patients with no disc displacements. Our results are in concordance with Sato et al. [13], who showed that the wide structure of PTF type 1 is more easily affected by TMJ disc displacement.

The length of DML was previously reported in different ways according to the imaging acquisition and measurement methods. Runci Anastasi et al. identified DML in axial CT images as a dense structure going from the upper end of the petrotympanic fissure to the neck of the malleus with a triangular shape (90%), rectangular shape (5%), and with a curved course (5%) [29]. The following dimensions of this structure were reported: mean length of the anteromedial side 2 $\pm$ 0.6 mm, the anterolateral side 1.63 $\pm$ 0.5, and mean area of 1.29 $\pm$ 0.83 mm^2. Ramírez Aristeguieta et al. measured the DML on new temporal blocks, and they found a mean length of the discomallear and anterior mallear ligaments of 6.88 mm (SD 0.81) and 4.22 mm (SD 1.17), respectively, with no statistically significant difference being revealed between the sides [30]. On CBCT, we measured the length of the PTF and the distance between the malleus head and the opening of PTF in the tympanic cavity, and the values of the interquartile range were between 3.35–4.70 mm and 2.09–3.56 mm, respectively, with no significant association to the PTF type, disc shape or disc position. Moreover, the distance between the malleus head and tegmen tympani varied between 0.95–4.45 mm, with no significant differences in DD. These results show that from an anatomical point of view, the malleus position in the tympanic cavity is not significantly influenced by DD in the studied subjects.

The condylar bone changes encountered in our patients were also correlated with malleus position. The overall outcome of our study does not reveal a significant association between bone changes and malleus position changes. Moreover, a shorter distance from malleus to PTF was found in patients with condylar erosions, and the PTF length was higher in presence of condylar osteophytes.

We found that erosive changes and condyle osteophytes were more prevalent in subjects with disc displacement than in those with normal disc position; malleus was closer to PTF in cases with erosive changes as well as those with condylar osteophytosis; PTF length was greater in cases with condylar osteophytosis than in those with normal disc position. These findings suggest that malleus position is modified in DD with degenerative bone changes and highlight the need for TMD assessment in patients with unexplained acoustic symptoms.

Our study found that TMJ disorders were connected with the morphology of the tympanic cavity's components. In addition, it has been theorized that the architecture of the PTF may play an important role in the movement of the malleus in the middle ear and the articular disc of the TMJ [13]. This might have future clinical implications for individuals with TMJ disc displacement since as the subjects in our study with DD had a shorter distance between the malleus head and PTF compared to those with normal disc positions. In addition, in individuals with TMD, condylar erosive alterations, and bone osteophytes, the malleus was seen to be closer to the PTF.

The main limitation of our study is that it is retrospective, and therefore the clinical data, such as associated acoustic symptoms, were not investigated. The malleus position evidence would be useful in patients with auditory symptoms and DD. However, the retrospective nature of the study does not preclude quality measurements on MRI and CBCT. The reduced number of cases investigated by MRI and CBCT in the same examining conditions represents another limitation of the study. Nevertheless, we found statistically significant associations between bone productive changes and malleus position.

A certain association related to the distance between the malleus and PTF needs further comparison of MRI and CBCT examinations on a higher number of TMD patients.

The strength relies upon the fact that, to the best of our knowledge, this is the first clinical study that evaluated the malleus position to DD and bone productive changes in TMD subjects. A certain association related to the malleus position in the middle ear and PTF needs further comparison of MRI and CBCT examinations on a higher number of TMD patients.

5. Conclusions

Our study could not identify the existence of a relationship between disc displacements and malleus position, PTF type, or dimensions. A significant association was found between the condylar bone changes in patients with disc displacements and the distance from the malleus to the petrotympanic fissure. The malleus was observed to be closer to the PTF in individuals with TMD, condylar erosive changes, and bone osteophytes. These findings show the value of imaging examination of the TMJ in patients with unexplained auditory disturbances. Our study suggests that in patients with unexplained auditory symptoms and a TMJ diagnosis, an assessment of disc position and condyle bone structure is necessary to diagnose a possible TMD early and to treat it as soon as possible in order to prevent further deterioration of the joints and improve the patient's quality of life. Nevertheless, we consider that our results are still preliminary, and due to the small number of studied cases, these results should be validated on a higher number of subjects.

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Data Availability Statement: The data presented in this study are available from the corresponding author upon reasonable request.

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References

1. Pinto, O.F. A New Structure Related to the Temporomandibular Joint and Middle Ear. *J. Prosthet. Dent.* **1962**, *12*, 95–103. [CrossRef]
2. Arai, H.; Sato, I. Anatomical Study of the Human Discomallear Ligament Using Cone Beam Computed Tomography Imaging and Morphological Observations. *Okajimas Folia Anat. Jpn.* **2011**, *88*, 89–101. [CrossRef] [PubMed]

3. Ioannides, C.A.; Hoogland, G.A. The Disco-Malleolar Ligament: A Possible Cause of Subjective Hearing Loss in Patients with Temporomandibular Joint Dysfunction. *J. Maxillofac. Surg.* **1983**, *11*, 227–231. [CrossRef]
4. Çakur, B.; Yaşa, Y. Correlation between Tinnitus and Petrotympanic Fissure Status Among Patients With Temporomandibular Joint Dysfunction. *J. Oral Maxillofac. Surg.* **2016**, *74*, 47–52. [CrossRef]
5. Cakur, B.; Sümbüllü, M.A.; Durna, D.; Akgül, H.M. Prevalence of the Types of the Petrotympanic Fissure in the Temporomandibular Joint Dysfunction. *Acta Radiol.* **2011**, *52*, 562–565. [CrossRef]
6. Kim, H.J.; Jung, H.S.; Kwak, H.H.; Shim, K.S.; Hu, K.S.; Park, H.D.; Park, H.W.; Chung, I.H. The Discomallear Ligament and the Anterior Ligament of Malleus: An Anatomic Study in Human Adults and Fetuses. *Surg. Radiol. Anat.* **2004**, *26*, 39–45. [CrossRef]
7. Loughner, B.A.; Larkin, L.H.; Mahan, P.E. Discomalleolar and Anterior Malleolar Ligaments: Possible Causes of Middle Ear Damage during Temporomandibular Joint Surgery. *Oral Surg. Oral Med. Oral Pathol.* **1989**, *68*, 14–22. [CrossRef]
8. Rowicki, T.; Zakrzewska, J. A Study of the Discomalleolar Ligament in the Adult Human. *Folia Morphol.* **2006**, *65*, 121–125.
9. Sencimen, M.; Yalçin, B.; Doğan, N.; Varol, A.; Okçu, K.M.; Ozan, H.; Aydintuğ, Y.S. Anatomical and Functional Aspects of Ligaments between the Malleus and the Temporomandibular Joint. *Int. J. Oral Maxillofac. Surg.* **2008**, *37*, 943–947. [CrossRef]
10. Sencimen, M.; Varol, A.; Baykal, B.; Altug, H.A.; Dogan, N.; Sahin, S.; Okcu, K.M.; Yalcin, B. Histological Characteristics of Ligaments between Middle Ear and Temporomandibular Joint. *Eur. J. Dent.* **2009**, *3*, 280–284.
11. Ogütcen-Toller, M.; Juniper, R.P. The Embryologic Development of the Human Lateral Pterygoid Muscle and Its Relationships with the Temporomandibular Joint Disc and Meckel's Cartilage. *J. Oral Maxillofac. Surg.* **1993**, *51*, 772–778. [CrossRef]
12. Anagnostopoulou, S.; Venieratos, D.; Antonopoulou, M. Temporomandibular Joint and Correlated Fissures: Anatomical and Clinical Consideration. *CRANIO®* **2008**, *26*, 88–95. [CrossRef] [PubMed]
13. Sato, I.; Arai, H.; Asaumi, R.; Imura, K.; Kawai, T.; Yosue, T. Classifications of Tunnel-like Structure of Human Petrotympanic Fissure by Cone Beam CT. *Surg. Radiol. Anat.* **2008**, *30*, 323–326. [CrossRef] [PubMed]
14. Hedesiu, M.; Marcu, M.; Salmon, B.; Pauwels, R.; Oenning, A.C.; Almasan, O.; Roman, R.; Baciut, M.; Jacobs, R. Irradiation Provided by Dental Radiological Procedures in a Pediatric Population. *Eur. J. Radiol.* **2018**, *103*, 112–117. [CrossRef] [PubMed]
15. Dworkin, S.F.; LeResche, L. Research Diagnostic Criteria for Temporomandibular Disorders: Review, Criteria, Examinations and Specifications, Critique. *J. Craniomandib. Disord.* **1992**, *6*, 301–355. [PubMed]
16. Orhan, K.; Nishiyama, H.; Tadashi, S.; Murakami, S.; Furukawa, S. Comparison of Altered Signal Intensity, Position, and Morphology of the TMJ Disc in MR Images Corrected for Variations in Surface Coil Sensitivity. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endodontol.* **2006**, *101*, 515–522. [CrossRef]
17. Almăşan, O.C.; Hedeşiu, M.; Băciuţ, G.; Leucuţa, D.C.; Băciuţ, M. Disk and Joint Morphology Variations on Coronal and Sagittal MRI in Temporomandibular Joint Disorders. *Clin. Oral Investig.* **2013**, *17*, 1243–1250. [CrossRef]
18. R Core Team. *A Language and Environment for Statistical Computing*; R Foundation for Statistical Computing: Vienna, Austria, 2021.
19. Matthias, G.; Jim, L.; Ian, S. Irr: Various Coefficients of Interrater Reliability and Agreement. Available online: https://cran.r-project.org/web/packages/irr/index.html (accessed on 16 August 2022).
20. Gorurgoz, C.; Orhan, K.; Sinanoglu, E.A.; Avsever, I.H. Evaluation of Mallear Ligaments in Different Voxel Resolutions Using Cone Beam Computed Tomography. *Dentomaxillofac. Radiol.* **2019**, *48*, 20180125. [CrossRef]
21. Emshoff, R.; Bertram, A.; Hupp, L.; Rudisch, A. A Logistic Analysis Prediction Model of TMJ Condylar Erosion in Patients with TMJ Arthralgia. *BMC Oral Health* **2021**, *21*, 374. [CrossRef]
22. Emshoff, R.; Bertram, A.; Hupp, L.; Rudisch, A. Condylar Erosion Is Predictive of Painful Closed Lock of the Temporomandibular Joint: A Magnetic Resonance Imaging Study. *Head Face Med.* **2021**, *17*, 40. [CrossRef]
23. Anastasi, M.R.; Rizzo, G.; Nicita, F.; Bramanti, A.; Milardi, D.; Macchi, V.; Brunetto, D.; Cascone, P.; Arco, A.; Nicita, A.; et al. Microscopic Reconstruction and Immunohistochemical Analysis of Discomalleolar Ligament. *Heliyon* **2020**, *6*, e04651. [CrossRef] [PubMed]
24. Edvall, N.K.; Gunan, E.; Genitsaridi, E.; Lazar, A.; Mehraei, G.; Billing, M.; Tullberg, M.; Bulla, J.; Whitton, J.; Canlon, B.; et al. Impact of Temporomandibular Joint Complaints on Tinnitus-Related Distress. *Front. Neurosci.* **2019**, *13*, 879. [CrossRef] [PubMed]
25. Algieri, G.M.A.; Leonardi, A.; Arangio, P.; Vellone, V.; Paolo, C.D.; Cascone, P. Tinnitus in Temporomandibular Joint Disorders: Is It a Specific Somatosensory Tinnitus Subtype? *Int. Tinnitus J.* **2016**, *20*, 83–87. [CrossRef] [PubMed]
26. Sobhy, O.A.; Koutb, A.R.; Abdel-Baki, F.A.; Ali, T.M.; El Raffa, I.Z.; Khater, A.H. Evaluation of Aural Manifestations in Temporo-Mandibular Joint Dysfunction. *Clin. Otolaryngol. Allied Sci.* **2004**, *29*, 382–385. [CrossRef]
27. Kijak, E.; Szczepek, A.J.; Margielewicz, J. Association between Anatomical Features of Petrotympanic Fissure and Tinnitus in Patients with Temporomandibular Joint Disorder Using CBCT Imaging: An Exploratory Study. *Pain Res. Manag.* **2020**, *2020*, 1202751. [CrossRef]
28. Villalba, Ó.; Rojas, S.; Ortega, M.; Solano, A.; Rodríguez-Baeza, A. Evaluation of the Human Petrotympanic Fissure Using Anatomized Cadaveric Specimens and Multi-Detector CT Imaging. *Surg. Radiol. Anat.* **2020**, *42*, 337–346. [CrossRef]
29. Runci Anastasi, M.; Macchi, V.; Vellone, V.; Nastro Siniscalchi, E.; Anastasi, G.; Morra, A.; Porzionato, A.; De Caro, R.; De Ponte, F.S.; Cascone, P. The Discomallear Ligament: Anatomical, Microscopical, and Radiologic Analysis. *Surg. Radiol. Anat.* **2020**, *42*, 559–565. [CrossRef]
30. Ramírez Aristeguieta, L.M.; Ballesteros Acuña, L.E.; Sandoval Ortiz, G.P. A Direct Anatomical Study of the Morphology and Functionality of Disco-Malleolar and Anterior Malleolar Ligaments. *Int. J. Morphol.* **2009**, *27*, 367–379. [CrossRef]

Oral splints in the management of nociceptive pain and migraines: A scoping review

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Abstract. Temporomandibular disorders (TMDs) are characterized by numerous pain manifestations. Their treatment often involves the use of an oral splint. Recent research has found a relationship between migraines, nociceptive pain and TMDs. The aim of the present study was to perform a scoping review of studies in order to evaluate the effectiveness of the various types of oral splint in the treatment of migraine or nociceptive pain. Publications were retrieved from seven databases (PubMed, Web of Science, EMBASE, Scopus, ProQuest, SpringerLink and Ovid). Out of the 15 included publications, three studies were before and after studies, with no control group, whereas the other twelve studies were clinical trials, among which two publications were crossover studies. A clear, single distinction of pain was difficult to describe. Therefore, numerous publications focused on a combination of various types of pains, including myofascial, temporomandibular joint, headaches and migraine-like symptoms, all of which mimicked TMD pain. Overall, six studies used the stabilization splint (SS), three explored the comparison between the SS and the nociceptive trigeminal inhibition splint (NTIS) and two the NTIS. The majority of publications reported a positive outcome of splint therapy. Regarding the type of oral splint usage, the most commonly used one was the SS, followed by the NTIS. The definition and assessment of pain were heterogenous in the identified articles. The findings of the current study showed that occlusal splints may help with pain management, and that effective treatment of TMD-related pain at an early stage can enhance the quality of life of patients.

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Introduction

Migraines are considered to be one of the most distressing disorders, especially in chronic cases. Moreover, patients frequently utilize excessive amounts of drugs in order to treat these intense headaches (1). The International Classification of Headache Disorders (3rd edition) diagnoses a migraine as a primary headache, whereas a headache that is attributed to temporomandibular disorders (TMDs) is considered to be a secondary one (2). Migraines can cause facial or dental pain, which demonstrates the trigeminal-vascular systems role, as well as the roles of inflammatory or pathological processes in the facial area that may trigger or aggravate migraines (3).

Preconscious nociceptive mechanisms are unconscious, whereas pain is a conscious subjective assessment of an organism's physical harm (4). Nociceptive pain is caused by the stimulation of nociceptive trigeminal receptors and the exposure of these receptors may result in neurogenic pain (5).

The gold standard for diagnosing TMD is based on the Diagnostic Criteria for TMD for clinical and research applications (6,7). Accordingly, the systematic classification of TMD comprises of temporomandibular joint (TMJ) disorders (including joint pain, joint disorders, joint diseases, fractures and congenital/developmental disorders), masticatory muscle disorders (including muscle pain, contracture, hypertrophy, neoplasm, movement disorders and masticatory muscle pain attributed to systemic/central pain disorders), headaches and craniofacial structures (6).

TMD can trigger headaches, as well as exacerbate existing primary headaches, and also contributes to the chronicity of migraines (8). A standardized therapeutic approach to treat TMDs has not yet been established due to the wide range of symptoms and a complex etiology (9). Oral splints (10), along with other treatment possibilities, have been proposed, such as drugs (11), self-care (12), exercise therapy (13,14), acupuncture (15), physiotherapy (16), photo-biomodulation (17), laser therapy (18) and surgery (19,20).

Oral splints are a reversible, non-invasive treatment for temporomandibular dysfunction; however, their clinical effectiveness is still unknown (21). Numerous types of oral appliances have previously been described, including stabilization splints (SSs), anterior repositioning appliances, bite planes and hard or soft splints (22).

The role of oral splints in the treatment of nociceptive pain or migraines is still unclear.

Manrriquez *et al* (23), in a systematic review and meta-analysis, demonstrated that SSs induces a reduction of headache intensity or frequency in patients with TMD headache comorbidity. However, the evidence quality in this study was low, with only nine studies being analyzed in the qualitative synthesis and five studies in the quantitative synthesis (meta-analysis). However, the authors reported no significant difference in the use of partial hard or soft splints or full arch splint use (23). A recent review investigating the effects of a SSs on headaches in patients with TMDs, revealed that even though SS therapy reduced headache intensity and frequency, the evidence quality was inadequate due to the high bias risk and small sample size, which indicated that there is a need for more research (23).

To the best of our knowledge this is the first scoping review which investigated both therapeutic approaches, stabilization splints and nociceptive trigeminal inhibition splints, with regards to nociceptive pain and migraines.

Materials and methods

Protocol and registration. The present review was performed according to the procedures proposed by the Joanna Briggs Institute Methods Manual for scoping reviews (24). The findings were reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for Scoping Reviews (25). The Open Science Framework platform (identification no. Y86QX) was used to register the study protocol prospectively on 30th May 2022 (https://osf.io/y86qx).

Eligibility criteria. Peer-reviewed journal studies that were written in the English language, without a time limit of publication, that addressed nociceptive pain or migraine and oral splints and engaged human participants, were included in the present review. Moreover, studies were included if they were peer-reviewed original studies, including nociceptive pain and migraine patients, and were focused on oral splints.

The exclusion criteria included, systematic reviews, literature and scoping reviews, meta-analyses, letters to the editor, comments, communications, case reports, conference abstracts, practice guidelines, editorials and articles written in languages other than English.

Information sources and the search strategy. Searches were performed without time restrictions using seven electronic databases directed in the English language in May 2022. The search strategy was drafted by a specialist in TMDs with over 10 years of experience and was adapted to other databases. The following terms were searched: 'nociceptive pain', 'migraine', 'migraine disorders', 'migraineous', 'oral splint', 'oral splints'. The research strategy was constructed using the Patient, Intervention, Comparison, Outcome (PICO) framework: P-subjects with nociceptive pain or migraine; I-oral splint; C-controls without an oral splint; and O-oral splint effect.

This comprehensive search was performed using the following databases: PubMed, Web of Science, Embase, Scopus, ProQuest, SpringerLink and Ovid, to find original articles using the following keywords, 'nociceptive pain', 'migraine' and 'oral splint'. The last search was conducted on 30th May 2022.

Screening. The study selection was performed using the Rayyan online platform (26), a web tool (https://www.rayyan.ai/) to assist in working on systematic reviews and scoping reviews. The publications were examined by two researchers who assessed the titles and abstracts for relevance and the presence of the eligibility criteria. The full text of the retrieved articles was assessed. The publications were classified into the following three groups: i) Included; ii) excluded; and iii) maybe. In the case of any possible disagreements, or articles that were put in the maybe group, a consensus was reached by discussion and differences in opinion were settled via a debate.

Data collection and analysis. Two reviewers participated in creating a data-charting template to establish which parameters to extract. A data extraction form was created using Microsoft Excel (Microsoft Office 2019®; Microsoft Corporation) software (27). The data collected and recorded included author and year of publication, country, study population, type of oral splint and effect of oral splint on pain or migraine. A descriptive analysis of the data was performed and the data were recorded independently by two researchers and subsequently confirmed.

Critical appraisal of individual sources of evidence. The methodological quality of the eligible studies included in the present review was rated using the quality assessment tools (questionnaires that help to assess the methodological quality of articles) provided by the National Heart Lung and Blood Institute (28).

Results

Selection of sources of evidence. The performed search within seven databases [PubMed (n=21), EMBASE (n=22), Scopus (n=6), Web of Science (n=21), SpringerLink (n=18), ProQuest (n=13), Ovid (n=13)] yielded 114 publications in total. After removing duplicates, a total number of 92 publications were considered. The remaining publications were screened for eligibility, eliminating studies that had a study design specified in the exclusion criteria (n=57), background articles (n=10), irrelevant articles (n=2) and duplicate records, which were removed manually (n=3); this led to 18 articles being retrieved. Out of the identified articles, two articles could not be retrieved. The 16 full texts of the relevant publications were acquired and reviewed according to the inclusion and exclusion criteria. One paper was excluded since the outcome was not reported. A final list of 15 publications was collated.

Characteristics of the studies and synthesis of results. The characteristics of the included studies are presented in Table I, including the country, study type, study population, main complaint, type of oral splint used, method of assessment and treatment effect.

All included publications were published in the last 15 years and came from a variety of sources, including one from Austria (29), four from Brazil (30-33), one from

Table I. Study characteristics.

First author/s, year	Country	Study type	Study population and splint wearing time	Main complaint	Oral splint type	Method of assessment	Oral splint effect	(Refs.)
Aksakalli *et al*, 2015	Turkey	CT	40 patients with TMD (34 women and 6 men; mean age, 31 years). Group 1, 20 subjects with SS And 20 subjects with NTIS for 3 months.	Clenching/grinding, pain in the TMJ, earache.	SS, NTIS	Fonseca questionnaire, OHQoL-UK and VAS	Both splints reduced the patients' pain and the patient experienced an improved quality of life following treatment.	(42)
Amin *et al*, 2016	India	RCT	45 patients with MMP. Group 1, 15 subjects with hard splints; group 2, 15 subjects with soft splints; group 3, 15 subjects with liquid splints for 3 months.	Myofascial pain dysfunction syndrome.	SSs, including hard splints, soft splints and liquid splint	Subjective pain, Mod-SSI objective pain, muscle palpation	Significant reduction in pain for all three groups at the end of 3 months. Hard splints proved to be very effective over a shorter period of time, followed by liquid splints and finally soft splints.	(36)
Baad-Hansen *et al*, 2007	Denmark	Blinded randomized CO	10 patients (3 men and 7 women; age, 23-39 years). Each splint was used for 2 weeks.	Painful muscles upon clinical palpation, TMD characteristic pain intensity. Tooth-grinding during Sleep and muscle soreness on awakening.	SS, NTIS	RDC/TMD, VAS	Reduced EMG activity of the masseter muscles during treatment with the NTIS, which was not associated with a short term reduction in TMD signs or symptoms (pain).	(34)
Blumenfeld and Boyd, 2022	USA	Single-blinded placebo-controlled CO	19 patients with chronic migraine. 2 months wearing time: 30 days of the placebo splint and 30 days the NTI splint	The severity of pain and the adverse impact that headaches had on the quality of life.	NTIS placebo device	HIT-6 score	The improvement produced by the NTIS suggested that patients with chronic migraines may have nocturnal jaw clenching as a contributing factor.	(41)
Conti *et al*, 2012	Brazil	Blinded, CS	51 patients with MMP. Group 1, 21 subjects-with SS and counselling; group 2, 16 subjects with NTIS and counselling; group 3, 14 subjects with no splint but with counselling and self-care. Duration, 2 weeks, 6 weeks and 3 months, respectively.	Pain of masticatory muscles	SS, NTIS, counselling/ self-care	RDC/TMD, VAS, PPT	Behavioral changes are effective in the management of pain in patients with masticatory muscle pain. Moreover, the simultaneous use of occlusal devices produces an earlier improvement.	(30)

Table I. Continued.

First author/s, year	Country	Study type	Study population and splint wearing time	Main complaint	Oral splint type	Method of assessment	Oral splint effect	(Refs.)
Conti *et al*, 2015	Brazil	Blinded, controlled RCT	33 patients. Group 1, 12 subjects with DDR and arthralgia, ARC and counselling; group 2, 12 patients with NTIS and counselling; group 3, 9 control patients with counselling. Duration, 2 weeks, 6 weeks and 3 months, respectively.	TMJ pain.	ARS, NTIS	RDC/TMD, VAS, PPT	Significant decrease in pain intensity in all groups. Patients wearing occlusal devices accompanied by counselling and behavioral changes reported faster significant improvements. This demonstrated the importance of the intraoral device in the management of TMJ pain. NTIS may be used in patients with TMD, TMJ and muscular pain, headaches or migraines.	(31)
Costa *et al*, 2016	Brazil	CT	Adults with MMP. Group 1, 17 patients with TMD-attributed headaches; group 2, 17 patients without TMD-attributed Headaches; both groups had SS and counselling. 5 months.	TMD attributed headaches and masticatory myofascial pain	SS	RDC/TMD, VAS, PPT	Reduction in facial pain intensity in TMD-attributed headaches in patients with MMP. This study changed the pattern for muscle pain improvement. The presence of a headache was demonstrated to modify muscle pain patterns in MMP subjects.	(32)
Didier *et al*, 2017	Italy	CT	88 patients with MOH and 49 patients with PIFP. 6, 12 months.	Neuromuscular component of patients suffering from chronic craniofacial pain.	Acrylic resin device	VAS, MIDAS questionnaire	Significant decrease in pain intensity (VAS). Significant decrease of the Migraine Disability Assessment Test, after treatment with an occlusal device.	(38)
Hasanoglu Erbasar *et al*, 2017	Turkey	RCT	40 patients. Group 1, 20 patients with guidance, assurance and counselling behavioral changes; group 2, 20 patients with an NTIS. 3 and 6 weeks.	Myofascial pain.	NTIS	RDC/TMD	Reduction in pain levels and improvement of jaw function. However, the integration of an NTIS into the therapy protocol did not provide any additional benefits in relieving symptoms of myofascial pain.	(43)

Table I. Continued.

First author/s, year	Country	Study type	Study population and splint wearing time	Main complaint	Oral splint type	Method of assessment	Oral splint effect	(Refs.)
Haggiag *et al*, 2017	Brazil	CT	74 patients (56 female, 18 male) with chronic migraine headaches. 6, 12 months.	Chronic migraine headaches, masticatory myofascial pain and awake bruxism.	Posterior occlusal device and an intraoral device called 'DIVA®'	Standard patient chart, Oral Behaviors Checklist, EMG recordings	Reduction in overall pain, including headaches.	(33)
La Mantia *et al*, 2018	Italy	RCT	60 patients. Group 1, 30 patients with treatment; group 2, 30 control patients.	Sleep bruxism and jaw muscle discomfort	SS	EMG, MIDAS	Short-term use of occlusal splint therapy was effective in reducing both bruxism activity and migraine related discomfort.	(39)
Mortazavi *et al*, 2010	Iran	R chart review (CS)	138 patients (26 males and 112 females).	Early TMD/TMJ pain.	SS	Chart review study	Overall, 64% of the patients were completely relieved of signs and symptoms and 22% were moderately relieved. Patients with pain and clicking had a better response to treatment.	(37)
Rampello *et al*, 2013	Italy	CT	50 patients. Group 1, 25 patients with splints; group 2, control patients. 3 months.	Muscle pain, TMJ pain, headaches or migraines.	'UNIRA' splint	VAS	Resolution or improvement of symptoms. Muscular pain, migraine and cervical pain improved in group 1.	(40)
Saha *et al*, 2019	Germany	RCT	60 patients. Group 1, 30 patients with SS and standard care; group 2, 30 patients, with usual care alone (no particular therapy).	Headache symptoms in patients with migraines and/or tension-type headaches.	SS	VAS	Day and night occlusal splint therapy, in addition to standard care, was not superior to standard care alone in patients with chronic headache and comorbid TMD.	(35)
Schmid-Schwap *et al*, 2009	Austria	R	97 patients. Group 1, 37 patients with splints; group 2-29 patient with exercise therapy; group 3, 31 patients with splints and exercise therapy. 18±12 weeks for exercise or splint therapy, 29±15 weeks	Muscle pain, TMJ pain, headache pain during chewing and pain during mouth opening.	SS	VAS	Significantly improved muscle pain upon palpation in all groups. A significant reduction of pain was found in all groups. Mouth opening exhibited the most marked improvement seen for the patients in the group with a combination of splint therapy and exercise therapy.	(29)

Table I. Continued.

First author/s, year	Country	Study type	Study population and splint wearing time	Main complaint	Oral splint type	Method of assessment	Oral splint effect	(Refs.)
			for patients receiving a combination of both therapies.					

CT, clinical trial; CO, crossover; RCT, randomized clinical trial; R, retrospective; TMD, temporomandibular disorder; TMJ, temporomandibular joint; SS, stabilization splint; NTIS, nociceptive trigeminal inhibition splint; ARS, anterior repositioning splint; OHQoL, oral-health-related quality of life; VAS, visual analog scale; Mod-SSI, Modified Symptom Severity Index; EMG, electromyographic; RDC/TMD, research diagnostic criteria for temporomandibular disorders; MMP, masticatory myofascial pain; DDR, disc displacement with reduction; HIT-6, Headache Impact Test questionnaire; PPT, pressure pain threshold; MOH, medication overuse headache; PIFP, persistent idiopathic facial pain; MIDAS, migraine disability score.

Denmark (34), one from Germany (35), one from India (36), one from Iran (37), three from Italy (38-40), one from the USA (41) and two from Turkey (42,43). The continental distribution of these publications was similar across America (33.33%), Asia (26.66%) and Europe (40%). Three studies were before and after studies (studies that made repeated observations on one group, before and after an intervention), with no control group (33,37,42), whereas the other 12 studies were clinical trials, among which two publications were crossover studies (each subject in the study received both treatments, but the order of receiving it was randomized) (34,41).

A clear, single distinction of pain was difficult to describe and therefore numerous publications focused on a combination of nociceptive pains, such as myofascial, TMJ pain, headaches and migraine-like symptoms, all of which mimicked TMD pain. Myofascial pain (29,30,33,34,36,40,43) and TMJ pain (29,31,34,37,40,42) were investigated in a number of studies. Pain assessment was usually assessed using questionnaires, like the Fonseca questionnaire (42) and a visual analog scale was cited by numerous studies (29-32,34,35,38,40,42). The migraine disability score was applied in two studies (38,39). The Headache Impact Test questionnaire was used by Blumenfeld and Boyd (41).

Regarding the type of oral splints used, numerous publications reported the use of SSs, including Amin *et al* (36), Costa *et al* (32), La Mantia *et al* (39), Mortazavi *et al* (37), Saha *et al* (35) and Schmid-Schwap *et al* (29). The nociceptive trigeminal inhibition splint (NTIS) was used by Blumenfeld and Boyd (41), who compared it to a placebo device and Hasanoglu Erbasar *et al* (43). Comparisons between the SS and the NTIS were reported in numerous studies (30,34,42). Haggiag *et al* (33) introduced an innovative splint, the 'posterior occlusal intraoral device named 'DIVA®', whereas Rampello *et al* (40) described a special, particularized splint called 'UNIRA'.

The reported outcomes of splint therapy varied. A number of studies (60%) reported a positive outcome for splint therapy, including Aksakalli *et al* (42), Amin *et al* (36), Blumenfeld and Boyd (41), Conti *et al* (30,31), Costa *et al* (32), Didier *et al* (38), Haggiag *et al* (33) and Mortazavi *et al* (37). Aksakalli *et al* (42) demonstrated that splint therapy decreased TMD complaints, improved the movements of the mandible in patients with TMD and reduced overall pain in patients with both SSs and NTISs. Amin *et al* (36) suggested that practitioners should consider using occlusal splints as a therapeutic option when treating patients with myofascial pain dysfunction, which demonstrated that the splints reduced pain symptoms. Blumenfeld and Boyd (41) demonstrated that patients with chronic migraines may experience nighttime jaw clenching, which may be a potential cause; however, an improvement of these symptoms was observed in patients using NTISs. Conti *et al* (30) reported that behavioral adjustments are helpful in pain management and that the simultaneous use of oral devices appears to lead to an earlier improvement. Furthermore, Conti *et al* (31), demonstrated that oral appliances are efficient in the management of disc displacement with pain reduction, in association with behavioral therapy. Costa *et al* (32) reported an early improvement of symptoms in patients with masticatory myofascial pain, wearing a SS. Didier *et al* (38) demonstrated that occlusal devices are effective and well-tolerated in the treatment of headaches and persistent idiopathic facial

Table II. National Heart Lung and Blood Institute quality assessment tool for before-after (pre-post) studies with no control group.

Criteria	Aksakalli *et al* (42)	Haggiag *et al* (33)	Mortazavi *et al* (37)
1. Was the study question or objective clearly stated?	Yes	Yes	No
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes	Yes	Yes
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?	CD	Yes	CD
4. Were all eligible participants that met the prespecified entry criteria enrolled?	NR	Yes	CD
5. Was the sample size sufficiently large to provide confidence in the findings?	No	NR	NR
6. Was the test/service/intervention clearly described and delivered consistently across the study population?	NR	Yes	Yes
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes	Yes	NR
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	No	No	NR
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Yes	Yes	NR
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided P-values for the pre-to-post changes?	Yes	CD	CD
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	No	Yes	NR
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	NA	NA	NA
Quality rating	Poor	Fair	Poor

CD, cannot determine; NA, not applicable; NR, not reported.

pain. Haggiag *et al* (33) reported that an intraoral device could aid in the reduction of pain in subjects suffering from chronic migraine headaches. Moreover, Mortazavi *et al* (37) demonstrated that oral splints were effective in >80% of the enrolled subjects in the treatment of TMDs, in a study that had a follow-up period of 1-9 years.

However, Baad-Hansen *et al* (34) reported that splints did not reduce pain in a short period of time, whereas Saha *et al* (35) demonstrated that the splint was not superior to standard care in pain reduction (drugs, including non-steroidal anti-inflammatory drugs, opioids, corticosteroids and muscle relaxants.). Hasanoglu Erbasar *et al* (43) reported that the NTIS, along with behavioral changes, guidance and counseling, did not add additional relief benefits to patients suffering from TMD myofascial pain.

Critical appraisal within sources of evidence. The risk of bias assessment in individual studies was assessed. The quality assessment of the included studies demonstrated a fair quality for eight studies and a good one for two studies, whereas only five studies were assessed as poor (Tables II and III).

Discussion

The connection between migraines, headaches, nociceptive pain and TMDs has preoccupied researchers for a long period of time. Furthermore, there is still debate on the role of oral splints in the treatment of associated pain. In the present review, 15 studies addressing the role of occlusal splints in the management of nociceptive pain or migraine, published between 2007-2022, were identified. The results indicated that there is still a scarcity of studies primarily focused on the influence of oral splints on nociceptive pain or migraines. Moreover, the type of splint varies between studies, and studies should focus on the same type of splints to improve outcome and symptom relief.

Table III. National Heart Lung and Blood Institute quality assessment of controlled intervention studies.

Criteria	Amin *et al* (38)	Baad-Hansen *et al* (34)	Blumenfeld and Boyd (41)	Conti *et al* (30)	Conti *et al* (31)	Costa *et al* (32)	Didier *et al* (38)	Hasanoglu Erbasar *et al* (43)	La Mantia *et al* (39)	Rampello *et al* (40)	Saha *et al* (35)	Schmid-Schwap *et al* (29)
1. Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	No	Yes	No
2. Was the method of randomization adequate (i.e., use of randomly generated assignment)?	CD	NA	NR	NR	NR	No	NR	NR	Yes	NR	Yes	No
3. Was the treatment allocation concealed (so that assignments could not be predicted)?	NR	Yes	NR	NR	NR	No	NR	NR	Yes	NR	Yes	No
4. Were study participants and providers blinded to treatment treatment group assignment?	NR	Yes	NA[a]	Yes	Yes	Yes	NR	NR	NR	No	NR	NR
5. Were the people assessing the outcomes blinded to the participants' group assignments?	NR	Yes	No	Yes	Yes	Yes	NR	NR	NR	No	NR	NR
6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?	Yes	Yes	No	No	No	Yes	NR	Yes	NR	NR	No	NR

Table III. Continued.

Criteria	Amin *et al* (38)	Baad-Hansen *et al* (34)	Blumenfeld and Boyd (41)	Conti *et al* (30)	Conti *et al* (31)	Costa *et al* (32)	Didier *et al* (38)	Hasanoglu Erbasar *et al* (43)	La Mantia *et al* (39)	Rampello *et al* (40)	Saha *et al* (35)	Schmid-Schwap *et al* (29)
8. Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?	Yes	Yes	No	No	Yes	Yes	NR	Yes	NR	NR	No	NR
9. Was there high adherence to the intervention protocols for each treatment group?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Were other interventions avoided or similar in the groups (e.g., similar background treatments)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?	No	Yes	No	No	No	Yes	No	Yes	NR	No	Yes	No
13. Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?	No	No	No	No	No	No	No	No	No	No	No	No

Table III. Continued.

Criteria	Amin *et al* (38)	Baad-Hansen *et al* (34)	Blumenfeld and Boyd (41)	Conti *et al* (30)	Conti *et al* (31)	Costa *et al* (32)	Didier *et al* (38)	Hasanoglu Erbasar *et al* (43)	La Mantia *et al* (39)	Rampello *et al* (40)	Saha *et al* (35)	Schmid-Schwap *et al* (29)
14. Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to- treat analysis?	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Quality rating	Fair	Good	Fair	Poor	Fair	Fair	Poor	Good	Fair	Fair	Fair	Poor

CD, cannot determine; NA, not applicable; NR, not reported. [a]just the participants were blinded.

Primary headache disorders, particularly migraines, are closely linked to TMD, as they exhibit similar dentofacial pain characteristics (44). A relationship between painful TMD and headaches has previously been reported (45). It has also been demonstrated that managing craniofacial pain using an oral splint and physical therapy in patients with TMDs and migraines significantly improves migraines, neck pain and head and neck posture (46). However, these effects, are not as noticeable in patients who have migraines before the onset of TMD (46).

Greene and Menchel (47) previously debated several controversies related to splint therapy, including full coverage vs. partial coverage, how oral appliances affect TMJ loading and how oral appliances work to relieve TMJ pain. Wiens (48) reported that patients with TMD can benefit from SSs as a reversible treatment. Kuzmanovic Pficer *et al* (49) reported that SSs have a positive effect on pain reduction and pain intensity in muscular disorders, as well as a decrease in muscle tenderness and result in improvements in mouth opening. Vrbanović and Alajbeg (50) demonstrated that SSs were effective in treating patients with chronic TMDs compared with placebo splints. The SS, constructed in centric relation out of hard acrylic or polycarbonate material, is one of the most frequently used types of splint. It causes minimal changes to the relationship between the maxilla and the mandible and therefore has the fewest adverse effects in comparison to irreversible treatment (such as occlusal adjustment, orthodontics or fixed prosthetic procedures) (51).

Al-Moraissi *et al* (52), when studying the hierarchy of different treatments for myogenous TMDs, found that manual therapy, along with counseling and occlusal devices, were considered effective treatments. Almoznino *et al* (53) investigated the long-term adherence of patients to occlusal splints and reported that those with mild to major pain reduction had higher adherence rates compared with those with no or complete pain relief. Moreover, Garstka *et al* (54) demonstrated that physical manifestations of TMDs are on the rise amongst individuals and posture disturbances and associated functional disorders are associated. Consequently, the diagnosis and medical therapy of patients with TMD ought to be comprehensive.

A recent study reported that the influence of occlusal splints on muscle strength is yet unknown, with no consensus on whether occlusal splints can be used as synergists, these results indicated the need for further research (55). Moreover, occlusal splints have been demonstrated to improve postural balance in patients suffering from TMD (56). Ferrillo *et al* (57), when analyzing the effects of occlusal splints on the spinal posture in subjects with TMDs, reported that occlusal splints have positive effects, which indicated their use as a non-invasive method in treating patients. Noguchi *et al* (10) also demonstrated efficient results for patients with myofascial pain and local myalgia using SSs. Honnef *et al* (58), in a systematic review investigating the effects of SSs on the signs and symptoms of TMDs, reported that the effect of the SS on the signs and symptoms of TMDs of muscle origin could not be determined. In spite of its extended benefits, the use of occlusal devices regarding their type, wearing time and splint type (full coverage splint or partial coverage splint), still need to be taught. Krief *et al* (59) also reported that a higher level of practitioner education is needed as well as an improvement in the homogeneity of treatment procedures. Cruz *et al* (44) demonstrated that by determining the onset sequence of concomitant diseases related to TMD, the impact of TMD therapy on clinical alterations of its comorbidity, such as migraines and cervical dysfunction, might be identified. This study also reported that SS therapy improves the symptoms of migraines and TMD-related craniofacial and cervical discomfort.

Taking into consideration the fact that occlusal splints produce reversible changes to the occlusion, the extension limits of the splint must be considered as well as its thickness. It has previously been reported that splints with a thickness of 2 and 4 mm are both effective in the treatment of muscle disorders (60), as well as 3 mm in thickness (61). Kostrzewa-Janicka *et al* (62) determined that the thickness of the SS should be individualized for each patient according to the vertical jaw separation and skeletal morphology (62). A specific vertical dimension of the splint is difficult to generalize due to the individual characteristics of the occlusion. The design of the splint is determined by the therapeutic goals, whereas the underlying mechanisms behind the treatment success are still unknown (47).

After assessing the efficiency of the SS integrated with a digital occlusal analysis device in the therapy of TMD with myofascial pain, Li *et al* (63) discovered that the guided occlusal adaptation of the splint using digital technology can achieve an enhancement of the curative implications and outcome of patients suffering from this condition.

SSs has been proven to be superior to NTISs (64). However, Oh *et al* (65) demonstrated that in subjects with TMDs and an SS, the onset of an anterior open bite can be induced. Moreover, Stapelmann and Turp (66) reported negative side effects related to teeth and occlusions; therefore, careful management of patients receiving these devices is mandatory. Dalewski *et al* (67), when studying the occlusal splint vs. the NTIS in subjects with bruxism, by means of using surface electromyography, reported that neither splint type had any influence on the muscles.

Over a long period of time, the side effects of a partial coverage splint should be considered, and side effects, if present, need to be managed adequately. NTISs have been proven to be efficient in the treatment of TMD muscle disorders (68), as well as migraine and tension headaches (69). However, being only partial coverage splints, NTISs have been shown to cause side effects, including unwanted changes in the occlusion (64). When compared to the Michigan splint, the NTIS is more efficient in reducing jaw muscle activity during sleep in patients with bruxism (70).

Of the publications investigated in the present study, according to the quality assessment, eight studies were fair, five were poor and two were good. The studies that were included clearly advocate study of the relationship between the oral splint and nociceptive pain and migraine to improve a patients' quality of life.

There are certain limitations to the present scoping review. The literature only contains a small number of papers on the relevant topic. A few of the reviewed papers used a before and after design and were therefore subject to several possible biases, including the attribution of the effect to the intervention, confounding bias and difficulty in sustaining causality. A number of the clinical trials were not randomized and suffered from a lack of controlling confounding bias. However, the main limitation was the quality of the reviewed papers. Regarding the controlled trials, there were problems in the reporting of the randomization method and allocation concealment, followed by a lack of blinding and an unequal percentage of subjects lost during follow-up. There was also a high heterogeneity between the splint types and methods of outcome assessment that made it challenging to perform meta-analyses. Finally, the studies were performed on a limited number of subjects.

The strength of the present review relies on the overview of splint therapy for nociceptive pain and migraines since the etiology and clinical manifestations are so broad. It brings together different types of occlusal splints, which are aimed at pain relief in patients with migraine-like headaches and TMDs. Furthermore, the search strategy used in the present study was complex and extensive, being performed in seven databases.

The present study demonstrated that the definition and assessment of nociceptive pain and migraine was heterogenous in the identified articles. A number of the studies (60%) reported a positive outcome for splint therapy. The most frequently used oral splint was a SS, followed by NTIS. Due to the complexity of nociceptive pain and migraines associated with TMJ dysfunction, the diagnosis and treatment should be comprehensive. Along with medication, physiotherapy, counselling, cognitive adjustments and splint therapy can be effective in the overall outcome of patients with migraine or nociceptive pain. The present study demonstrated that occlusal splints may assist in pain reduction and the early and feasible treatment of TMD-related pain will improve a patient's quality of life. A specialist in TMDs, along with a neurologist, a psychiatrist, a psychologist, a physiotherapist and a dentist, should be involved in the treatment of nociceptive pain and migraines. Therefore, nociceptive pain and migraine should be identified as early as possible and treated by a multidisciplinary team, using a multifaceted approach, including oral splints, to diminish pain and improve the well-being of new patients as well as individuals with chronic conditions. To establish a clear relationship between oral splint therapy and migraines or nociceptive pain, more randomized controlled trials with a proper methodology and a systematic review are warranted.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

OA came up with the idea. OA, SB and MH devised the methodology. MH, SB and CD validated the data. OA and DCL performed the formal analysis. OA, CD and MH contributed to the investigation. OA and DCL performed data curation. OA and DCL prepared the original draft. OA, DCL, MH, CD and SB contributed to writing of the article, its review and editing. OA and DCL performed the visualization. CD and SB supervised the project. OA administered the project. MH and CD confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Fischer MA and Jan A: Medication-overuse Headache. In: StatPearls [Internet]. StatPearls Publishing, Treasure Island, FL, 2022.
2. Headache Classification Committee of the International Headache Society (IHS): The International Classification of Headache Disorders. Cephalalgia 38: 1-211, 2018.
3. Teruel A and Romero-Reyes M: Interplay of oral, mandibular, and facial disorders and migraine. Curr Pain Headache Rep 26: 517-523, 2022.
4. Apkarian AV: Nociception, pain, consciousness, and society: A plea for constrained use of pain-related terminologies. J Pain 19: 1253-1255, 2018.
5. Burstein R, Blumenfeld AM, Silberstein SD, Manack Adams A and Brin MF: Mechanism of action of onabotulinumtoxina in chronic migraine: A narrative review. Headache 60: 1259-1272, 2020.
6. Schiffman E, Ohrbach R, Truelove E, Look J, Anderson G, Goulet JP, List T, Svensson P, Gonzalez Y, Lobbezoo F, *et al*: Diagnostic criteria for temporomandibular disorders (DC/TMD) for clinical and research applications: Recommendations of the International RDC/TMD consortium network* and orofacial pain special interest group†. J Oral Facial Pain Headache 28: 6-27, 2014.
7. Peck CC, Goulet JP, Lobbezoo F, Schiffman EL, Alstergren P, Anderson GC, de Leeuw R, Jensen R, Michelotti A, Ohrbach R, *et al*: Expanding the taxonomy of the diagnostic criteria for temporomandibular disorders. J Oral Rehabil 41: 2-23, 2014.
8. Bevilaqua Grossi D, Lipton RB and Bigal ME: Temporomandibular disorders and migraine chronification. Curr Pain Headache Rep 13: 314-318, 2009.
9. Manfredini D, Bucci MB, Montagna F and Guarda-Nardini L: Temporomandibular disorders assessment: Medicolegal considerations in the evidence-based era. J Oral Rehabil 38: 101-119, 2011.
10. Noguchi T, Kashiwagi K and Fukuda K: The effectiveness of stabilization appliance therapy among patients with myalgia. Clin Exp Dent Res 6: 244-253, 2020.
11. Ruiz-Romero V, Toledano-Serrabona J and Gay-Escoda C: Efficacy of the use of chondroitin sulphate and glucosamine for the treatment of temporomandibular joint dysfunction: A systematic review and meta-analysis. Cranio 1-10, 2022 (Epub ahead of print).
12. Eliassen M, Hjortsjö C, Olsen-Bergem H and Bjørnland T: Self-exercise programmes and occlusal splints in the treatment of TMD-related myalgia-Evidence-based medicine? J Oral Rehabil 46: 1088-1094, 2019.
13. Zhang L, Xu L, Wu D, Yu C, Fan S and Cai B: Effectiveness of exercise therapy versus occlusal splint therapy for the treatment of painful temporomandibular disorders: A systematic review and meta-analysis. Ann Palliat Med 10: 6122-6132, 2021.
14. Giannakopoulos NN, Rauer AK, Hellmann D, Hugger S, Schmitter M and Hugger A: Comparison of device-supported sensorimotor training and splint intervention for myofascial temporomandibular disorder pain patients. J Oral Rehabil 45: 669-676, 2018.
15. Fernandes AC, Duarte Moura DM, Da Silva LGD, De Almeida EO and Barbosa GAS: Acupuncture in temporomandibular disorder myofascial pain treatment: A systematic review. J Oral Facial Pain Headache 31: 225-232, 2017.
16. Derwich M, Gottesman L, Urbanska K and Pawlowska E: Craniovertebral and craniomandibular changes in patients with temporomandibular joint disorders after physiotherapy combined with occlusal splint therapy: A prospective case control study. Medicina (Kaunas) 58: 684, 2022.
17. Dias WCFG DS, Cavalcanti RVA, Magalhães Júnior HV, Pernambuco LA and Alves GÂDS: Effects of photobiomodulation combined with orofacial myofunctional therapy on the quality of life of individuals with temporomandibular disorder. Codas 34: e20200313, 2022.
18. Ekici Ö, Dündar Ü and Büyükbosna M: Effectiveness of high-intensity laser therapy in patients with myogenic temporomandibular joint disorder: A double-blind, placebo-controlled study. J Stomatol Oral Maxillofac Surg 123: e90-e96, 2022.
19. Sari BC and Develi T: The effect of intraarticular botulinum toxin-A injection on symptoms of temporomandibular joint disorder. J Stomatol Oral Maxillofac Surg 123: e316-e320, 2022.
20. Guarda-Nardini L, De Almeida AM and Manfredini D: Arthrocentesis of the temporomandibular joint: Systematic review and clinical implications of research findings. J Oral Facial Pain Headache 35: 17-29, 2021.
21. Riley P, Glenny AM, Worthington HV, Jacobsen E, Robertson C, Durham J, Davies S, Petersen H and Boyers D: Oral splints for patients with temporomandibular disorders or bruxism: A systematic review and economic evaluation. Health Technol Assess 24: 1-224, 2020.
22. Fricton J, Look JO, Wright E, Alencar FG Jr, Chen H, Lang M, Ouyang W and Velly AM: Systematic review and meta-analysis of randomized controlled trials evaluating intraoral orthopedic appliances for temporomandibular disorders. J Orofac Pain 24: 237-254, 2010.
23. Manrriquez SL, Robles K, Pareek K, Besharati A and Enciso R: Reduction of headache intensity and frequency with maxillary stabilization splint therapy in patients with temporomandibular disorders-headache comorbidity: A systematic review and meta-analysis. J Dent Anesth Pain Med 21: 183-205, 2021.
24. Peters M, Godfrey CM, McInerney P, Soares CB, Khalil H and Parker D: Methodology for JBI scoping reviews. The Joanna Briggs Institute Reviewers manual 2015: 3-24, 2015.
25. McGowan J, Straus S, Moher D, Langlois EV, O'Brien KK, Horsley T, Aldcroft A, Zarin W, Garitty CM, Hempel S, *et al*: Reporting scoping reviews-PRISMA ScR extension. J Clin Epidemiol 123: 177-179, 2020.
26. Ouzzani M, Hammady H, Fedorowicz Z and Elmagarmid A: Rayyan-a web and mobile app for systematic reviews. Syst Rev 5: 210, 2016.
27. Microsoft Excel (version 365), Microsoft: Redmond, WA, USA, https://office.microsoft.com/excel, 2019.
28. National Heart, Lung, and Blood Institute (NHLBI): Study Quality Assessment Tools. NHLBI, Bethesda, MD, 2022. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools. Accessed June 20, 2022.
29. Schmid-Schwap M, Bristela M, Kundi M and Piehslinger E: Treatment of patients with temporomandibular disorders-a retrospective treatment comparison. Int J Stomat Occ Med 2: 59-64, 2009.
30. Conti PC, de Alencar EN, Da Mota Corrêa AS, Lauris JR, Porporatti AL and Costa YM: Behavioural changes and occlusal splints are effective in the management of masticatory myofascial pain: A short-term evaluation. J Oral Rehabil 39: 754-760, 2012.
31. Conti PC, Corrêa AS, Lauris JR and Stuginski-Barbosa J: Management of painful temporomandibular joint clicking with different intraoral devices and counseling: A controlled study. J Appl Oral Sci 23: 529-535, 2015.
32. Costa YM, Porporatti AL, Stuginski-Barbosa J, Bonjardim LR, Speciali JG and Conti PC: Headache attributed to masticatory myofascial pain: Impact on facial pain and pressure pain threshold. J Oral Rehabil 43: 161-168, 2016.

33. Haggiag A and Speciali JG: A new biofeedback approach for the control of awake bruxism and chronic migraine headache: Utilization of an awake posterior interocclusal device. Arq Neuropsiquiatr 78: 397-402, 2020.
34. Baad-Hansen L, Jadidi F, Castrillon E, Thomsen PB and Svensson P: Effect of a nociceptive trigeminal inhibitory splint on electromyographic activity in jaw closing muscles during sleep. J Oral Rehabil 34: 105-111, 2007.
35. Saha FJ, Pulla A, Ostermann T, Miller T, Dobos G and Cramer H: Effects of occlusal splint therapy in patients with migraine or tension-type headache and comorbid temporomandibular disorder: A randomized controlled trial. Medicine (Baltimore) 98: e16805, 2019.
36. Amin A, Meshramkar R and Lekha K: Comparative evaluation of clinical performance of different kind of occlusal splint in management of myofascial pain. J Indian Prosthodont Soc 16: 176-181, 2016.
37. Mortazavi SH, Motamedi MH, Navi F, Pourshahab M, Bayanzadeh SM, Hajmiragha H, and Isapour M: Outcomes of management of early temporomandibular joint disorders: How effective is nonsurgical therapy in the long-term? Natl J Maxillofac Surg 1: 108-111, 2010.
38. Didier HA, Curone M, Tullo V, Didier AH, Cornalba R, Giannì AB and Bussone G: Usefulness of an occlusal device in the treatment of medication overuse headache and persistent idiopathic facial pain: Preliminary results. Neurol Sci 38 (Suppl 1): S57-S61, 2017.
39. La Mantia I, Grillo C and Andaloro C: Short-Term use of occlusal splint in patients with sleep bruxism: A case-Controlled study. Acta Med Mediterr 34: 301-305, 2018.
40. Rampello A, Saccucci M, Falisi G, Panti F, Polimeni A, and Di Paolo C: A new aid in temporomandibular joint disorders' therapy: The universal neuromuscular immediate relaxing appliance. J Biol Regul Homeost Agents 27: 1011-1019, 2013.
41. Blumenfeld AM and Boyd JP: Adjunctive treatment of chronic migraine using an oral dental device: Overview and results of a randomized placebo-controlled crossover study. BMC Neurol 22: 72, 2022.
42. Aksakalli S, Temucin F, Pamukcu A, Ezirganlı S, Kazancioglu HO and Malkoc MA: Effectiveness of two different splints to treat temporomandibular disorders. J Orofac Orthop 76: 318-327, 2015.
43. Hasanoglu Erbasar GN, Alpaslan C and Eroglu Inan G: Can an NTI-tss device be effective as a first-line therapy in patients with TMD myofascial pain? J Oral Rehabil 44: 589-593, 2017.
44. Cruz D, Monteiro F, Paço M, Vaz-Silva M, Lemos C, Alves-Ferreira M and Pinho T: Genetic overlap between temporomandibular disorders and primary headaches: A systematic review. Jpn Dent Sci Rev 58: 69-88, 2022.
45. Réus JC, Polmann H, Souza BDM, Flores-Mir C, Gonçalves DAG, de Queiroz LP, Okeson J and De Luca Canto G: Association between primary headaches and temporomandibular disorders. J Am Dent Assoc 153: 120-131.e6, 2022.
46. Kang JH: Effects on migraine, neck pain, and head and neck posture, of temporomandibular disorder treatment: Study of a retrospective cohort. Arch Oral Biol 114: 104718, 2020.
47. Greene CS and Menchel HF: The use of oral appliances in the management of temporomandibular disorders. Oral Maxillofac Surg Clin North Am 30: 265-277, 2018.
48. Wiens JP: A progressive approach for the use of occlusal devices in the management of temporomandibular disorders. Gen Dent 64: 29-36, 2016.
49. Kuzmanovic Pficer J, Dodic S, Lazic V, Trajkovic G, Milic N and Milicic B: Occlusal stabilization splint for patients with temporomandibular disorders: Meta-analysis of short and long term effects. PLoS One 12: e0171296, 2017.
50. Vrbanović E and Alajbeg IZ: Long-term effectiveness of occlusal splint therapy compared to placebo in patients with chronic temporomandibular disorders. Acta Stomatol Croat 53: 195-206, 2019.
51. Dhannawat PV, Shrivastav S, Kamble R and Banerjee S: Different Types of Occlusal Splint Used In Management of Temporomandibular Joint Disorders-A Review. Eur J Mol Clin Med 7: 1787-1794, 2020.
52. Al-Moraissi EA, Conti PCR, Alyahya A, Alkebsi K, Elsharkawy A and Christidis N: The hierarchy of different treatments for myogenous temporomandibular disorders: A systematic review and network meta-analysis of randomized clinical trials. Oral Maxillofac Surg, 2021 (Epub ahead of print).
53. Almoznino G, Barsheshet S, Mazor S, Yanko R, Sharav Y and Haviv Y: Long-term adherence to oral stabilization splints: Does pain matter? Quintessence Int 53: 68-76, 2021.
54. Garstka AA, Brzózka M, Bitenc-Jasiejko A, Ardan R, Gronwald H, Skomro P and Lietz-Kijak D: Cause-Effect relationships between painful TMD and postural and functional changes in the musculoskeletal system: A preliminary report. Pain Res Manag 2022: 1429932, 2022.
55. Dias A, Redinha L, Mendonça GV and Pezarat-Correia P: A systematic review on the effects of occlusal splint therapy on muscle strength. Cranio 38: 187-195, 2020.
56. El Zoghbi A, Halimi M, Hobeiche J and Haddad C: Effect of occlusal splints on posture balance in patients with temporomandibular joint disorder: A prospective study. J Contemp Dent Pract 22: 615-619, 2021.
57. Ferrillo M, Marotta N, Giudice A, Calafiore D, Curci C, Fortunato L, Ammendolia A and de Sire A: Effects of occlusal splints on spinal posture in patients with temporomandibular disorders: A systematic review. Healthcare (Basel) 10: 739, 2022.
58. Honnef LR, Pauletto P, Conti Réus J, Massignan C, Souza BDM, Michelotti A, Flores-Mir C and De Luca Canto G: Effects of stabilization splints on the signs and symptoms of temporomandibular disorders of muscular origin: A systematic review. Cranio 1-12, 2022 (Epub ahead of print).
59. Krief S, Jeany M, Orthlieb JD, Re JP and Lan R: Occlusal devices in France: An assessment of professional practice. J Prosthet Dent 125: 816.e1-816.e7, 2021.
60. Bilir H and Kurt H: Influence of stabilization splint thickness on temporomandibular disorders. Int J Prosthodont 35: 163-173, 2022.
61. Akbulut N, Altan A, Akbulut S and Atakan C: Evaluation of the 3 mm Thickness splint therapy on temporomandibular joint disorders (TMDs). Pain Res Manag 2018: 3756587, 2018.
62. Kostrzewa-Janicka J, Mierzwińska-Nastalska E, Jarzębski G and Okoński P: Vertical jaw separation for vertical thickness of occlusal stabilization splint. J Stomat Occ Med 5: 20-27, 2012.
63. Li Z, Liu L, Bai Q, Huang L, Li B, Yang L, Liang T, Sun H and Li D: Evaluation of the effect of T-Scan™ as an adjunct to stabilization splint in the treatment of temporomandibular joint disorders. Cranio 1-10, 2022 (Epub ahead of print).
64. Magnusson T, Adiels AM, Nilsson HL and Helkimo M: Treatment effect on signs and symptoms of temporomandibular disorders-comparison between stabilisation splint and a new type of splint (NTI). A pilot study. Swed Dent J 28: 11-20, 2004.
65. Oh JW, Ahn YW, Jeong SH, Ju HM, Song BS and Ok SM: Prediction of anterior open-bite development after stabilization splint treatment in patients with temporomandibular disorder. Cranio 40: 324-333, 2022.
66. Stapelmann H and Türp JC: The NTI-tss device for the therapy of bruxism, temporomandibular disorders, and headache-Where do we stand? A qualitative systematic review of the literature. BMC Oral Health 8: 22, 2008.
67. Dalewski B, Chruściel-Nogalska M and Frączak B: Occlusal splint versus modified nociceptive trigeminal inhibition splint in bruxism therapy: A randomized, controlled trial using surface electromyography. Aust Dent J 60: 445-454, 2015.
68. Boulad JMK, Al-Sabbagh RA, Burhan AS, Kouchaji CN and Nawaya FR: Effects of treatment with nociceptive trigeminal inhibition splints on electromyography in temporomandibular joint disorder patients. J Contemp Dent Pract 20: 598-602, 2019.
69. Bereznicki T, Barry E and Wilson NHF: Unintended changes to the occlusion following the provision of night guards. Br Dent J 225: 715-722, 2018.
70. Lukic N, Saxer T, Hou M, Zumbrunn Wojczyńska A, Gallo LM and Colombo V: Short-term effects of NTI-tss and Michigan splint on nocturnal jaw muscle activity: A pilot study. Clin Exp Dent Res 7: 323-330, 2021.

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Systematic Review

Influence of Human Papillomavirus on Alveolar Bone and Orthodontic Treatment: Systematic Review and Case Report

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Abstract: Background: As the human papillomavirus (HPV) infections are detected in healthy oral mucosa as well as in oral lesions, dental practitioners have an important role in detecting any possible lesions that might be caused by this virus. Therefore, the aim of this study was to investigate the outcomes of orthodontic treatments and HPV infections and to report a rare case of ongoing orthodontic treatment superposed on an HPV infection. Methods: An electronic English literature research of the articles published between the years 2011–2021 was conducted between December 2021–February 2022, accessing PubMed, Web of Science, Embase, Scopus, and Google Scholar. The terms "HPV", "orthodontics", "orthodontic treatment", "tooth movement", "tooth mobility", and "malocclusion" were searched. The following inclusion criteria were pursued: articles published in English language; studies reporting HPV infection in subjects with past or ongoing orthodontic treatment; and case reports of subjects with HPV and orthodontic treatment. Exclusion criteria were: articles in languages other than English, studies related to malignancies other than HPV and orthodontic treatment; and studies reporting patients with HPV and no orthodontic treatment. Results: Following the systematic review, which includes six papers, a case of orthodontic treatment superposed on a HPV infection is presented. Conclusion: Incumbent, postponed HPV infection on an ongoing orthodontic treatment might affect treatment outcome and patient compliance.

Keywords: papillomavirus infection; orthodontics; biomechanics; tooth mobility

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1. Introduction

Human papillomavirus (HPV) infections have become more remarkable during the last years, with oropharyngeal manifestations that have to be considered when planning a complex dental treatment plan, especially when the infection occurs during the treatment period. There are more than 200 different HPV genotypes with high or low risk of malignancy [1,2]. Oral squamous papilloma is one of the oral cavity lesions that manifests as a verrucous or papillary exophytic mass [3]. HPV types 6 and 11 are responsible for benign lesions, and type 16 and 18 are responsible for dysplasia [4].

However, new perspectives have been developed for the prevention of these infections by the application of HPV testing technologies and vaccines [5]. There are many different sub-types of HPVs, the majority being asymptomatic and resolving spontaneously within two years [6]. The World Health Organization's recommends the use of human papillomavirus vaccines as a national immunization program [7]. HPV infection with high-risk types 16 and 18 has been widely reported as a prominent mechanism behind the development of squamous cell carcinoma (SCC) of the oropharynx [8]. HPV is responsible for more than 5% of cancers worldwide, oropharyngeal squamous cell carcinomas and cervical cancers being reported [9], with leading HPV genotypes being HPV 16, 52, 58, 53, 56, and 81 [10]. A subset of oropharyngeal squamous cell carcinoma is associated with human papillomavirus infection, particularly with high-risk type 16 (HPV-16) [11]. Treatment options vary from application of ointments to cryotherapy and surgical removal using lasers, electro surgery, and curettage [12].

HPV infections are detected in healthy oral mucosa as well as in oral lesions [13], and therefore, the dentist has an important role in the inspection and palpation of the oral tissues. Oral healthcare should be thorough supervised during dental appointments. Contrary to other viral infections, no treatment is provided for HPV oral lesions, with the management of these including the patient's follow-up and the periodic probation of the immune system [14]. Surgical treatment of some lesions might be accompanied by the application of low-level laser therapy (LLLT) protocols [15]. However, the surgical removal of the lesion does not guarantee the eradication of the infection since the DNA of the virus could persist in the healthy mucosa [16]. Therefore, the HPV vaccine should be considered, as it is more reliable in preventing the disease than curing it. It has been shown that there is no positive correlation between HPV and the severity of periodontal lesions [17]. When considering dental follow up of patients with complete dentures, it is stated that it may help in monitoring the appearance of possible malignant oral lesions [18]. HPV may be found in the oral cavity of patients with dentures; therefore, HPV-associated diseases, such as oral cancer and other oral lesions, may develop [19]. It has been shown that in subjects with HPV-positive tumors, there has been higher mean alveolar bone loss [20]. Tooth mobility, as a result of alveolar bone and periodontal ligament loss, was associated with an increased risk of HPV-negative oral SCC [21].

Human papillomavirus is rare in children and patients with orthodontic treatment need. Usually, orthodontic treatment is not initiated in cases with positive HPV infection, but when the infection is discovered, by the presence of oral condyloma, warts, or papilloma, orthodontic treatment has already been initiated. There are a few publications worldwide focused on the of HPV infection in subjects with ongoing orthodontic treatment since orthodontics is contraindicated in subjects with malignancies.

To the best of our knowledge, there has not yet been published a paper related to the possible impact of the genital HPV-58 infection on the outcomes of orthodontic treatments. Therefore, the aim of this study was to review the English literature related to human papillomavirus infections in subjects with ongoing orthodontic treatment and to report a rare case of HPV infection.

2. Materials and Methods

This systematic review was performed in accordance with the recommendations of the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA) statement" [22].

2.1. Information Sources

A structured search was conducted (between December 2021–February 2022) on articles published between the years 2011–2021, accessing PubMed, Web of Science, Embase, Scopus, and Google Scholar databases. In addition, a handsearching of the reference lists of included studies or relevant reviews was performed.

2.2. Search Strategy

The terms "HPV", "orthodontics", "orthodontic treatment", "tooth movement", "tooth mobility", and "malocclusion" were searched in combination with the Boolean operators "AND" and "OR" All references were imported and organized in the bibliographic software Mendeley® (Mendeley Software, London, UK).

2.3. Selection of Articles

The following inclusion criteria were pursued: (1) articles published in English language; (2) studies reporting HPV infection in subjects with past or ongoing orthodontic treatment; and (3) case reports of subjects with HPV and orthodontic treatment. Exclusion criteria were: (1) articles in languages other than English; (2) studies related to malignancies other than HPV and orthodontic treatment; and (3) studies reporting patients with HPV and no orthodontic treatment (Table 1).

Table 1. Inclusion and exclusion criteria.

Criterion	Inclusion	Exclusion
Time period	Publications available between January 2011 and December 2021	All publications published before January 2011
Language	English	Non-English
Type of articles	Publications reporting HPV infection with past or ongoing orthodontic treatment; case reports of subjects with HPV and orthodontic treatment. Publications for which full text is available	Studies related to malignant lesions other than HPV and orthodontic treatments; Research only focusing on HVP oral lesions without orthodontic treatments

2.4. Data Collection

All the eligible citations imported into the bibliography were checked, and all the duplicates were removed. Two reviewers carried out the evaluations independently. For the assessment of each publication, Excel (Microsoft Office 2019®, MS, Redmond, WA, USA) spreadsheets were compiled. This way, data were extracted using a standardized form, which included the following information: (1) authors' names and publication year; (2) study design; (3) aim of the study; (4) methodology; (5) key findings; and (6) conclusions. Afterwards, both authors compared their assessments and confirmed the data on the basis of the compiled spreadsheets. Both researchers compared their assessments and confirmed the data. When in doubt regarding the study data, the two researchers resolved disagreements by discussion, or a third researcher solved discrepancies.

3. Results

From the articles published between the years 2011–2021, the terms "HPV and orthodontics" comprised 799 articles in Google Scholar, 192 articles in Scopus, 12 articles in Embase, 10 articles in PubMed, and 1 article Web of Science; "HPV and orthodontic treatment" comprised 235 articles in Google Scholar, 121 articles in Scopus, 2 articles in Embase, 1 article Web of Science, and 1 article in PubMed; "HPV and tooth movement" comprised 563 articles in Google Scholar, 80 articles in Scopus, 1 article in Embase, and 1 article Web of Science; "HPV and tooth mobility" comprised 309 articles in Google Scholar, 29 articles in Scopus, 3 articles in Embase, 3 articles in PubMed, and 3 articles in Web of Science; and "HPV and malocclusion" comprised 97 articles in Google Scholar, 25 articles in Scopus, and 3 articles in Embase (Table 2).

Table 2. English literature research of articles.

English Literature Research of Articles Published between 2011–2021	HPV and Orthodontics	HPV and Orthodontic Treatment	HPV and Tooth Movement	HPV and Tooth Mobility	HPV and Malocclusion
PubMed	10	1	0	3	0
Web of Science	1	1	1	3	0
Embase	12	2	1	3	3
Scopus	192	121	80	29	25
Google Scholar	799	235	563	309	97

After excluding the duplicates, 89 records were included for screening. From the initial literature review, 11 articles were identified, which met the inclusion criteria. The remaining eight articles were checked for eligibility by the full-text review, and six full-text articles were selected (Figure 1).

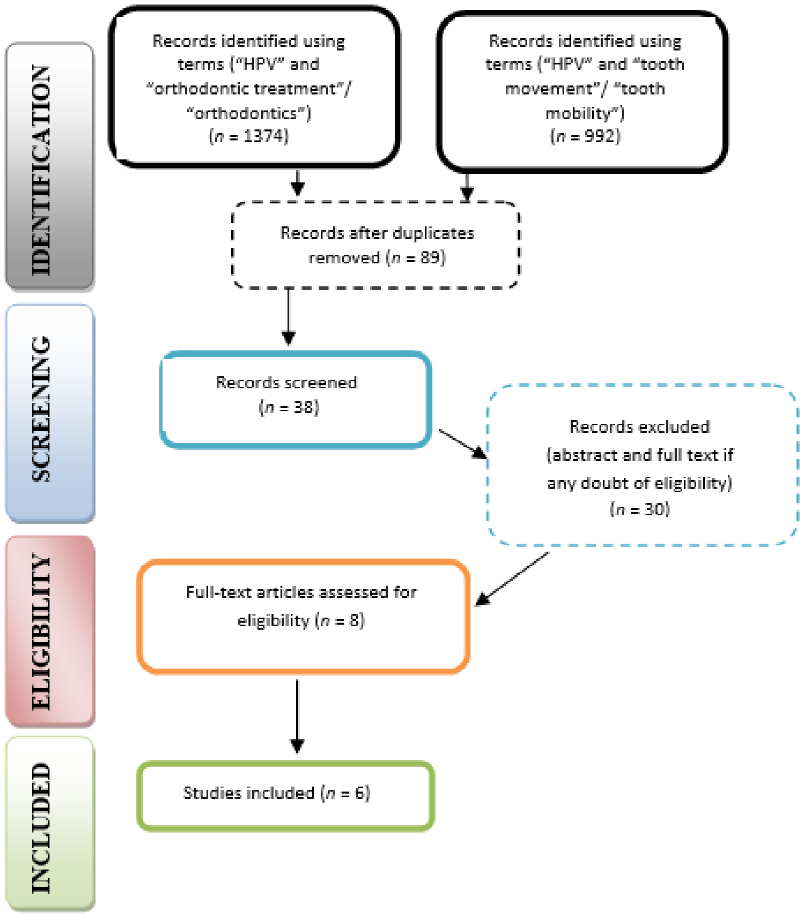

Figure 1. PRISMA flow diagram for research stages; literature search showed the following articles that reported a relationship between HPV and orthodontic treatment (Table 3).

Table 3. Selected articles who met the inclusion criteria.

Authors	Methods	Orthodontic Treatment	HPV Relationship	Results
Schott S. et al., 2019 [23]	Case-control	In the past (childhood)	omen with orthodontic treatment in the past were more prone to prevention strategies for HPV in adulthood	"... concordance with the argumentation that cervical dysplasia occurs more frequently among lower income and education levels; women without orthodontic treatment was significant less aware of prevention strategies such as the HPV vaccination".
Santos-Silva A.R. et al., 2014 [24]	Case reports (3 cases)	In the past (recently)	Tongue squamous cell carcinoma, HPV uncertain	"... full oral examinations, including the entire oral mucosa, as routine in orthodontia could significantly contribute to the early diagnosis of oral cancer".
	Case 1: 21-year-old woman	Final stage of orthodontic treatment	SCC (squamous cell carcinoma)–biopsy	
	Case 2: 34-year-old man	Completed orthodontic treatment 4 years earlier	SCC–biopsy	
	Case 3: 29-year-old woman	After an initial orthodontic evaluation, approximately 40 days before	SCC–biopsy	
Noonan V.L. et al., 2017 [25]	Case report, 17 year-old male, Caucasian	Orthodontic retainer nightly/	Possible HPV etiology, although uncertain	"... the lesions presented exclusively in patients in the second decade localized to the anterior maxillary attached gingiva sparing the marginal gingiva and stopping abruptly at the mucogingival junction".

Table 3. *Cont.*

Authors	Methods	Orthodontic Treatment	HPV Relationship	Results
Henn IW et al., 2014 [26]	Case report, 37 year-old male	Yes, ongoing	HPV infection	"Oral condyloma acuminatum was noted in the patient in the form of multiple lesions verrucous, and staining with variable sizes".
Moine L., Gilligan G., 2018 [27]	Case report, 13 year-old male	Yes, ongoing	Possible HPV etiology, although uncertain	Localized juvenile spongiotic gingival hyperplasia (LJSGH) was treated with trichloroacetic acid (TA) after a conventional surgical treatment. TA could be a safe alternative and a non-invasive technique to treat lesions associated to LJSGH.
Magalhaes M.A. et al., 2016 [28]	Case report, 8-year-old male	Yes, ongoing	Squamous cell carcinoma, with positive staining for p16 in a patchy pattern suggestive of HPV	This rare case of squamous cell carcinoma was located in the gingiva and alveolar ridge, a common location for this demographic group; the post-operative evolution was without events, and the patient was considered disease free at 16 months after surgical resection.

3.1. Case Series and Case Report Studies

Out of the six references included in this systematic review, five were case presentations. Santos-Silva et al. (2011) [24] published a paper that aimed to describe a series of cases of nonsmoking and nondrinking young patients diagnosed with tongue squamous cell carcinoma and who also recently received orthodontic treatment or evaluation. While the HPV could not be excluded in the history of these patients, the authors emphasized the importance of malignant lesions screening, as the incidence of such lesions in this segment of population seems to be increasing.

Noonan et al. (2017) presented a series of seven cases of gingival papillary keratosis with unknown etiology. The lesions were bilateral and symmetric, characterized by yellow-white plaques. While the authors did not exclude a HPV infection, the authors suggested that identification of additional patients diagnosed with such lesions may help in the understanding of their etiology [25].

Henn et al. (2014) presented a case of condyloma acuminatum lesion on a HIV-positive patient (undergoing an orthodontic treatment) and HPV induced. For this case, the treatment plan included surgical removal and chemical cauterization using trichloroacetic acid (TA). The authors emphasized the importance of correct diagnosis and planning for HPV-induced lesions, as there is a high risk for recurrences [26]. The use of trichloroacetic acid (TA) was investigated also by Moine and Gilligan. (2018) in a case report of a 13-year-old patient suffering from localized juvenile spongiotic hyperplasia (LJSGH) [27]. The authors concluded that TA could be a safe, non-invasive alternative for the treatment of lesions, such as LJSGH.

Magalhaes et al. (2016) presented a case of oral squamous cell carcinoma on an 8-year-old patient undergoing orthodontic treatment. Histopathological exam was p16-positive in a patchy pattern, which is suggestive of HPV. The lesions were located in the gingiva and alveolar ridge, a common location for this demographic group; the post-operative evolution was without events, and the patient was considered disease free at 16 months after surgical resection [28].

3.2. Case-Control Study

Schott et al. (2019) [23] conducted a research based on a questionnaire aiming to investigate women's personal history of orthodontic care, long-term satisfaction, as well as adherence to dental and gynecological screening. The data gathered from 233 participants suggested that women with orthodontic treatment in childhood were more concerned regarding prevention strategies in adulthood, which meant that compliant behavior in this context might be established in childhood.

Further, we will present a case-report of an HPV infection interposed with an orthodontic treatment.

3.3. Case Report

A 25-year-old female, with a skeletal class II relationship and who had crowding on both arches, seeking orthodontic treatment, presented to our clinic with the main complaint of crowding in both arches (Figure 2, Table 4). The patient showed no signs or symptoms of temporomandibular disorders, no periodontal disease, and no history of medical problems. Periodontal examination showed a pink-colored gingiva with no signs of swelling, bleeding, or tenderness. Clinical assessment of tooth mobility and instrumental mobilometry revealed grade 0 physiological mobility with no signs of ankylosis, gingivitis, or periodontal disease. Radiologic examination showed normal bone height and a thin periodontal biotype (Figure 3). The treatment objective was to address the malocclusion, to improve the crowding, and to level the occlusal plane. Treatment progress: no tooth extractions for space gaining were performed. Occlusal plane was corrected by intrusion of upper molars using skeletal anchorage. Arches were aligned using 0.22 slot metallic brackets. Because no surgical aiding procedures for shortening treatment time were practiced, low forces were applied using light orthodontic wires.

Figure 2. Lateral cephalogram.

Table 4. Cephalometric tracing.

Measurements	Result	Mean	S.D.	Meaning
SNA	80.03	81.08	3.7	Normal A-P position of the maxilla
SNB	75.40	79.17	3.8	Normal A-P position of the mandible
ANB	2.46	4.63	1.8	skeletal class II
FMA	26.32	29.63	3.0	Hypodivergent facial pattern
Gonial angle	123.44	124.31	5.4	Normal gonial angle
APDI	74.22	85.74	4.0	Skeletal class II
A to N-Perp (FH)	−2.58	0.4	2.3	Retruded maxilla
B to N-Perp (FH)	−12.06	−3.5	2.0	Retruded mandible
Pog to N-Perp (FH)	−9.14	−1.8	2.5	Retruded chin point
FH to AB	76.26	81	3.0	Skeletal class II
A-B to mandibular plane	77.41	69.3	2.5	Large angle
Wits appraisal	5.61	−2.74	0.3	Skeletal class II
Overjet	4.79	2	2.0	Large overjet
Overbite	2.46	2	2.0	Normal overbite

Table 4. *Cont.*

Measurements	Result	Mean	S.D.	Meaning
U1 to FH	100.88	113.8	6.4	Retroclined upper incisor
U1 to SN	93.59	105.28	6.6	Retroclined upper incisor
U1 to UOP	70.28	55	4.0	Retroclined upper incisor
IMPA	80.50	91.62	3.2	Retroclined lower incisor
L1 to LOP	74.77	66	5.0	Retroclined lower incisor
Interincisal angle	152.29	128	5.3	Uprighted interincisal angle
Cant of occlusal plane	5.66	9.3	3.8	Normal occlusal plane angle
U1 to NA(mm)	0.10	4	3.0	Retruded upper incisor
U1 to NA(deg)	13.55	22	5.0	Retroclined upper incisor
L1 to NB(mm)	1.5	4	2.0	Retruded lower incisor
L1 to NB(deg)	9.52	25	5.0	Retroclined lower incisor
Upper incisal display	3.17	2.5	1.5	Normal incisal display
Upper lip to E-plane	−3.42	0	2.0	Retruded upper lip
Lower lip to E-plane	−2.22	0	2.0	Retruded lower lip
Nasolabial angle	114.84	95	5.0	Retruded lip
Extraction Index	159.69	153.8	7.8	Normal

Figure 3. Initial panoramic radiograph.

Orthodontic treatment was initiated before the onset of the SARS-CoV-2 pandemic. At that time, the patient did not have the HPV or SARS-CoV-2 infection and followed her regular orthodontic appointments at about 4–6 weeks. After the pandemic onset, which comprised also a period of two months of closed dental offices in our country (mid-March to mid-May 2020), treatment visits became rare, about 8–10 weeks, and the patient missed a few appointments. Protocols for treating patients during the pandemic have been continuously updated. Risk assessment of the pandemic situation has to be adhered [29], and the new dental guidelines related to treating patients should be honored according to the office's location [30], emergencies being admissive and other dental procedures being postponed.

During the above mentioned period, the patient failed to follow a few appointments, which usually were scheduled monthly, due to the overlap of a genital HPV infection (May 2020). The patient achieved a genital HPV 58 infection, which was diagnosed by real-time PCR multiplex technology, a test that allows simultaneous detection of 19 HPV high-risk types (16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 69, 73, 82) and 9 low-risk HPV types (6, 11, 40, 42, 43, 44, 54, 61, 70) as well as intern control. Intern control inspected PCR reaction to each sample. Every reaction was monitored by using six positive intern controls and two negative intern controls. Biopsy of the cervix revealed cervical intraepithelial neoplasia grade 1. Immunohistochemistry using Benchmark Gx Ventana-Roche platform showed intense inflammatory cervicitis and pavement epithelium with nuclear atypia, suggestive for a low-grade squamous intraepithelial lesion (LSIL).

No signs or symptoms of oral HPV were noted. During the infection and treatment for HPV, the patient missed three appointments due to her medical condition; whilst she had her surgery, the orthodontic treatment time was prolonged and tooth movement difficult; in addition, the response of the periodontium to the orthodontic forces was impracticable and incompliant. An increase of tooth mobility was observed clinically. Unanticipated difficulties, such as debonded brackets, space appearance, broken wires, lower incisor proclination, lost springs, and exposed end of wire, occurred. In spite of the HPV onset, leveling and alignment of the arches were acceptable, and the occlusal plane was successfully corrected. However, no significant periodontal pathology (severe alveolar bone loss, gingival recession, loss of tooth vitality) occurred at the end of the treatment (Figure 4).

Figure 4. Final panoramic radiograph.

4. Discussion

As previously stated, HPV infections became more frequent among young patients in an oropharyngeal manifestation, which have to be considered when planning a complex treatment plan, especially an orthodontic therapy. While this systematic review aimed to identify any correlations between ongoing orthodontic treatments along with their outcomes and HPV infection, the literature suggests a lack of such data so far. Out of the six articles included, five were case reports or case series of different oral lesions superposed with an HPV infection (confirmed or not). These studies do not concentrate whatsoever on the effects of the orthodontic therapy but rather on the diagnostic, treatment, and prognostic of the oral manifestations presented. In addition, an interesting approach was identified in the paper published by Schott et al., which investigated, through a questionnaire form, 233 women's personal history of orthodontic care, long-term satisfaction, as well as adherence to dental and gynecological screening [23]. Based on the findings, the authors suggested that it might be strong association between the level of interest towards orthodontic treatments in childhood and the level of prevention in adulthood along with the level of education, making referrals to HPV infection as well.

Orthodontic tooth movement is consequent of an alternation of bone resorption and bone formation, which takes place yearlong [31], and could reach a period of two or more years [32,33], being stimulated by remodeling of the periodontal ligament and the alveolar bone and these remodeling processes of the ligaments and alveolar bone being accompanied by an inflammatory process [34].

Treating class 2 malocclusion is challenging relating to the dental and skeletal problems as regards achieving stable results and sparing the periodontal tissues. This prolonged time interval could influence the teeth mobility as well as the support tissues: the periodontal ligament and alveolar bone. Associated pathology or general disease may also have a major role on tooth movement and the response to orthodontic forces. Prolonging the appliance activation period for better healing and optimal stability could improve prevention of alveolar bone loss or tooth ankylosis. Another aid in delivering a safe treatment strategy is to shorten the treatment time. Procedures that could shorten the treatment time have been described, such as distraction osteogenesis [35], corticotomies of the alveolar process [36], osteoperforation [37–39], corticision [40], piezocision [41], vibrational forces [42], and low-dose laser application [43]. The amount and rate of tooth movement are hinged to the biological response of the applied forces and the amount of bone turnover [38].

The HPV infection of the patient was discovered due to the appearance of a characteristic macroscopic wart in the genital area. Cervical cytology by Pap test revealed atypical squamous cells of undetermined significance (ASC-US). After that, orthodontic treatment became subsidiary.

Deferring orthodontic treatment until the cure of the HPV infection will prolong the treatment period, with possible repercussions. Ankylosis, root resorption, and marginal bone loss can be associated with prolonged orthodontic treatment time due to the superposition of the HPV infection. The increased treatment time may also lead to unsatisfactory treatment outcome, as also reported by Umeh et al. [44]. Shortening treatment time would aid in avoiding problems that might occur during orthodontic treatment, especially in case of a general disease superposition, which might affect final outcome. Likewise, iatrogenic disorders might occur during orthodontic treatment if forces are heavy or treatment time prolonged: root resorption (inflammatory or of unknown etiology), alveolar bone loss, increased tooth mobility, and periodontal pockets. Shortening treatment time would aid in avoiding problems that might occur during orthodontic treatment, achieving the treatment goal without affecting the treatment outcome.

Human papillomavirus was first described as "human warts virus" implicated in the pathogenesis of laryngeal papillomatosis and genital warts, also being described as having a potential carcinogenetic role [45]. In as far as having such an important role in developing malignancies of the upper digestive tract, it is interesting to note a possible influence also on ongoing treatments, especially those who induce a modification of the cellular response to bone resorption and bone remodeling, as an orthodontic treatment does. It may play a role in the pathogenesis of cell turnover. However, in the literature are a few reports linked to orthodontics and HPV infection. A higher prevalence of HPV infection is reported in the anogenital region compared to the oral cavity [46], with women presenting the highest disease burden [47]. The management of the disease depends upon its evolution, which can be spontaneous regression or high-grade dysplasia or invasive carcinoma [48].

Routine screening of patients needing orthodontic treatment is not performed although screening for HPV infection is extremely important. We want to emphasize this aspect and draw attention on this subject, as such rare cases can occur by chance. It is essential to know about the etiology, prevention, and treatment of HPV related tooth mobility in as much as HPV is a risk factor for increasing tooth mobility in patients with ongoing orthodontic treatment. Screening for HPV is extremely important, as HPV genotyping significantly improves detection rate of high-grade cervical intraepithelial lesions [49]. It is shown that HPV status of tumors has a relationship with response to treatment and survival rates [50]; therefore, the major role of the dentist in prevention and patient education must be emphasized.

Unfortunately, there are no available guidelines regarding screening for HPV-related malignancies in other anatomic sites [51]. In light of these findings, knowing the effects of HPV infection on oral cavity, vaccines should be considered and their preventive role discussed with the patient. A good alternative would be the administration of the vaccine by dentists or orthodontists. Therefore, discussions about HPV vaccinations in the dental practice are welcome [52].

Future recommendations: screening children and young adolescences for HPV is an area of great interest, which necessitates future research since HPV may relate to the treatment encroachment. Complete oral examinations as a routine in orthodontic treatment may contribute to the early diagnosis of HPV-related symptoms.

A limitation of this study may be the absence of any oral manifestations of the HPV infection and the lack of communication between patient and practitioner due to the embarrassment associated with HPV infection.

5. Conclusions

Based on the findings obtained through the systemic review, literature suggests that HPV infections are increasing in young patients, and the oral manifestations might be identified via intraoral examinations by dental practitioners of any specialization, including orthodontics.

Incumbent, postponed ongoing orthodontic treatment because of HPV infection might affect treatment outcome and patient compliance. Treatment time lengthens, and unwanted impediments can come into existence. Orthodontists should treat patients while taking into account superposed disease that might influence treatment outcome by prolonging treatment time and influencing the responding support tissues.

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References

1. Bihl, M.P.; Tornillo, L.; Kind, A.B.; Obermann, E.; Noppen, C.; Chaffard, R.; Wynne, P.; Grilli, B.; Foerster, A.; Terracciano, L.M.; et al. Human papillomavirus (HPV) detection in cytologic specimens: Similarities and differences of available methodology. *Appl. Immunohistochem. Mol. Morphol.* **2017**, *25*, 184. [CrossRef]
2. Ozaydin-Yavuz, G.; Bilgili, S.G.; Guducuoglu, H.; Yavuz, I.H.; Elibuyuk-Aksac, S.; Karadag, A.S. Determinants of high-risk human papillomavirus infection in anogenital warts. *Postepy Dermatol. Alergol.* **2019**, *36*, 76–81. [CrossRef]
3. Ameli, N.; Sohanian, S.; Jalili Sadrabad, M. Dysplasia in Papilloma at the Tip of the Tongue; a Rare Entity-importance of on Time Prevention. *Casp. J. Health Res.* **2021**, *6*, 147–150. [CrossRef]
4. Nayak, A.; Nayak, M.T. Oral squamous papilloma occurring on the palate with review of literature. *J. Exp. Ther. Oncol.* **2016**, *11*, 319–324.
5. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Human Papillomaviruses. In *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*; WHO: Geneva, Switzerland, 2007; Volume 90, 636p.
6. Poelman, M.R.; Brand, H.S.; Forouzanfar, T.; Daley, E.M.; Jager, D.H.J. Prevention of HPV-Related Oral Cancer by Dentists: Assessing the Opinion of Dutch Dental Students. *J. Cancer Educ.* **2018**, *33*, 1347–1354. [CrossRef]
7. World Health Organization. Electronic address: Sageexecsec@who.int. Human papillomavirus vaccines: WHO position paper, May 2017-Recommendations. *Vaccine* **2017**, *35*, 5753–5755. [CrossRef]
8. Toner, M.; O'Regan, E.M. Head and neck squamous cell carcinoma in the young: A spectrum or a distinct group? Part 1. *Head Neck Pathol.* **2009**, *3*, 246–248. [CrossRef]
9. Berman, T.A.; Schiller, J.T. Human papillomavirus in cervical cancer and oropharyngeal cancer: One cause, two diseases. *Cancer* **2017**, *123*, 2219–2229. [CrossRef]
10. Ao, M.; Zheng, D.; Wang, J.; Gu, X.; Xi, M. A retrospective study of cytology and HPV genotypes results of 3229 vaginal intraepithelial neoplasia patients. *J. Med. Virol.* **2022**, *94*, 737–744. [CrossRef]
11. Jnaneswar, A.; Goutham, B.S.; Pathi, J.; Jha, K.; Suresan, V.; Kumar, G. A Cross-sectional Survey Assessing Knowledge, Attitude, and Practice Regarding Oral Cancer among Private Medical and Dental Practitioners in Bhubaneswar City. *Indian J. Med. Paediatr. Oncol.* **2017**, *38*, 133–139. [PubMed]
12. Matkins, P.P. Sexually transmitted infections in adolescents. *North Carol. Med. J.* **2013**, *74*, 48–52. [CrossRef]
13. Rautava, J.; Syrjänen, S. Human papillomavirus infections in the oral mucosa. *J. Am. Dent. Assoc.* **2011**, *142*, 905–914. [CrossRef] [PubMed]
14. Fiorillo, L.; Cervino, G.; Surace, G.; De Stefano, R.; Laino, L.; D'Amico, C.; Fiorillo, M.T.; Meto, A.; Herford, A.S.; Arzukanyan, A.V.; et al. Human Papilloma Virus: Current Knowledge and Focus on Oral Health. *Biomed. Res. Int.* **2021**, *2021*, 6631757. [CrossRef] [PubMed]

15. Crimi, S.; Fiorillo, L.; Bianchi, A.; D'Amico, C.; Amoroso, G.; Gorassini, F.; Mastroieni, R.; Marino, S.; Scoglio, C.; Catalano, F.; et al. Herpes Virus, Oral Clinical Signs and QoL: Systematic Review of Recent Data. *Viruses* **2019**, *11*, 463. [CrossRef]
16. Gameiro, S.F.; Zhang, A.; Ghasemi, F.; Barrett, J.W.; Nichols, A.C.; Mymryk, J.S. Analysis of Class I Major Histocompatibility Complex Gene Transcription in Human Tumors Caused by Human Papillomavirus Infection. *Viruses* **2017**, *9*, 252. [CrossRef]
17. Fuster-Rossello, L.; Ribotta, E.; Cuffini, C.; Fuster-Juan, M. Human papilloma virus in oral mucosa and its association with periodontal status of gynecologically infected women. *Acta Odontol. Latinoam.* **2014**, *27*, 82–88.
18. Nascimento, A.C.D.S.; Nocetti, M.C.; Lugo, L.Z.A.; Jacob, C.M.B.; Machado, A.P.; Padovani, C.T.J.; Ferreira, A.M.T.; Fernandes, C.E.D.S.; Tozetti, I.A. Oncogenic high-risk human papillomavirus in patients with full denture. *Braz. Oral Res.* **2019**, *33*, e091. [CrossRef]
19. Nishimura, Y.; Maeda, H.; Hattori, M.; Azumaya, F.; Muramatsu, I.; Kameyama, Y.; Tanaka, Y.; Kawaguchi, T. Human papillomavirus infection in the oral cavity of denture wearers. *Nihon Hotetsu Shika Gakkai Zasshi* **2004**, *48*, 713–722. [CrossRef]
20. Tezal, M.; Sullivan Nasca, M.; Stoler, D.L.; Melendy, T.; Hyland, A.; Smaldino, P.J.; Rigual, N.R.; Loree, T.R. Chronic periodontitis-human papillomavirus synergy in base of tongue cancers. *Arch. Otolaryngol.-Head Neck Surg.* **2009**, *135*, 391–396. [CrossRef]
21. Mazul, A.L.; Taylor, J.M.; Divaris, K.; Weissler, M.C.; Brennan, P.; Anantharaman, D.; Abedi-Ardekani, B.; Olshan, A.F.; Zevallos, J.P. Oral health and human papillomavirus-associated head and neck squamous cell carcinoma. *Cancer* **2017**, *123*, 71–80. [CrossRef]
22. Moher, D.; Shamseer, L.; Clarke, M.; Ghersi, D.; Liberati, A.; Petticrew, M.; Shekelle, P.; Stewart, L.A.; PRISMA-P Group. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 Statement. *Syst. Rev.* **2015**, *4*, 1. [CrossRef] [PubMed]
23. Schott, S.; Heinzler, J.; Rippinger, N.; Bruckner, T.; Brucker, J.; Hoffmann, J.; Dornhöfer, N.; Dinkic, C.; Seitz, S.; Rom, J.; et al. Adherence to gynecological screening impacted by experienced orthodontic treatment in childhood. *Arch. Gynecol. Obstet.* **2019**, *299*, 167–171. [CrossRef] [PubMed]
24. Santos-Silva, A.R.; Carvalho Andrade, M.A.; Jorge, J.; Almeida, O.P.; Vargas, P.A.; Lopes, M.A. Tongue squamous cell carcinoma in young nonsmoking and nondrinking patients: 3 clinical cases of orthodontic interest. *Am. J. Orthod. Dentofac. Orthop.* **2014**, *145*, 103–107. [CrossRef]
25. Noonan, V.L.; Woo, S.B.; Sundararajan, D.; Kabani, S.; Gallagher, G. Idiopathic gingival papillokeratosis with crypt formation, a report of 7 cases of a previously undescribed entity: Possible unusual oral epithelial nevus? *Oral Surg. Oral Med. Oral Pathol. Oral Radiol.* **2017**, *123*, 358–364. [CrossRef] [PubMed]
26. Henn, I.W.; Galina, G.; Chaiben, C.L.; Kula, J.; dos Santos, J.N.; Soares de Lima, A.A. Multiple oral condyloma acuminatum in a patient with HIV/AIDS—A case report. *Pol. Przegląd Otorynolaryngologiczny* **2014**, *3*, 160–164. [CrossRef]
27. Moine, L.; Gilligan, G. Trichloroacetic Acid for localized juvenile spongiotic gingival hyperplasia: A case report with a novel treatment. *Pediatr. Dent. J.* **2018**, *28*, 47–51. [CrossRef]
28. Magalhaes, M.A.; Somers, G.R.; Sikorski, P.; Forte, V.; Abouzgia, M.; Barrett, E.; Bradley, G. Unusual presentation of squamous cell carcinoma of the maxilla in an 8-year-old child. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol.* **2016**, *122*, e179–e185. [CrossRef]
29. Malekshoar, M.; Malekshoar, M.; Javanshir, B. Challenges, limitations, and solutions for orthodontists during the coronavirus pandemic: A review. *Am. J. Orthod. Dentofac. Orthop.* **2021**, *159*, e59–e71. [CrossRef]
30. Suri, S.; Vandersluis, Y.R.; Kochhar, A.S.; Bhasin, R.; Abdallah, M.N. Clinical orthodontic management during the COVID-19 pandemic. *Angle Orthod.* **2020**, *90*, 473–484. [CrossRef]
31. Nishimura, M.; Chiba, M.; Ohashi, T.; Sato, M.; Shimizu, Y.; Igarashi, K.; Mitani, H. Periodontal tissue activation by vibration: Intermittent stimulation by resonance vibration accelerates experimental tooth movement in rats. *Am. J. Orthod. Dentofac. Orthop.* **2008**, *133*, 572–583. [CrossRef]
32. Cramer, C.L.; Campbell, P.M.; Opperman, L.A.; Tadlock, L.P.; Buschang, P.H. Effects of micro-osteoperforations on tooth movement and bone in the beagle maxilla. *Am. J. Orthod. Dentofac. Orthop.* **2019**, *155*, 681–692. [CrossRef] [PubMed]
33. Mavreas, D.; Athanasiou, A.E. Factors affecting the duration of orthodontic treatment: A systematic review. *Eur. J. Orthod.* **2008**, *30*, 386–395. [CrossRef] [PubMed]
34. Yamaguchi, M.; Fukasawa, S. Is Inflammation a Friend or Foe for Orthodontic Treatment?: Inflammation in Orthodontically Induced Inflammatory Root Resorption and Accelerating Tooth Movement. *Int. J. Mol. Sci.* **2021**, *22*, 2388. [CrossRef] [PubMed]
35. Liou, E.J.; Huang, C.S. Rapid canine retraction through distraction of the periodontal ligament. *Am. J. Orthod. Dentofac. Orthop.* **1998**, *114*, 372–382. [CrossRef]
36. Wilcko, W.; Wilcko, M.T. Accelerating tooth movement: The case for corticotomy-induced orthodontics. *Am. J. Orthod. Dentofac. Orthop.* **2013**, *144*, 4–12. [CrossRef]
37. Alikhani, M.; Raptis, M.; Zoldan, B.; Sangsuwon, C.; Lee, Y.B.; Alyami, B.; Corpodian, C.; Barrera, L.M.; Alansari, S.; Khoo, E.; et al. Effect of micro-osteoperforations on the rate of tooth movement. *Am. J. Orthod. Dentofac. Orthop.* **2013**, *144*, 639–648. [CrossRef]
38. Al-Khalifa, K.S.; Baeshen, H.A. Micro-osteoperforations and Its Effect on the Rate of Tooth Movement: A Systematic Review. *Eur. J. Dent.* **2021**, *15*, 158–167. [CrossRef]
39. Nimeri, G.; Kau, C.H.; Abou-Kheir, N.S.; Corona, R. Acceleration of tooth movement during orthodontic treatment: A frontier inorthodontics. *Prog. Orthod.* **2013**, *14*, 42. [CrossRef]
40. Kim, S.J.; Park, Y.G.; Kang, S.G. Effects of Corticision on paradental remodeling in orthodontic tooth movement. *Angle Orthod.* **2009**, *79*, 284–291. [CrossRef]

41. Papadopoulos, N.; Beindorff, N.; Hoffmann, S.; Jost-Brinkmann, P.G.; Präger, T.M. Impact of piezocision on orthodontic tooth movement. *Korean J. Orthod.* **2021**, *51*, 366–374. [CrossRef]
42. Telatar, B.C.; Gungor, A.Y. Effectiveness of vibrational forces on orthodontic treatment: A randomized, controlled clinical trial. *J. Orofac. Orthop.* **2021**, *82*, 288–294. [CrossRef] [PubMed]
43. Abdelhameed, A.N.; Refai, W.M.M. Evaluation of the effect of combined low energy laser application and micro-osteoperforations versus the effect of application of each technique sepa-rately on the rate of orthodontic tooth movement. *Open Access Maced. J. Med. Sci.* **2018**, *6*, 2180–2185. [CrossRef] [PubMed]
44. Umeh, O.D.; Utomi, I.L.; Isiekwe, I.G.; Aladenika, E.T. Impact of the coronavirus disease 2019 pandemic on orthodontic patients and their attitude to orthodontic treatment. *Am. J. Orthod. Dentofac. Orthop.* **2021**, *159*, e399–e409. [CrossRef] [PubMed]
45. zur Hausen, H. Papillomaviruses in the causation of human cancers—A brief historical account. *Virology* **2009**, *384*, 260–265. [CrossRef]
46. Giuliano, A.R.; Nyitray, A.G.; Kreimer, A.R.; Pierce Campbell, C.M.; Goodman, M.T.; Sudenga, S.L.; Monsonego, J.; Franceschi, S. EUROGIN 2014 roadmap: Differences in human papillomavirus infection natural history, transmission and human papillomavirus-related cancer incidence by gender and anatomic site of infection. *Int. J. Cancer* **2015**, *136*, 2752–2760. [CrossRef]
47. Ntanasis-Stathopoulos, I.; Kyriazoglou, A.; Liontos, M.A.; Dimopoulos, M.; Gavriatopoulou, M. Current trends in the management and prevention of human papillomavirus (HPV) infection. *J. BUON* **2020**, *25*, 1281–1285.
48. zur Hausen, H. Papillomaviruses and cancer: From basic studies to clinical application. *Nat. Rev. Cancer* **2002**, *2*, 342–350. [CrossRef]
49. Lewitowicz, P.; Nasierowska-Guttmejer, A.; Rokita, W.; Adamczyk-Gruszka, O.; Gluszek, S.; Chrapek, M.; Kolos, M.; Wrona-Cyranowska, A.; Misiek, M. HPV genotyping and p16/Ki-67 test significantly improve detection rate of high-grade cervical squamous intraepithelial lesion. *Arch. Med. Sci.* **2019**, *16*, 87–93. [CrossRef]
50. Tastekin, E.; Caloglu, V.Y.; Durankus, N.K.; Sut, N.; Turkkan, G.; Can, N.; Puyan, F.O.; Caloglu, M. Survivin expression, HPV positivity and microvessel density in oropharyngeal carcinomas and relationship with survival time. *Arch. Med. Sci.* **2017**, *13*, 1467–1473. [CrossRef]
51. Burd, E.M.; Dean, C.L. Human Papillomavirus. *Microbiol. Spectr.* **2016**, *4*. Available online: https://journals.asm.org/doi/10.1128/microbiolspec.DMIH2-0001-2015 (accessed on 28 January 2022). [CrossRef]
52. Stull, C.; Freese, R.; Sarvas, E. Parent perceptions of dental care providers' role in human papillomavirus prevention and vaccine advocacy. *J. Am. Dent. Assoc.* **2020**, *151*, 560–567. [CrossRef] [PubMed]

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Review

Intrusion of Maxillary Posterior Teeth by Skeletal Anchorage: A Systematic Review and Case Report with Thin Alveolar Biotype

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Abstract: This study aimed to review the literature related to the intrusion of maxillary posterior teeth in subjects needing pre-prosthetic restoration or orthodontic treatment due to anterior open bite, and to report a thin alveolar biotype case needing a pre-prosthetic intrusion of maxillary teeth by introducing a novel, personalized method of intrusion measurement. An electronic search was conducted between February 2022 and March 2022 in the following databases: PubMed, Scopus, Embase, Web of Science, and Lilacs; the terms "tooth movement techniques", "orthodontic anchorage procedures", "tooth intrusion", "intrusion", "molar", "premolar", and "human" were surveyed. Eighteen articles were included in this review; the mean amount of intrusion ranged from between 2.1 ± 0.9 mm and 4.57 ± 0.98 mm (being mostly 2–3 mm). The intrusion force varied between 100 and 500 g; 10 articles reported miniscrews (MS), 7 reported zygomatic plates (ZP), and 1 publication reported both anchorage types. The average treatment time was 6.9 months for MS and 7.9 months for ZP. Levelling the occlusal plane by intrusion of the upper posterior teeth can be achieved by skeletal anchorage. The stability of the obtained results, shortening treatment time, and controlling treatment outcome are the main goals for a complex surgical and orthodontic treatment approach.

Keywords: maxillary posterior tooth intrusion; skeletal anchorage; orthodontics; thin alveolar bone

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1. Introduction

Levelling the occlusal plane remains one of the major concerns in dentistry, especially in adult patients, due to the complex and multidisciplinary approach, as well as the skeletal component of the condition. Intrusion of the maxillary posterior teeth needs to be performed for open bite correction [1], or for prosthetic reasons, in order to level the occlusal plane due to overerupted molars attributable to post-extraction consequences. The true molar intrusion was considered rendered when the reference point to quantify the vertical movement of the molar in the dentoalveolar bone was the center of resistance of the tooth [2].

Occlusal interferences and functional disturbances may result in difficulties during prosthetic reconstruction [3]. Levelling the occlusal plane, including occlusal equilibration, is needed in cases with overerupted upper posterior teeth. This can be accomplished by root canal therapy with dental reshaping and prosthetic treatment [4], or by orthodontic intrusion using skeletal anchorage [5,6], surgical assisted impaction using corticotomy [7], or orthodontic surgery [8], ranging to much more extensive surgery, such as a LeFort I osteotomy with maxillary rotation [9]. A more frequent surgical technique in such cases is represented by the lateral maxillary segmental osteotomy, followed by the apical repositioning of the bone fragment [10]. This way, the intrusion effect is achieved instantly. However, the disadvantages associated with this technique (extensive surgery with the inherent postoperative discomfort, the need for a surgical splint) often convince the patient to decide in favor of a less invasive technique.

Temporary anchorage devices (TADs) represent an orthodontic treatment option, which is minimally invasive and aids in molar intrusion without needing the patient's compliance [11]. Miniscrews, or miniplates, usually placed in the zygomatic buttress, can be used as TADs; molar intrusion obtained by skeletal anchorage is preferred compared to jaw surgery in severe open bite cases [12]. From a surgical point of view, miniscrew efficiency depends on bone density and soft tissue health [13]. The greatest amount of alveolar bone is located in the maxilla between the second premolar and the first molar [14]. Placement for the insertion of the miniscrews is influenced by the malocclusion and the quality and amount of appropriate bone, particularly in the interdental root space [15].

In adult patients, one of the most challenging malocclusions to correct with orthodontic treatment is anterior open bite [16], as this requires a complex multidisciplinary approach which draws on both surgical and orthodontic approaches. Treatment alternatives comprise molar intrusion, incisor extrusion, and maxillary impaction. A surgical approach, such as corticotomy, may aid in molar intrusion, limiting treatment time [17], although there are complications related to this strategy.

In performing an intrusive movement, the relationship between the maxillary posterior root apices to the inferior wall of the sinus should be considered, since the cortical bone layer of the maxillary sinus wall could represent a barrier to the intrusion [18]. Cone-beam computed tomography (CBCT) provides an accurate evaluation of the maxillary bone quality and quantity around the root apices of posterior teeth [19]. There is a current lack of studies evaluating true molar intrusion. A systematic review, due to its methodological rigor, represents evidence-based medicine when referring to unbiased knowledge syntheses [20].

To the best of our knowledge, a review related to the pre-prosthetic and orthodontic intrusion need of the maxillary posterior teeth has not yet been published. The aim of this study was to review the literature related to the intrusion of maxillary posterior teeth in subjects needing pre-prosthetic restoration or orthodontic treatment due to anterior open bite, and to report a thin alveolar biotype case needing pre-prosthetic intrusion of maxillary premolars and molars in order to develop a customized maxillary plane to propose a novel, personalized method of measuring intrusion. The clinical significance arises from the belief that the new palatal plane is simple to construct, assists in aligning the maxilla parallel to a specified reference line, and can also be performed in segmental CBCT images.

2. Materials and Methods

This review was performed following the recommendations of the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA) Statement" [21].

2.1. Information Sources

A structured electronic search was conducted between February 2022 and March 2022 in the following databases: PubMed, Scopus, Embase, Web of Science, and Lilacs. Additionally, MeSH and Emtree terms were used, where applicable. Finally, a handsearching of relevant studies was performed.

2.2. Search Strategy

The research strategy was constructed on the PICO framework (P—patient; I—intervention; C—Comparison; O—Outcome), as follows: P—patients with extrusion of upper posterior teeth; I—intrusion; C—no intervention; O—the amount of intrusion [22].

The terms "tooth movement techniques", "orthodontic anchorage procedures", "tooth intrusion", "intrusion", "molar", "premolar", and "human" were surveyed. The retrieved publications were imported into and organized in the Rayyan online software [23]. This software permitted a structured organization of the publications. Additionally, an automatized removal of the duplicates was possible, after carefully reading and deciding if the highlighted publication was a real duplicate. Two researchers independently accomplished the search and performed the selection, with the “blind on” mode turned on, for eliminating selection bias. Any disagreements were resolved by discussion and consultation between them and with a third author. For the assessment of each publication, Microsoft Excel spreadsheets (Microsoft Office 365, MS, Redmond, WA, USA) [24] were assembled, using Zotero 6.0.6 software (Corporation for Digital Scholarship, previously Center for History and New Media at George Mason University) [25].

The following inclusion criteria were pursued: human subjects requiring maxillary posterior tooth intrusion (molar or premolar), due to pre-prosthetic reasons to anterior open bite malocclusion; intrusion performed by skeletal anchorage (miniscrews or zygomatic plate); no previous orthodontic treatment; no orthognathic surgery; no tooth extractions; no active periodontal disease; no associated pathologies; publications with available full text in English language. The following exclusion criteria were considered: patients with systemic diseases; metabolic bone disorders; surgical assisted maxillary posterior teeth intrusion; photobiomodulation or other intrusion aiding techniques; intrusion followed by distalisation with the same anchorage device; mandibular molar intrusion; orthodontic treatments which involved tooth extractions, distalisation, mesialisation or rapid palatal expansion; orthognathic surgery; case reports; literature reviews, abstracts, and animal studies.

3. Results

3.1. Data Collection

A total of 1522 records were identified, consisting of 191 from PubMed, 483 from Scopus, 140 from Embase, 363 from Web of Science, and 345 from Lilacs. After screening the duplicates, 333 records were excluded by automation tools. The titles, keywords, and abstracts of the remaining 1189 records were read, and 1091 records were excluded for not being related to the topic, or for not respecting the inclusion and exclusion criteria, as well as for being background articles, books, case reports, reviews, or animal studies. Ninety-eight records were sought for retrieval. Ninety-six articles were identified for eligibility, which met the inclusion criteria, and were checked for eligibility by full-text analysis. After careful reading and assessing the publications, a final number of 18 articles were selected and included in this review. The PRISMA diagram is shown in Figure 1.

3.2. Description of the Studies

Data were extracted using a standardized form, which included the following information: (1) authors’ names and publication year; (2) country; (3) aim of intrusion, (4) sample size, age range, and gender; (5) anchorage type; (6) intrusion measurement method; (7) intrusion range; (8) intrusion force; (9) treatment time; (10) outcomes; (11) side effects; and (12) conclusions.

Table 1 summarizes the basic characteristics of the publications evaluated in this research. Due to the heterogeneousness and the multiplicity of outcome measures among the included studies, meta-analysis was not achievable [26].

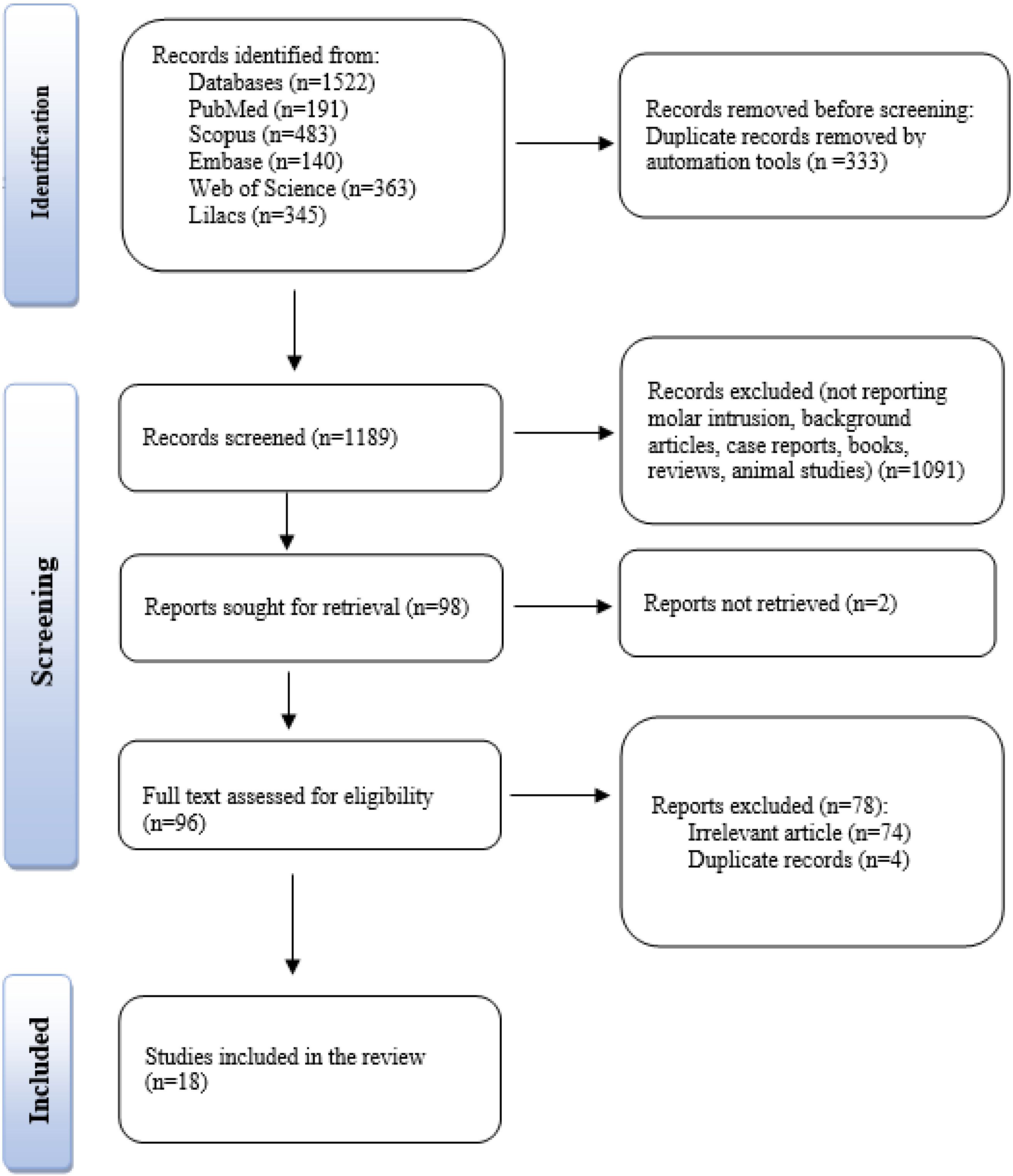


Figure 1. The PRISMA flowchart of the publication selection.

Table 1. Characteristics of the reviewed studies. Abbreviations are as defined as follows: IA—intrusion aim; IMM—intrusion measurement method; IR—Intrusion range; IF—intrusion force; TT—treatment time; OVE—overerupted; AOB—anterior open bite; MS—miniscrew, ZP—zygomatic plate, LC—lateral cephalogram, PAR—postero-anterior radiographs; PR—panoramic radiograph, CBCT—cone-beam computed tomography, NiTi—nickel-titanium; U6—upper first molar, PP—palatal plane; OB—overbite; FH—Frankfurt horizontal plane; T—trifurcation; PM—premolar; EARR—external apical root resorption; SN—sella to nasion plane, NA—not available.

Author, Publication Year	Country	IA	Sample Size, Age Range, Gender	Anchorage Type	IMM	IR	IF	TT	Outcomes	Side Effects	Conclusions
Akan B et al., 2020 [27]	Turkey	AOB	19 patients, (5 boys, 14 girls) 16.5 years	ZP, bilateral, acrylic appliance	LC	2.32 ± 2.13 mm	400 g, NiTi close coil springs	9.4 ± 0.7 months	U6 to PP occlusal plane OB anterior facial height	NA	"posterior dentoalveolar intrusion by zygomatic anchorage was an effective method for anterior open bite treatment"
Akl HE et al., 2020 [28]	Egypt	AOB	Intervention group: 10 subjects Control group: 10 subjects 18 to 25 years	4 MS: 2 infrazygomatic and 2 palatal	CBCT	Intervention group: 2.26 ± 1.87 mm Control group: 2.42 ± 2.06 mm	intervention group: 400 g NiTi closed coil springs control group: 200 g	6 months	U6 T or PM center to FH OB	Soft tissue overgrowth loose of two miniscrews	"no statistically significant difference in the amount of posterior teeth intrusion between 200 g and 400 g of applied intrusive force" "amount of intrusion increased gradually as the tooth was located more posteriorly, closer to the line of traction"

Table 1. *Cont.*

Author, Publication Year	Country	IA	Sample Size, Age Range, Gender	Anchorage Type	IMM	IR	IF	TT	Outcomes	Side Effects	Conclusions
Al-Falahi B et al., 2018 [29]	Egypt	AOB	15 patients (13 females and 2 males), 14.5 to 22 years (mean age 18.1 ± 2.03 years)	MS, buccal	CBCT	2.79 ± 0.46 mm	300 g, elastomeric chain	5.1 ± 1.3 months	U6 to PP	EARR	"all evaluated teeth had statistically significant EARR; but, because of its small magnitude, it should be considered as clinically irrelevant"
Ari-Demirkaya A et al., 2005 [30]	Turkey	AOB	Study group: 16 (13 females, 3 males) 19.25 years (range 14–26 years) subjects control group: 16 subjects 19.43 years (range 14–25 years)	ZP	PR	NA	NA, closed Ni-Ti coil springs	NA	U6 tooth length	EARR	"apical root resorption of maxillary first molars after intrusion was done using zygomatic miniplates as skeletal anchorage was not clinically significantly different from apical root resorption associated with fixed orthodontic treatment without intrusion mechanics"

Table 1. *Cont.*

Author, Publication Year	Country	IA	Sample Size, Age Range, Gender	Anchorage Type	IMM	IR	IF	TT	Outcomes	Side Effects	Conclusions
Ding WH et al., 2015 [31]	China	AOB	36 patients: 18 hyperdivergent 18 hypodivergent females (aged 20–42 years (28.93 ± 7.55	MS, buccal	CBCT	Hyperdivergent: 4.57 mm ± 0.98 Hypodivergent: 3.64 mm ± 1.25	100 g, elastomeric chains	Hyperdivergent: 3.13 months ± 0.90 Hypodivergent: 4.71 months ± 1.50	Difference of U6 distal buccal cusp-FH plane (DB-FH) + mesial buccal cusp-FH plane (MB-FH)/2	Miniscrew implants loose difference and change of bone during intrusion	"absolute molar intrusion could be achieved by miniscrew implant... more easily in hyperdivergent"
Heravi F et al., 2011 [32]	Iran	AOB	10 females (mean age 43.6 years, range 25 to 57 years)	MS, buccal, and palatal	Parallel periapical radiographs	2.1 ± 0.9 mm	100 g, occlusal arm with a force gauge hook	7.7 months (range: 4.3 to 11.5 months)	A reference axis of 2 landmarks in adjacent teeth a perpendicular line from this axis to each root apex	Dull pain on the day after surgery tongue irritation root resorption (mean 0.2 mm) intrusion relapse	"there was a significant correlation between treatment duration and mesiobuccal root resorption. No significant correlation was found between patient age and the amount of root resorption and intrusion"

Table 1. *Cont.*

Author, Publication Year	Country	IA	Sample Size, Age Range, Gender	Anchorage Type	IMM	IR	IF	TT	Outcomes	Side Effects	Conclusions
Kim K et al., 2018 [33]	Korea	AOB	21 patients (3 men, 18 women); mean age 23.9 years (range 18.5–36.4)	MS, buccal, and palatal	LC	2.2 ± 0.8 mm	NA	9.7 ± 3.2 months (range, 6.2–15.2 months)	U6 to PP	NA	"mandible exhibited counterclockwise rotation after maxillary molar intrusion; the center of mandibular autorotation was located behind and below condylion with individual variations" "the amount of molar intrusion demonstrated relationships with vertical and sagittal cephalometric parameters"
Li W et al., 2013 [34]	China Australia	OVE U6	12 patients (4 male; 8 female) 18 to 32 years, mean age: 24.3 ± 1.26 years	MS, buccal, and palatal	CBCT	3.3 ± 1.6 mm	150 g, elastic chain	6 ± 1.59 months; range: 4 to 9 months	Crown's central fossa to reference plane	Root resorption	"volume measurements using CBCT could effectively evaluate the root resorption caused by mini-screw intrusion"
Marzouk ES et al., 2015 [35]	Egypt	AOB	13 patients (9 females; 4 males) mean age 18 years, 8 months ± 2 years, 2 months	ZP	LC	3.1 ± 0.74 mm (range: 2–4 mm)	450 g, NiTi closed coil spring	9 ± 2.5 months	U6 to PP	NA	"intrusion of the posterior teeth with skeletal anchorage induced counterclockwise rotation of the mandible"

Table 1. *Cont.*

Author, Publication Year	Country	IA	Sample Size, Age Range, Gender	Anchorage Type	IMM	IR	IF	TT	Outcomes	Side Effects	Conclusions
de Oliveira TFM et al., 2015 [36]	Brazil	AOB	9 patients (6 females, 3 males; mean age 18.7 ± 5.1 years)	ZP	LC oblique radiographs at 45°	2.03 ± 0.87 mm	450–500 g, elastomeric chains	6 months	Anteroposterior position of the molar cusp and root apex The vertical position of the molar cusp and root apex	Possible root resorption	"skeletal anchorage provided intrusion of molars without changing the palatal plane angle"
Paccini JV et al., 2016 [37]	Brazil	OVE U6	19 patients (4 males, 15 females) Group 1: mean age 34.25 years ± 8.22 (range: 22.66–46.99) Group 2: mean age 39.47 years ± 8.12 (range: 21.07–47.44)	MS group 1: 2 MS: 1 buccal, 1 palatal group 1: 3 MS: 2 buccal,1 palatal	LC	Group 1: 1.79 ± 1.28 mm Group 2: 2.12 ± 1.25 mm	150 g, elastomeric chain	Group 1: 0.81 years ± 0.5 (range 0.41–1.64 years) Group 2: 1.17 years ± 0.48 (range 0.75–2.14 years)	U6 to PP U6 to SN OB	NA	"protocols of maxillary molar intrusion with two or three mini-implants presented the same efficiency of skeletal anchorage"
Pinzan-Vercelino CRM et al., 2015 [38]	Brazil	PP	9 patients (7 females, 2 males) mean age 37.17 years (range: 28.5–46.41	MS, buccal, and palatal	LC	Mean 2.4 mm (range: 1.2–4.5 mm)	NA	9.03 ± 4.04 months (range: 3.16–16.23 months)	U6 to PP	NA	"orthodontic intrusion using direct anchorage of mini-implants was an effective method for the intrusion of maxillary molars"

Table 1. *Cont.*

Author, Publication Year	Country	IA	Sample Size, Age Range, Gender	Anchorage Type	IMM	IR	IF	TT	Outcomes	Side Effects	Conclusions
Scheffler NR et al., 2014 [39]	USA	AOB	30 patients (11 male and 19 female)	16 patients MS, buccal 14 patients ZP	LC	2.3 mm	NA, NiTi coil springs occlusal splint		Anterior face height mandibular plane angle OB	relapse no failures of miniplate anchorage 1 loose MS 1 MS fell out	"intrusion of the maxillary posterior teeth can give satisfactory correction of moderately severe anterior open bites, but 0.5 to 1.5 mm of reeruption of these teeth is likely to occur"
Seres L, Kocsis A, 2009 [40]	Hungary	AOB	7 patients (4 women and 3 men), mean age 21 years (range, 15–29 years)	ZP	LC, PR, periapical radiographs	NA	100 to 120 g, NiTi closed coil springs	6 months	Mandibular plane closed Point B rotated anteriorly and upward	Mild discomfort after surgery No signs or symptoms of a temporomandibular dysfunction were observed, No miniplate movement was detected no significant root resorption	" skeletal anterior open bites due to posterior maxillary dentoalveolar hyperplasia can be closed without orthognathic surgery"

Table 1. *Cont.*

Author, Publication Year	Country	IA	Sample Size, Age Range, Gender	Anchorage Type	IMM	IR	IF	TT	Outcomes	Side Effects	Conclusions
Sherwood K.H. et al., 2002 [41]	USA	AOB	4 patients (2 men and 2 women)	ZP	LC, PR	Mean: 1.99 mm Range: 1.45–3.32	Coated elastic thread	5.5 months	2 measurement lines on PR anterior facial height mandibular plane occlusal plane	No discernable movement of any miniplate	"true intrusion of molars can be accomplished in adults" "Anterior open bites can be closed by intruding posterior teeth, resulting in reduced anterior vertical face height, decreased mandibular plane angle, and counterclockwise rotation of the mandible"
Turkahraman H., Sarioglu M, 2016 [42]	Turkey	AOB	40 patients: 20 treatment group (14 female, 6 male) mean age: 16.68 ± 2.80 years 20 control group (11 female, 9 male) mean age: 16.63 ± 2.83 years	ZP	LC	Treatment group: 3.59 ± 1.34 mm control group: 0.51 ± 0.44 mm	200 g Ni-Ti coil springs	Treatment group: 1.00 ± 0.31 years control group: 0.95 ± 0.14 years	U6 to PP	Mesial movement of the molars by 1.52 mm was found in the treatment group	"mild to moderate skeletal anterior open bites could easily be treated with TADs without orthognathic surgery. With the rigid anchorage of mini plates, true molar intrusion was achieved"

Table 1. *Cont.*

Author, Publication Year	Country	IA	Sample Size, Age Range, Gender	Anchorage Type	IMM	IR	IF	TT	Outcomes	Side Effects	Conclusions
Xun CL et al., 2013 [43]	China	OVE U6	30 patients 35.5 ± 9.0 years (range 19 to 50)	MS	LC. PR	3.4 mm (range 1.5 to 6.5 mm)	100–150 g, elastic chain	6.2 ± 2.1 months	U6 to PP	Crown of the molars mesially tilted by averages of 3.1 degrees root resorption 0.2–0.4 mm on average	"intrusion treatment of over erupted molars with miniscrew anchorages could be used as an efficient and reliable method to recover lost restoration space for prosthesis"
Yao CC, et al., 2005 [3]	Taiwan	OVE U6	22 patients mean age 27.6 years (range: 15 to 42 years)	MS	Dental casts	mean: 3.1 ± 1.7 mm (range 0.34 to 8.67 mm)	150–200 g, elastic chain	7.6 months (range 5–12 months)	Three-dimensional (3D) digitizer, superimposing two sets of data to assess the relocation of cusp tips	Buccal–lingual tipping of the intruded U6 Clinical crown shortening of the intruded teeth	"a combination of mini-implants and fixed appliances is a a predictable and effective procedure to achieve maxillary molar intrusion"

3.3. Study Characteristics

Eighteen publications were evaluated in this review. In terms of publishing country, three of them were from Brazil, Egypt, and Turkey, respectively; two were from China and the USA, respectively, while there was one from China and Australia, Hungary, Iran, Korea, and Taiwan, respectively. Thirteen studies aimed at intruding upper first molars due to anterior open bite, whilst in the other studies the objective was the correction of the overeruption of the first molar, and just one study clearly stated the pre-prosthetic reason for intrusion. The vast majority of research that targeted correcting intrusion for open bite included participants aged between 18 and 30 years, whereas in the studies which aimed at intruding molars for overeruption, ages ranged between 20 and 46 years. The mean age, among the studies that reported it (15 studies) was 26.475 years. Regardless of the intrusion goal, there was a gender difference, with females being more prevalent. Ten studies used miniscrews (MS) as the anchorage type, seven used a zygomatic plate (ZP), and one publication used a combination of MS and ZP. In some of the publications, the reported method of intrusion technique was nickel-titanium (NiTi) coil springs [27,28,30,35,39,40]. Other authors reported the use of elastomeric chain [3,31,34,36,37,43].

The mean amount of intrusion was similar across studies, with a range of between 2.1 ± 0.9 mm and 4.57 ± 0.98 mm, being mostly situated between 2–3 mm. The intrusion force varied between 100 and 500 g and, although most of the studies (n = 8) reported a force between 100 to 200 g, one study reported 300 g [29], and four studies reported an intrusion force between 400 to 500 g [27,28,35,36]. In five of the studies, we could not identify the amount of force used.

The intrusion amount was measured in lateral cephalograms (LC) in eight studies, lateral cephalograms (LC) and panoramic radiographs (PR) in two studies, lateral cephalograms (LC), panoramic radiographs (PR) and periapical radiographs in one study, CBCT scans in four studies, only panoramic radiographs (PR) in one study, parallel periapical radiographs in one study, and dental cast models also in one study. Eight of the eighteen papers measured the distance between U6 to PP, while the others used mixed methods or custom measurement techniques.

The treatment time was reported in 16 studies, ranging from 3 to 12 months, with a mean value of 7.56 months.

Thirteen studies reported side effects, while the other five mentioned no issues during or associated with the intrusion. One paper reported soft tissue overgrowth, seven articles described external apical root resorption (EARR) of various degrees, and three studies reported mini-screw loosening. Relapse appeared to be an issue in one study, different degrees of post-surgical discomfort and tongue irritation was mentioned in two studies while three studies reported coronal tilting and other unwanted movements, accompanying the intrusion process.

All the articles state the fact that TADs are an efficient treatment option for obtaining a correction of either anterior open bite or levelling of the occlusal plane, with minor side effects if any, and, more importantly, reducing the need for much more invasive and complex interventions, such as orthognathic surgery.

3.4. Risk of Bias in Studies

The risk of bias was assessed according to the Newcastle–Ottawa Quality Assessment Scale for case-control studies to evaluate the methodological quality of the selected publications [44] (Table 2). According to this scale, each numbered item in the "selection" and "exposure" categories could yield a maximum of one star, whereas "comparability" could receive a maximum of two stars.

Table 2. The Newcastle–Ottawa Quality Assessment Scale for case-control studies. *-fulfilled criteria.

Author, Year of Publication	**Akan B et al., 2020 [27]**	**Akl HE et al., 2020 [28]**	**Al-Falahi B et al., 2018 [29]**	**Ari-Demirkaya A et al., 2005 [30]**	**Ding WH et al., 2015 [31]**	**Heravi F et al., 2011 [32]**	**Kim K et al., 2018 [33]**	**Li W et al., 2013 [34]**	**Marzouk ES et al., 2015 [35]**
1. Is the case definition adequate?		*	*	*	*	*	*	*	*
2. Representativeness of the cases	*	*	*	*	*		*	*	*
3. Selection of controls		*		*	*				
4. Definition of controls		*		*					
1. Comparability of cases and controls on the basis of the design or analysis		*		*	*				
1. Ascertainment of exposure	*	*	*	*	*	*	*	*	*
2. Same method of ascertainment for cases and controls		*		*					
3. Non-response rate									
Author, Year of Publication	**de Oliveira TFM et al., 2015 [36]**	**Paccini JV et al., 2016 [37]**	**Pinzan-Vercelino CRM et al., 2015 [38]**	**Scheffler NR et al., 2014 [39]**	**Seres L, Kocsis A, 2009 [40]**	**Sherwood K.H. et al., 2002 [41]**	**Turkahraman H., Sarioglu M, 2016 [42]**	**Xun CL et al., 2013 [43]**	**Yao CC, et al., 2005 [3]**
Selection									
1. Is the case definition adequate?	*	*	*	*	*	*	*	*	*
2. Representativeness of the cases	*	*	*	*	*	*	*	*	*
3. Selection of controls							*		
4. Definition of controls							*		
Comparability									
1. Comparability of cases and controls on the basis of the design or analysis							*		
Exposure									
1. Ascertainment of exposure	*	*	*	*	*	*	*	*	*
2. Same method of ascertainment for cases and controls							*		
3. Non-response rate									

3.5. Case Report

A 28-year-old woman, seeking replacement of missing lower first molars, with second mandibular premolars shifted distally and rotated to the edentulous space, came to our practice. Prosthetic treatment of the edentulous spaces was limited by overeruption of upper first molars and premolars, as well as by the rotated teeth. The occlusal plane was irregular, with extrusion of the upper first molars and premolars into the edentulous spaces and a lower midline shift of 2 mm towards the right side (Figure 2). She had a hypodivergent skeletal pattern, a class II skeletal pattern with a small anterior facial height, skeletal deep bite tendency, and increased overbite and overjet (Table 3).

(**a**) (**b**) (**c**) (**d**) (**e**)

Figure 2. *Cont*.


(f)


(g)

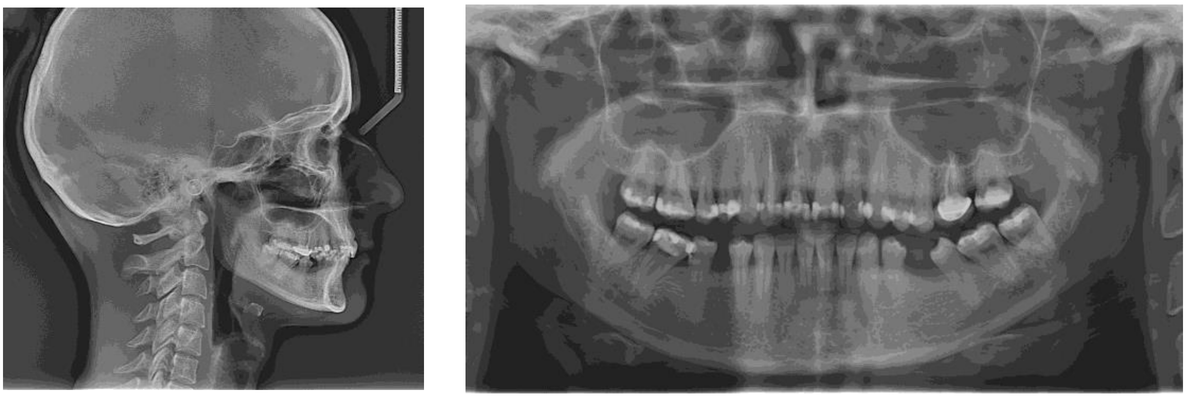
Figure 2. Initial situation (**a**) Right lateral occlusal view; (**b**) Left lateral occlusal view; Initial situation (**c**) Frontal occlusal view; Initial situation (**d**) Upper arch; (**e**) Lower arch; Initial situation, extraoral photos (**f**) Frontal view; (**g**) Lateral view.

Table 3. Lateral cephalometric measurements.

Parameter	Value	Mean ± SD
SNA angle	84.94°	82 ± 2°
ANB angle	4.23°	2 ± 2°
SNB angle	80.71°	80 ± 2°
FMA angle	21.53°	25 ± 2°
Occlusal plane to Gonion–menton	13.83°	19.09 ± 4.7°
Occlusal plane to Sella–nasion	16.33°	14 ± 4°
Lower facial height	65.64 mm	66.7 ± 4.1 mm
Anterior facial height	114.80 mm	128.68 ± 6 mm
Upper molar to pterygoid vertical plane	21.39 mm	21.10 ± 3 mm
Interincisal angle	145.21°	128.0 ± 5°
Overbite	3.73 mm	2 ± 2 mm
Overjet	3.3 mm	2 ± 2 mm
Gonion–Gnation to Sella–nasion	28.91°	32 ± 4°
U1 to Nasion–point A line	10.27°	22.0 ± 5°
U1 to Sella–nasion	95.21°	105.28 ± 6°

SNA-sagittal position of the maxilla; SNB-sagittal position of the mandible; FMA-facial pattern; U1-upper incisor; S = sella point; N = nasion point; SD-standard deviation.

The initial radiographs are shown in Figure 3. No signs of periodontal disease or other associated pathologies were encountered on panoramic radiography.



(a) (b)

Figure 3. Radiographic examination before treatment: (**a**) Initial lateral cephalogram; (**b**) Initial panoramic radiograph.

The main treatment objectives included obtaining a functional occlusion, intruding the maxillary first molars and premolars, levelling the occlusal plane, creating space for prosthetic replacement of the lower molars, achieving functional arch relationships, and enhancing masticatory efficiency. The treatment plan involved orthodontic intrusion of the overerupted upper teeth, followed by fixed appliance therapy. On the right hemiarch, one miniscrew on the buccal side and two on the palatal side were placed, whereas on the left hemiarch, a zygomatic plate was placed on the buccal area, along with two miniscrews on the palatal area.

In the first quadrant, four mini screw implants, temporary anchorage devices (TAD) were inserted, as follows:

- 12 mm (Ø 1.6 mm) Jeil Dual Top JA Screw–Palatal, between tooth 1.3 and 1.4
- 12 mm (Ø 1.6 mm) Jeil Dual Top JA Screw–Buccal, between tooth 1.4 and 1.5
- 12 mm (Ø 1.6 mm) Jeil Dual Top JA Screw–Buccal, between tooth 1.6 and 1.7
- 12 mm (Ø 1.6 mm) Jeil Dual Top JA Screw–Palatal, distal of tooth 1.7

All the TADs were inserted under local anesthesia (Ubistesin Forte, articaine hydrochloride 4% with adrenaline (epinephrine) 1:200,000, 2 × 1.7 mL). The preoperative planning aimed for bicortical anchorage (confirmed by postoperative CBCT scan, Figure 4).

(a) (b)

Figure 4. Preoperative surgical planning: (**a**) Buccal miniscrews; (**b**) Palatal miniscrews.

The TADs were inserted using the NSK Surgical Pro Fiziodispenser and NSK Ti-Max Contra Angle Handpiece (20:1 Reduction), using a rotation speed of 30 rpm and a 30 N/cm insertion torque. No prior preparation of the insertion site was required.

In the second quadrant, two mini screw implants were inserted in the palatal region (12 mm (Ø 1.6 mm) Jeil Dual Top JA Screw), the first one between tooth 2.3 and 2.4 and the second distal to tooth 2.7, using the same protocol as for the first quadrant. The only difference consisted of the use of a surgical guide for the two screws in the second quadrant (Figure 5). A printed 3D model was obtained using the patient's preoperative scan with a Formlabs Form 3 printer.

(a) (b)

Figure 5. Surgical guide for the two screws in the second quadrant: (**a**) 3D printed cast; (**b**) Surgical guide applied in the oral cavity.

In addition, due to reduced bone volume compared to the first quadrant and reduced interproximal space, an orthodontic anchor plate was chosen for the buccal area, which was customized on the 3D model.

For this region, the same type of local nerve block was used. An incision was placed at the mucogingival junction starting from tooth 2.7 to tooth 2.3, followed by the elevation of the mucoperiosteal flap, with the exposure of the zygomaticomaxillary buttress (Figure 6). The plate was sterilized after personalization and before surgery. This preoperative step dramatically reduces surgery time and provides perfectly predictable results. The plate was anchored to the zygomaticomaxillary buttress using three 2.0 self-tapping screws. Nonresorbable 4/0 Supramid simple interrupted sutures were used, and these were then removed seven days after surgery.

(a) (b)

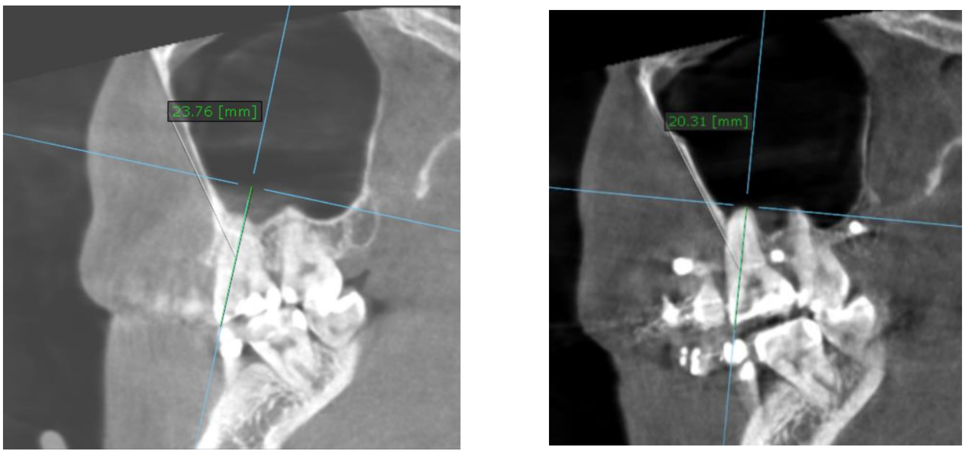
Figure 6. Zygomatic anchorage on the left maxillary buccal area: (**a**) with the exposure of the zygomaticomaxillary buttress; (**b**) Nonresorbable 4/0 Supramid simple interrupted suture.

To calculate the amount of performed molar intrusion, the difference of the linear distance from the mesiobuccal cusp of the maxillary first molar to a custom palatal plane (CPP) was measured on CBCT images before and after intrusion mechanics. The CPP was defined by the following three points: ANS, and the lowest points of the pterygoid hamulus on the left and right sides. The measurements were performed by one maxillofacial surgeon and one orthodontist, twice, and mean values were considered (Table 4).

Table 4. The CBCT measurements before and after intrusion at the level of upper first molar and upper first premolar.

CBCT Parameter	T0–Before Intrusion (mm)	T1–After Intrusion (mm)	Intrusion Amount (T1-T0; mm)
Mesiobuccal cusp of the left upper first molar	22.26	20.73	1.53
Palatal root apex of the left upper first molar	4.20	1.62	2.58
Upper left first molar furcation	11.35	8.74	2.61
Buccal cusp of the left upper first premolar	24.8	22.16	2.64
Palatal root apex of the left upper first premolar	5.67	4.53	1.14
Mesiobuccal cusp of the right upper first molar	23.76	20.31	3.45
Palatal root apex of the right upper first molar	4.18	2.37	1.81
Upper right first molar furcation	12.79	9.74	3.05
Buccal cusp of the right upper first premolar	24.72	20.45	4.27
Palatal root apex of the right upper first premolar	6.04	3.42	2.62

The measurement method is shown in Figure 7.



(**a**) (**b**)

Figure 7. Intrusion amount, at the level of the mesiobuccal cusp of the right upper first molar (the distance between the cusp tip and CPP): (**a**) before intrusion: 23.76 mm; (**b**) after intrusion: 20.31 mm.

The left zygomatic plate and miniscrews were placed initially, and intrusion mechanics began with the aid of an elastic chain on this side after two weeks of soft tissue healing. Subsequently, at approximately 1.5 months after the left maxillary arch, the right hemiarch was implanted and miniscrews were inserted. No associated symptoms were described by the patient, and no signs of tissue irritation were found. No loose miniscrews or other accidents occurred.

Elastomeric chains were changed every four weeks. Approximately 3.59 mm of intrusion was achieved on the right buccal side and 2.21 mm on the right palatal side in six months, 2.26 mm on the left buccal side, and 1.86 mm on the left palatal side in nine months. After intrusion, ligature stainless steel wires were used to keep the intruded teeth in place. Subsequently, upper and lower teeth were included in a full arch appliance, with a 0.022 MBT prescription.

The main aim of the treatment objectives, namely the intrusion of the upper posterior teeth, has been achieved. The orthodontic treatment is ongoing in order to solve additional objectives, such as midline correction and space distribution for prosthetic treatment (Figure 8).

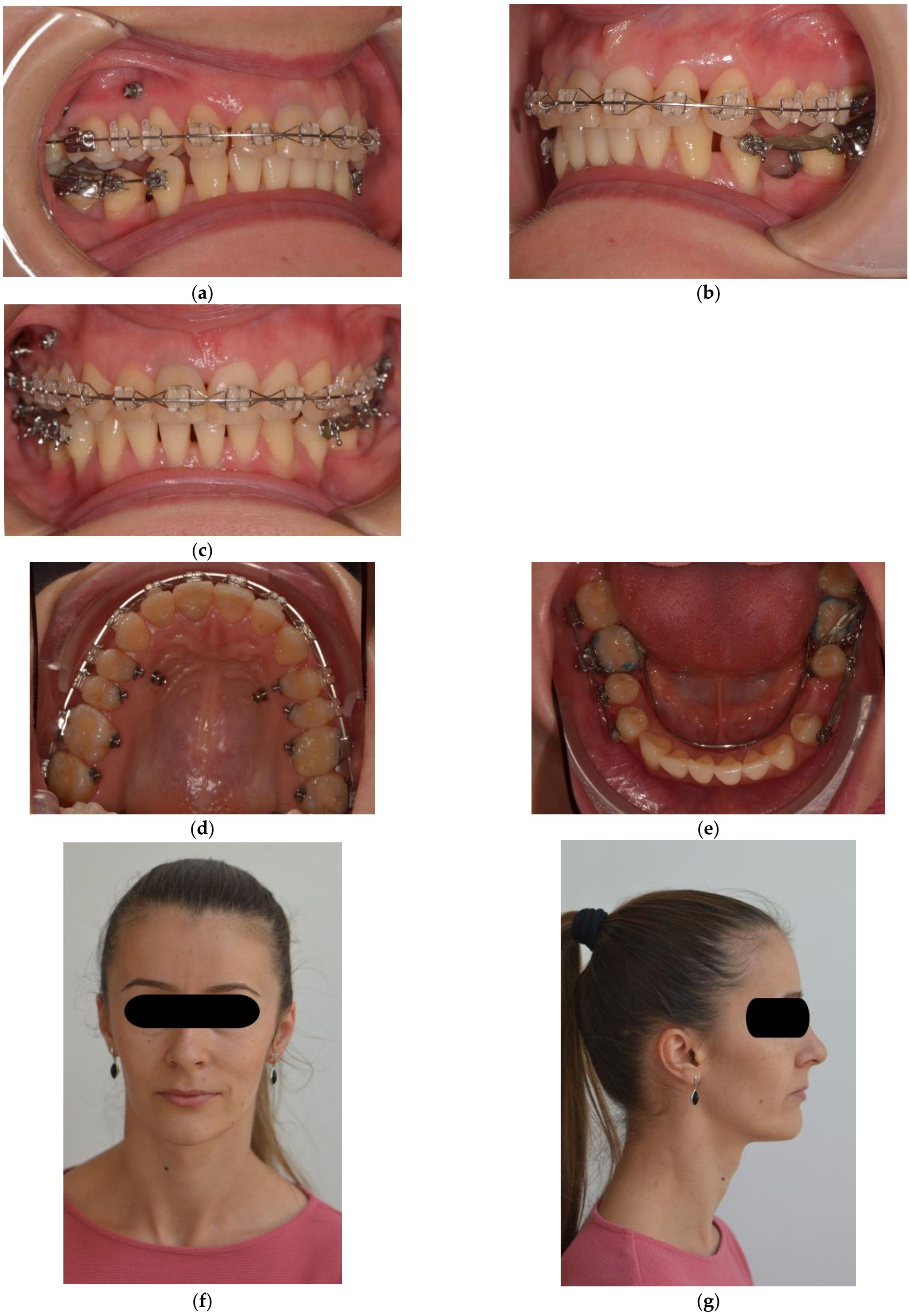


Figure 8. Post-intrusion intraoral photographs (**a**,**b**) Left lateral occlusal view; (**c**) Frontal occlusal view; (**d**) Upper arch; (**e**) Lower arch; Post-intrusion intraoral extraoral photos (**f**) Frontal view; (**g**) Lateral view.

4. Discussion

We initially searched for intrusion aims, such as pre-prosthetic molar or premolar intrusion, as well as an orthodontic intrusion for open bite correction. We only found a few papers linked to the pre-prosthetic intrusion goal, most of which were case reports, hence, they were not included in this review. Nonetheless, a few articles on the subject were found. There are a few reviews related to intrusion for open bite correction, but none of them focused on both orthodontic and pre-prosthetic aspects. Furthermore, non-orthodontic cases of overerupted molars are rare, and the number of included subjects is small.

Sherwood et al., reported just four cases, treated for anterior open bite [41]. The largest number of cases, 36, was reported by Ding et al., also for anterior open bite treatment [31]. The publications aiming at intruding overerupted upper molars for prosthetic reasons included 9 subjects [38], 12 subjects [34], 19 subjects [37], 22 subjects [3], and 30 subjects, respectively [43].

Adults with overerupted molars because of antagonist loss are still a common clinical finding. Occlusal plane rehabilitation should use a multidisciplinary approach. Molar intrusion is required to provide adequate space for prosthetic rehabilitation. If possible, the implant location should be chosen based on the availability of sufficient cortical bone [45]. Due to the maxillary sinus and the thin alveolar biotype, we encountered risks in the intrusion mechanism and miniscrew placement, prolonging the intrusion time.

The recommended loading force of the anchorage devices has been suggested to vary between 50–500 g, reported as 50 g [46,47], 100–200 g [48,49], or 300–500 g of force [50]. If intrusion of more than one single tooth is needed at the same time, the force should be higher, around 400 g [51]. The recommended amount of intrusion of the overerupted maxillary molars is approximately 0.5–1.0 mm per month, without the occurrence of unwanted secondary effects, such as root resorption, periodontal effects, or vitality loss [11]. In the reviewed publications, intrusion force varied between 100 and 500 g. The use of skeletal anchorage can aid in an increased amount of molar intrusion, allowing for accelerated orthodontic forces [52]. Nonetheless, we encourage close monitoring to minimize the risk of undesired side effects. In most studies, the amount of intrusion was obtained by measuring the distance between a reference point on the first molar and the palatal plane on lateral cephalograms. Most of the available studies using 3D imaging measure distance from various tooth landmarks to the palatal plane, defined as passing through anterior nasal spine (ANS), posterior nasal spine (PNS), and perpendicular to the mid-sagittal plane [29]. Baek et al., using 2D imaging, defined the plane as crossing through the ANS and PNS [53]. Although this study met most of our inclusion criteria, it was excluded due to the fact that the study protocol included extractions. Although 2D measurements are easier to perform and more reproducible, very few parameters can be evaluated, leaving 3D imaging as the most precise and relevant alternative. Due to the uncertainty of the definition of the mid-sagittal plane, selecting this landmark might be a source of bias since various factors can influence measurements from pre-treatment and post-treatment CBCT scans. This is the reason why, for the present case report, we decided to define a custom plane, that can always be reproduced with maximum accuracy. This plane is defined by ANS and the lowest points of the pterygoid hamulus on the left and right sides.

Out of the 18 reviewed articles, 10 reported MS, 7 reported ZP, and 1 used both anchorage types. The average treatment time was 7.1 months for those using MS, and 7.9 months for the ones that had ZP, which follows the results presented in our case. This might lead to the conclusion that the intrusion using MS could be quicker. One must keep in mind, though, that ZPs are frequently used for the more severe cases, where the requirement for intrusion is increased, leading to the fact that efficiency cannot be evaluated solely based on the type of TAD. Additionally, it might be assumed that ZPs are used when broader movements are needed. However, within the findings of the present review, the average intrusion was similar between the two groups (2.6 mm for the ZPs and 2.7 mm for the MSs). The mean amount of intrusion reported in the selected articles was quite similar, being mostly between 2–3 mm.

Everdi N et al., when intruding upper first molars with the aid of zygomatic plates and NiTi coil springs, reported an average intrusion of 2.6 mm, but the authors included patients with extractions. However, they found buccal tipping of the maxillary molars, as well as inflammation at the TAD site [54]. Various strategies for assessing molar intrusion have been described, depending on the methodology of assessment. It has been postulated by Burstone that true molar intrusion can only be verified when the molar's center of resistance is utilized as a point of comparison to measure the molar's vertical displacement into the alveolar bone [55]. In that regard, using other reference points, such as cusp tips or root apex, would make it difficult to distinguish intrusion from tipping [55]. It has been shown that the treatment of anterior open bite by molar intrusion, accomplished by reducing the distance between the mesial buccal cusp of the first molar and the palatal plane, can be achieved [56].

The intrusion time ranged from 3 [31] to 12 months [42], with the majority of publications (n = 8) reporting an average of 5 to 6 months, 2 studies of 7 months, and 5 publications of 9 months. However, due to the heterogeneity of the included studies, a relationship between anchorage type and time could not be revealed. The recommended intrusion rate for a single molar is 0.75 mm per month, whilst for the intrusion of grouped teeth (first molar and second premolar) it is 0.5 mm per month [54].

Molar intrusion has grown more successful and efficient because of skeletal anchoring, yet it is still considered a challenging orthodontic technique [6]. It is an effective method of intruding molars to address an open bite [52].

The relationship between arch bracketing and the intrusion mechanism has been intensely studied. It has been shown that when the arch is not braced, true posterior segment intrusion ensues [41]. However, the inferior wall of the maxillary sinus must be considered when intruding upper molars. The movement of posterior teeth across the maxillary sinus has been linked to moderate apical root resorption and increased tipping [57,58]. In our case, no movement of the zygomatic buttress miniplate or the buccal or palatal microscrews occurred neither during their use nor before clinical removal. The CBCT showed no discernible signs of root resorption.

There are also some important risks and complications of TAD placement, as follows: root trauma, anchorage failure, sinus perforation, nerve injury, soft tissue irritation, relapse [11], contact of the TAD with the adjacent roots, miniscrew loosening or fracture, damage to anatomic tissues, soft tissue overgrowth [15]. Among the possible side effects, most studies reported external apical root resorption. Additionally, loose miniscrews, soft tissue irritations, relapse, mesial movement of molars, and tipping have been described. Although MSs were used more commonly, the complications were fewer in the ZP cases. Only one article showed certain EARR. On the other hand, several cases presented EARR in the MS group, along with soft tissue overgrowth and irritation and, most important of all, frequent MS loosening. Another advantage of the ZP TAD system is represented by the traction forces that it can withstand (an average of 327 g, compared to the average of 187 g for the MS group).

True molar intrusion as described by de Oliveira et al., with no modifications of the anteroposterior orientation of molars, mesial tipping of posterior teeth, or no changes in the palatal plane angle [36], has been encountered as well in the reported case. The more common usage of MS shows the clinicians' bias towards this type of TAD, due to their ease of application, low risks, and elevated success rate. Additionally, ZP were used more commonly when a translation of molars was needed to correct the malocclusion [39].

Since the approach of posterior teeth intrusion may offer predictable results without relying largely on patient compliance, orthodontic correction of the occlusal plane using a skeletal anchorage should be regarded as state-of-the-art. Nevertheless, due to a high degree of relapse, the intrusion must be maintained by retention procedures. Gonzales et al., have shown that, due to a high degree of recurrence, the stability of open bite treatment with molar intrusion employing skeletal anchoring in adult patients might be regarded as relatively unstable [59].

A dual assessment of the risk of bias was conducted by two authors (O.A. and A.M) to identify potential sources of bias, which is critical for future research quality. Although there was a moderate risk of bias in the selected studies, mainly due to the lack of controls, the flaws were not severe enough to invalidate the findings. The absence of untreated control groups, a short follow-up time, a small sample size, and the lack of intrusion force measurement in some articles were all found to be shortcomings in the reviewed publications. There is still little valid scientific research available to assess actual molar intrusion [2].

Among the limitations of this study might be the reduced number of cases included in the selected articles, the lack of controls, and the variability of used skeletal anchorage, intrusion force, and intrusion mechanism. Additionally, some authors did not report the intrusion amount, intrusion force, intrusion mechanism, or side effects. A major concern is the lack of an untreated control group, although some authors compared the intervention group to another treated group, but with different force amounts. Due to the heterogeneity of the publications, a meta-analysis could not be performed.

A strong point of the present study, besides the thorough literature analysis regarding TADs, is the definition of a custom plane that can be used for exact measurements, to evaluate tooth intrusion. The classical PP can be affected by several patient- and device-specific factors, rendering the pre- and post-operative measurements ineffective. Measuring the distance from certain tooth landmarks to the CPP will always yield useful and relevant findings, since this plane is defined by anatomical landmarks that can not suffer changes throughout tooth ingression.

Our future recommendations are as follows: a fundamental goal is to define a customized reference plane to ensure optimal reproducibility of pre-and post-surgical measurements. The CBCT scans must be performed under the same conditions, on the same equipment, and, if feasible, by the same operator to improve data consistency and reliability. Optimal anchorage and force management must be aimed, thus, reducing tooth movement (intrusion) time and limiting side effects.

5. Conclusions

According to the findings of this study, there is evidence that levelling the occlusal plane by the intrusion of the upper posterior teeth can be achieved by skeletal anchorage.

In the presented case it was possible to obtain a well-controlled intrusion of the maxillary molars and premolars without unwanted side effects. Stability of the obtained results, shortened treatment time, and controlling treatment outcome are the main goals for a complex treatment approach, which draws on both surgical and orthodontic practices.

The manuscript's strengths rely on a thorough analysis of the existing literature and the definition of a CPP (a custom palatal plane defined by ANS and the lowest points of the pterygoid hamulus on the left and right side), which aims to reduce the inaccuracy of true tooth intrusion evaluation.

To achieve the highest possible long-term outcomes, dental practitioners should be up to date on the latest technologies to be used as alternatives for specialized treatment planning and patient monitoring.

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References

1. Gurton, A.U.; Akin, E.; Karacay, S. Initial Intrusion of the Molars in the Treatment of Anterior Open Bite Malocclusions in Growing Patients. *Angle Orthod.* **2004**, *74*, 454–464. [PubMed]
2. Ng, J.; Major, P.W.; Flores-Mir, C. True Molar Intrusion Attained during Orthodontic Treatment: A Systematic Review. *Am. J. Orthod. Dentofac. Orthop.* **2006**, *130*, 709–714. [CrossRef] [PubMed]
3. Yao, C.-C.J.; Lee, J.-J.; Chen, H.-Y.; Chang, Z.-C.J.; Chang, H.-F.; Chen, Y.-J. Maxillary Molar Intrusion with Fixed Appliances and Mini-Implant Anchorage Studied in Three Dimensions. *Angle Orthod.* **2005**, *75*, 754–760. [CrossRef]
4. Chun, Y.S.; Row, J.; Yang, S.J.; Cha, H.S.; Han, J.S. Management of Extruded Maxillary Molars to Accommodate a Mandibular Restoration: A Clinical Report. *J. Prosthet. Dent.* **2000**, *83*, 604–606. [CrossRef]
5. Yao, C.-C.J.; Wu, C.-B.; Wu, H.-Y.; Kok, S.-H.; Chang, H.-F.F.; Chen, Y.-J. Intrusion of the Overerupted Upper Left First and Second Molars by Mini-Implants with Partial-Fixed Orthodontic Appliances: A Case Report. *Angle Orthod.* **2004**, *74*, 550–557.
6. Park, H.-S.; Jang, B.-K.; Kyung, H.-M. Maxillary Molar Intrusion with Micro-Implant Anchorage (MIA). *Aust. Orthod. J.* **2005**, *21*, 129–135.
7. Uysal, C.; Baloş Tuncer, B.; Tuncer, C. Maxillary Posterior Intrusion with Corticotomy-Assisted Approaches with Zygomatic Anchorage-a Finite Element Stress Analysis. *Prog. Orthod.* **2019**, *20*, 8. [CrossRef]
8. Sandler, P.J.; Madahar, A.K.; Murray, A. Anterior Open Bite: Aetiology and Management. *Dent. Update* **2011**, *38*, 522–524, 527–528, 531–532. [CrossRef]
9. Aifa, A.; Sorel, O.; Gebeile-Chauty, S. Openbite in hyperdivergent adult: Le Fort I impaction versus maxillary molar intrusion using bone anchorage. A literature review. *Orthod. Fr.* **2021**, *92*, 215–238. [CrossRef]
10. Lorean, A.; Mazor, Z.; Mijiritsky, E.; Barbu, H.; Levin, L. Segmental Dento-Alveolar Intrusive Osteotomy in Posterior Maxilla with Lack of Inter-Arch Distance for Prosthetic Rehabilitation. A Technique Combined with Sinus Floor Elevation. *N. Y. State Dent. J.* **2015**, *81*, 37–41.
11. Kravitz, N.D.; Kusnoto, B.; Tsay, T.P.; Hohlt, W.F. The Use of Temporary Anchorage Devices for Molar Intrusion. *J. Am. Dent. Assoc.* **2007**, *138*, 56–64. [CrossRef] [PubMed]
12. Kuroda, S.; Sakai, Y.; Tamamura, N.; Deguchi, T.; Takano-Yamamoto, T. Treatment of Severe Anterior Open Bite with Skeletal Anchorage in Adults: Comparison with Orthognathic Surgery Outcomes. *Am. J. Orthod. Dentofac. Orthop.* **2007**, *132*, 599–605. [CrossRef] [PubMed]
13. Miyawaki, S.; Koyama, I.; Inoue, M.; Mishima, K.; Sugahara, T.; Takano-Yamamoto, T. Factors Associated with the Stability of Titanium Screws Placed in the Posterior Region for Orthodontic Anchorage. *Am. J. Orthod. Dentofac. Orthop.* **2003**, *124*, 373–378. [CrossRef]
14. Poggio, P.M.; Incorvati, C.; Velo, S.; Carano, A. "Safe Zones": A Guide for Miniscrew Positioning in the Maxillary and Mandibular Arch. *Angle Orthod.* **2006**, *76*, 191–197. [CrossRef] [PubMed]
15. Mizrahi, E.; Mizrahi, B. Mini-Screw Implants (Temporary Anchorage Devices): Orthodontic and Pre-Prosthetic Applications. *J. Orthod.* **2007**, *34*, 80–94. [CrossRef]
16. Tuncer, C.; Ataç, M.S.; Tuncer, B.B.; Kaan, E. Osteotomy Assisted Maxillary Posterior Impaction with Miniplate Anchorage. *Angle Orthod.* **2008**, *78*, 737–744. [CrossRef]
17. Chung, K.R.; Oh, M.Y.; Ko, S.J. Corticotomy-Assisted Orthodontics. *J. Clin. Orthod.* **2001**, *35*, 331–339.
18. Ahn, N.-L.; Park, H.-S. Differences in Distances between Maxillary Posterior Root Apices and the Sinus Floor According to Skeletal Pattern. *Am. J. Orthod. Dentofac. Orthop.* **2017**, *152*, 811–819. [CrossRef]
19. Hodges, R.J.; Atchison, K.A.; White, S.C. Impact of Cone-Beam Computed Tomography on Orthodontic Diagnosis and Treatment Planning. *Am. J. Orthod. Dentofac. Orthop.* **2013**, *143*, 665–674. [CrossRef]
20. McGowan, J.; Sampson, M.; Salzwedel, D.M.; Cogo, E.; Foerster, V.; Lefebvre, C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. *J. Clin. Epidemiol.* **2016**, *75*, 40–46. [CrossRef]
21. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews. *BMJ* **2021**, *372*, n71. [CrossRef] [PubMed]
22. da Costa Santos, C.M.; de Mattos Pimenta, C.A.; Nobre, M.R.C. The PICO Strategy for the Research Question Construction and Evidence Search. *Rev. Lat.-Am. Enferm.* **2007**, *15*, 508–511. [CrossRef] [PubMed]
23. Ouzzani, M.; Hammady, H.; Fedorowicz, Z.; Elmagarmid, A. Rayyan—A Web and Mobile App for Systematic Reviews. *Syst. Rev.* **2016**, *5*, 210. [CrossRef] [PubMed]

24. *Microsoft Excel*; 365; Microsoft: Redmond, WA, USA, 2019.
25. Zotero. Corporation for Digital Scholarship. Available online: https://www.zotero.org/ (accessed on 18 April 2022).
26. Cumpston, M.; Li, T.; Page, M.J.; Chandler, J.; Welch, V.A.; Higgins, J.P.; Thomas, J. Updated Guidance for Trusted Systematic Reviews: A New Edition of the Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Database Syst. Rev.* **2019**, *10*, 14651858. [CrossRef]
27. Akan, B.; Ünal, B.K.; Şahan, A.O.; Kızıltekin, R. Evaluation of Anterior Open Bite Correction in Patients Treated with Maxillary Posterior Segment Intrusion Using Zygomatic Anchorage. *Am. J. Orthod. Dentofac. Orthop.* **2020**, *158*, 547–554. [CrossRef] [PubMed]
28. Akl, H.E.; Abouelezz, A.M.; El Sharaby, F.A.; El-Beialy, A.R.; El-Ghafour, M.A. Force Magnitude as a Variable in Maxillary Buccal Segment Intrusion in Adult Patients with Skeletal Open Bite. *Angle Orthod.* **2020**, *90*, 507–515. [CrossRef]
29. Al-Falahi, B.; Hafez, A.M.; Fouda, M. Three-Dimensional Assessment of External Apical Root Resorption after Maxillary Posterior Teeth Intrusion with Miniscrews in Anterior Open Bite Patients. *Dent. Press J. Orthod.* **2018**, *23*, 56–63. [CrossRef]
30. Ari-Demirkaya, A.; Al Masry, M.; Erverdi, N. Apical Root Resorption of Maxillary First Molars after Intrusion with Zygomatic Skeletal Anchorage. *Angle Orthod.* **2005**, *75*, 761–767.
31. Ding, W.H.; Li, W.; Chen, F.; Zhang, J.F.; Lv, Y.; Chen, X.Y.; Lin, W.W.; Fu, Z.; Shi, J.J. Comparison of Molar Intrusion Efficiency and Bone Density by CT in Patients with Different Vertical Facial Morphology. *J. Oral Rehabil.* **2015**, *42*, 355–362. [CrossRef]
32. Heravi, F.; Bayani, S.; Madani, A.S.; Radvar, M.; Anbiaee, N. Intrusion of Supra-Erupted Molars Using Miniscrews: Clinical Success and Root Resorption. *Am. J. Orthod. Dentofac. Orthop.* **2011**, *139*, S170–S175. [CrossRef]
33. Kim, K.; Choy, K.; Park, Y.C.; Han, S.Y.; Jung, H.; Choi, Y.J. Prediction of Mandibular Movement and Its Center of Rotation for Nonsurgical Correction of Anterior Open Bite via Maxillary Molar Intrusion. *Angle Orthod.* **2018**, *88*, 538–544. [CrossRef] [PubMed]
34. Li, W.; Chen, F.; Zhang, F.; Ding, W.; Ye, Q.; Shi, J.; Fu, B. Volumetric Measurement of Root Resorption Following Molar Mini-Screw Implant Intrusion Using Cone Beam Computed Tomography. *PLoS ONE* **2013**, *8*, e60962. [CrossRef] [PubMed]
35. Marzouk, E.S.; Abdallah, E.M.; El-Kenany, W.A. Molar Intrusion in Open-Bite Adults Using Zygomatic Miniplates. *Int. J. Orthod. Milwaukee* **2015**, *26*, 47–54. [PubMed]
36. Oliveira, T.F.; Nakao, C.Y.; Gonçalves, J.R.; Santos-Pinto, A. Maxillary Molar Intrusion with Zygomatic Anchorage in Open Bite Treatment: Lateral and Oblique Cephalometric Evaluation. *Oral Maxillofac. Surg.* **2015**, *19*, 71–77. [CrossRef]
37. Paccini, J.V.; Cotrim-Ferreira, F.A.; Ferreira, F.V.; Freitas, K.M.; Cançado, R.H.; Valarelli, F.P. Efficiency of Two Protocols for Maxillary Molar Intrusion with Mini-Implants. *Dent. Press J. Orthod.* **2016**, *21*, 56–66. [CrossRef]
38. Pinzan-Vercelino, C.R.; Gurgel, J.A.; Carvalho, K.R.; Tiago, C.M.; Pinzan, A. Clinical Evaluation of a Direct Method for the Intrusion of Supraerupted Maxillary Molars: A Preliminary Study. *Int. J. Prosthodont.* **2015**, *28*, 610–611. [CrossRef]
39. Scheffler, N.R.; Proffit, W.R.; Phillips, C. Outcomes and Stability in Patients with Anterior Open Bite and Long Anterior Face Height Treated with Temporary Anchorage Devices and a Maxillary Intrusion Splint. *Am. J. Orthod. Dentofac. Orthop.* **2014**, *146*, 594–602. [CrossRef]
40. Seres, L.; Kocsis, A. Closure of Severe Skeletal Anterior Open Bite with Zygomatic Anchorage. *J. Craniofacial Surg.* **2009**, *20*, 478–482. [CrossRef]
41. Sherwood, K.H.; Burch, J.G.; Thompson, W.J. Closing Anterior Open Bites by Intruding Molars with Titanium Miniplate Anchorage. *Am. J. Orthod. Dentofac. Orthop.* **2002**, *122*, 593–600. [CrossRef]
42. Turkkahraman, H.; Sarioglu, M. Are Temporary Anchorage Devices Truly Effective in the Treatment of Skeletal Open Bites? *Eur. J. Dent.* **2016**, *10*, 447–453. [CrossRef]
43. Xun, C.L.; Zhao, H.; Zeng, X.L.; Wang, X. Intrusion of Overerupted Maxillary Molars with Miniscrew Implant Anchorage: A Radiographic Evaluation. *J. Huazhong Univ. Sci. Technol. Med. Sci.* **2013**, *33*, 780–785. [CrossRef] [PubMed]
44. Wells, G.; Shea, B.; O'Connell, D.; Peterson, J.; Welch, V.; Losos, M.; Tugwell, P. Ottawa Hospital Research Institute. Available online: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed on 29 April 2022).
45. Baumgaertel, S.; Smuthkochorn, S.; Palomo, J.M. Intrusion Method for a Single Overerupted Maxillary Molar Using Only Palatal Mini-Implants and Partial Fixed Appliances. *Am. J. Orthod. Dentofac. Orthop.* **2016**, *149*, 411–415. [CrossRef] [PubMed]
46. Dalstra, M.; Cattaneo, P.; Melsen, B. Load Transfer of Miniscrews for Orthodontic Anchorage. *Orthodontics* **2004**, *1*, 53–62.
47. Melsen, B.; Fiorelli, G. Upper Molar Intrusion. *J. Clin. Orthod.* **1996**, *30*, 91–96.
48. Tseng, Y.-C.; Hsieh, C.-H.; Chen, C.-H.; Shen, Y.-S.; Huang, I.-Y.; Chen, C.-M. The Application of Mini-Implants for Orthodontic Anchorage. *Int. J. Oral Maxillofac. Surg.* **2006**, *35*, 704–707. [CrossRef]
49. Park, Y.-C.; Lee, S.-Y.; Kim, D.-H.; Jee, S.-H. Intrusion of Posterior Teeth Using Mini-Screw Implants. *Am. J. Orthod. Dentofac. Orthop.* **2003**, *123*, 690–694. [CrossRef]
50. Büchter, A.; Wiechmann, D.; Koerdt, S.; Wiesmann, H.P.; Piffko, J.; Meyer, U. Load-Related Implant Reaction of Mini-Implants Used for Orthodontic Anchorage. *Clin. Oral Implant. Res.* **2005**, *16*, 473–479. [CrossRef]
51. Erverdi, N.; Usumez, S.; Solak, A. New Generation Open-Bite Treatment with Zygomatic Anchorage. *Angle Orthod.* **2006**, *76*, 519–526. [CrossRef]
52. Sugawara, J.; Baik, U.B.; Umemori, M.; Takahashi, I.; Nagasaka, H.; Kawamura, H.; Mitani, H. Treatment and Posttreatment Dentoalveolar Changes Following Intrusion of Mandibular Molars with Application of a Skeletal Anchorage System (SAS) for Open Bite Correction. *Int. J. Adult Orthodon. Orthognath. Surg.* **2002**, *17*, 243–253.

53. Baek, M.S.; Choi, Y.J.; Yu, H.S.; Lee, K.J.; Kwak, J.; Park, Y.C. Long-Term Stability of Anterior Open-Bite Treatment by Intrusion of Maxillary Posterior Teeth. *Am. J. Orthod. Dentofac. Orthop.* **2010**, *138*, 396.e1–396.e9. [CrossRef]
54. Erverdi, N.; Keles, A.; Nanda, R. The Use of Skeletal Anchorage in Open Bite Treatment: A Cephalometric Evaluation. *Angle Orthod.* **2004**, *74*, 381–390. [PubMed]
55. Burstone, C.R. Deep Overbite Correction by Intrusion. *Am. J. Orthod.* **1977**, *72*, 1–22. [CrossRef]
56. Malara, P.; Bierbaum, S.; Malara, B. Outcomes and Stability of Anterior Open Bite Treatment with Skeletal Anchorage in Non-Growing Patients and Adults Compared to the Results of Orthognathic Surgery Procedures: A Systematic Review. *J. Clin. Med.* **2021**, *10*, 5682. [CrossRef] [PubMed]
57. Abdulghani, E.A.; Al-Sosowa, A.A.; Alhammadi, M.S.; Al-Fakeh, H.; Al-Gumaei, W.S.; Almashraqi, A.A.; Sharhan, H.M.; Cao, B. Three-Dimensional Assessment of the Favorability of Maxillary Posterior Teeth Intrusion in Different Skeletal Classes Limited by the Vertical Relationship with the Maxillary Sinus Floor. *Head Face Med.* **2022**, *18*, 13. [CrossRef]
58. Son, W.-S.; Kim, Y.-I.; Kim, S.-S.; Park, S.-B.; Kim, S.-H. Anatomical Relationship between the Maxillary Posterior Teeth and the Sinus Floor According to an Anterior Overbite. *Orthod. Craniofac. Res.* **2020**, *23*, 160–165. [CrossRef]
59. González Espinosa, D.; de Oliveira Moreira, P.E.; da Sousa, A.S.; Flores-Mir, C.; Normando, D. Stability of Anterior Open Bite Treatment with Molar Intrusion Using Skeletal Anchorage: A Systematic Review and Meta-Analysis. *Prog. Orthod.* **2020**, *21*, 35. [CrossRef]

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Research article

Irradiation provided by dental radiological procedures in a pediatric population

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ABSTRACT

Background: Children are more sensitive to ionizing radiation effects due to their high radiosensitivity.
Purpose: To estimate doses and risks for dental radiological examinations in children.
Material and methods: A pediatric population consisting of 7150 children and young adults which underwent 12252 dental radiological examinations (4220 intraoral, 1324 cephalometric, 5284 panoramic radiographs and 1424 CBCTs) within two years were included. Two groups were studied: CBCT group (exposed to CBCT ± conventional radiographs) and 2D group (exposed only to 2D radiological examinations). The effective doses were corrected according to age at exposure and settings parameters (mA;FOV) by using logarithmic fit equations for dose interpolation. The individual cumulative dose, per-caput collective dose and radiation risk were calculated for each group.
Results: The median effective and cumulative doses for conventional radiographs were lower than 20 μSv and did not vary with age. Children exposed to CBCT had a higher median effective dose (127.2 μSv) and cumulative dose (156.5 μSv) with a significant increased cumulative dose between 11 and 14 years. The CBCT contributed with 70% to the collective dose and per caput collective dose was 184 μSv for CBCT exposures. The Life Attributable Risk (LAR) and Relative Radiation Level (RRL) were significantly higher for children exposed to CBCT under the age of 18. The highest radiation dose for CBCT was equivalent with 34.1 days of natural background radiation and it was found for ages between 11 and 15.
Conclusion: The CBCT doses and radiation risk vary but remain in the lower levels of the relative risk of medical exposures.

1. Introduction

Although dental radiological examinations deliver a low dose of radiation, they represent one third of all radiological examinations in Europe [1]. The use of CBCT in children population has recently increased and a particular attention regarding radiation protection is needed [2].

The SedentexCT guidelines showed that CBCT examinations should be recommended to clinical situations in which the information provided may change the diagnosis or improve the treatment plan [3]. However, the efficacy of CBCT in revealing the three-dimensional morphology of maxillofacial bone structure has led to increased examinations in many fields of dentistry, including orthodontics [4].

The American Academy of Oral and Maxillofacial Radiology (AAOMR) has revealed the efficacy of CBCT for dental anomalies and treatment planning in moderate and severe skeletal discrepancies and

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Table 1
The effective doses and dosimetric methods reported in the literature for CBCT and 2D examinations on radiological units used in the current study.

X-ray unit	Dosimetric method	Phantom	kV	mAs	Scanning volume(WxH) (cm^2)	Effective dose (μSv)	References
NewTom 3G (Cefla Dental Group, Imola, Italy)	OSLD	10-years-old	110	9	15 × 15	94	Ludlow et al. [11]
		child	110	9	20 × 20	56	Ludlow et al. [11]
		adult	110	9.1	15 × 15	57	Loubele 2009 [15]
			110	9	30 × 30	30	Loubele 2009 [15]
ProMax 3D Max (Planmeca, Finland)	TLD	10-years-old	84	19.6	8 × 8	24	Theodorakou [16]
		child	84	19.9	8 × 8	28	Pauwels et al. [6]
			90	217	16 × 16	277	Ludlow et al. [11]
		adult	84	192	8 × 5[a]	171	Qu et al. [17]
			84	192	8 × 5[b]	131	Qu et al. [17]
			84	169	8 × 8	122	Pauwels et al. [6]
			84	168	8 × 8	272	Qu et al. [17]
			90	325	16 × 16	283	Ludlow et al. [18]
			90	271	16 × 16	223	Ludlow et al. [18]
Scanora 3D (Soredex, Tuusula, Finland)	TLD	adult	85	48	14.5 × 13.5	68	Pauwels et al. [6]
			85	30	10 × 7.5[b]	46	Pauwels et al. [6]
			85	30	10 × 7.5[a]	47	Pauwels et al. [6]
CranexTome(CCD) (Soredex, Finland)	TLD	adult	70	64	Panoramic	8.1	Gijbels et al. [19]
ProMax 3D (SPP) (Planmeca, Finland)	TLD	adult	66	144	Panoramic	8	Al-Okshi et al. [20]
Intraoral, indirect digital exposure, round collimation	TLD		70	25.6	Bitewing	0.6	Ludlow et al. [11]
					Periapical	1.9	
					Occlusal	7	

OSLD- optical stimulated luminescent dosimeter, TLD – thermoluminiscent dosimeter; kV-kilovoltage, mAs-milliampere-seconds, scanning volume – WxH – width x height, μSv-microsievert, a – for mandibular exposure, b- for maxillary exposure

the median age of children exposed to CBCT was found to be 12 years [5].

A wide range in patient dose for dental CBCT has been reported in literature [6]. CBCT was described as a low-dose radiological method but in fact it can reach doses similar to those of medical CT in using large field of view (FOV) and high-resolution protocols [7]. In light of the need to weigh the benefits and the risks of radiological exposure from a pediatric perspective, the DIMITRA project (Dentomaxillofacial pediatric imaging: An Investigation Towards Low Dose Radiation Induced Risks) aims to characterize the doses and the potential biological effects of radiological exposures in pediatric dentistry [8].

The estimation of doses and a potential radiation risk in children through epidemiological studies could increase the efficacy of using the patient – oriented CBCT protocols in dentistry. However, the evaluation of CBCT doses under clinical condition is still a difficult issue due to the variability of the scanning protocols and CBCT units [9]. The majority of CBCT doses currently estimated in literature involved dosimetric measurements on anthropomorphic phantoms. However, a large discrepancy was observed between phantoms and patient doses, mainly for children, due to immature tissues, growth potential and their developmental stage [10].

In addition, even the dosimetric measurements revealed higher effective doses for CBCT compared to other dental radiological investigations [11] the question that arises is whether CBCT significantly influenced the radiation risk considering the age and frequency in using CBCT for children.

Several studies demonstrated that the risk of cancer incidence may theoretically be increased after repeated radiological procedures during childhood and adolescence for various medical exposures such as interventional radiology [12], multiple CT for emergency situations [13] or cardiac imaging radiology [14]. However, until now there has been no evidence of a potential oncologic effect of low dose radiological examinations. Moreover, the extrapolation of the linear no-threshold model (LNT) that provides the estimated cancer risk for high dose exposures is very controversial and it is considered of little relevance for doses less than 100mSv.

Regardless of technical difficulties in estimating the CBCT effective doses in clinical condition, an overall estimation of the CBCT contribution in dental radiological exposures for various ages of children still remains of great interest.

The aim of this study was to estimate the overall differences between a group of patients exposed to CBCT compared with a group exposed only with 2D dental radiographic modalities, with regard to the variation of the cumulative dose and radiation risks in a pediatric population.

2. Materials and methods

2.1. Patient inclusion and data collection

A retrospective cohort study was conducted in five oral radiology departments from two European countries (Romania and France), with a long lasting expertise in oral and facial radiology. The selected population included children and young adults, aged between 0 and 22 years, who underwent at least one dental radiological examination (CBCT or 2D dental X-ray) within two years (from 1st January 2014 to 31st December 2015).

The selected population included healthy children who underwent a radiography for screening diagnosis of dental lesions (e.g. bite-wing radiography for caries detection) and also children with various dental or maxillofacial pathologies. The following data regarding exposure was collected from the radiological units: personal data (age and gender), radiological examination (type of examination and equipment) and exposure protocol (FOV, kV, mAs). Only patients with a complete set of information regarding the exposure were included in the study. The lack of clinical data for which the patients were referred to dental radiological examination was not considered as an exclusion criterion in the present study.

The pediatric population was divided into two groups: children who underwent a CBCT ± 2D dental radiological examination within two years (CBCT group) and children who underwent only 2D dental radiological examination (2D group). Each group was also classified according to age at the time of the radiological exposure.

The ethics committee of "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca, Romania has approved the epidemiological study (230/5.05/2015) and ethical committee of Katholieke Universiteit Leuven, Belgium has approved the DIMITRA project (S5694/15.07.2015).

2.2. Estimation of radiation doses

The x-ray units used for the CBCT and 2D dental radiological procedures in the selected centers are presented in Table 1. For this type of units, the most suitable effective doses (ED) reported in the literature were considered according to the type of radiological examination and the exposure protocol used for the pediatric population [6,11,15–20]. The effective doses presented in Table 1 were calculated on child and adult anthropomorphic dosimetric phantoms and were considered for the estimation of radiation doses in children. The quality control tests for radiographic and CBCT exposures have shown that all radiological equipments operated at their technical performance level in all included radiological centers within the time period of the study.

The CBCT effective doses reported in literature were then corrected according to mAs and FOV used for the radiological exposure of the selected population. A previously published volume-dose model for CBCT, in which the ED/mAs was expressed as a function of FOV diameter and height based on a set of measurements obtained using various FOVs, was used [9]. A CBCT-dependent correction factor for ED/mAs was obtained by using at least two values of the effective doses measured on anthropomorphic phantoms with different FOVs and the logarithmic fit equation of the volume parameter (diameter × height^2). The logarithmic fit equations for FOV dose correction are presented in Appendix (A) in Supplementary material. The effective doses for CBCT exposures were then calculated based on the tube current exposure time used in clinical condition for the selected pediatric population.

The coefficient for the adjustment of CBCT doses to the age of the pediatric cohort was obtained by using the linear interpolation of the ED/mAs parameter estimated in 10- years-old child phantom and adult phantoms using the ProMax 3D CBCT unit, with a large FOV scan (16 × 16 cm) and 90 kV exposure protocol. All equations for linear extrapolation of doses according to age and the logarithmic fit equations for FOV are presented in the Appendix (A) in Supplementary material.

The effective doses for conventional radiological exposures in the pediatric population were corrected for tube current exposure time and a linear interpolation with age was also applied. The kV was fixed in 92% of cases examined by CBCT and no correction of doses was applied for kV in the current study.

The total individual cumulative dose for dental radiological exposures represents the total amount of radiation given to a patient considering one-year lag for multiple exposures. The individual cumulative dose for the CBCT group of patients was calculated for all dental exposures including CBCT and conventional x-rays. The median (Q_2), interquartile range (IQR) and the maximum value of the cumulative and effective dose were calculated at different ages for the CBCT group and 2D group of patients (Table 2).

For the CBCT group, the cumulative dose incurred by each person according to dental radiological procedures was calculated as follows: the cumulative dose for a single CBCT (single CBCT dose), for repeated CBCTs (multiple CBCTs dose) and for conventional dental x-rays (2D_CBCT group) (Fig. 1).

The collective effective dose for the selected population represents the total radiation dose incurred by the selected population from dental radiological exposures. Per caput collective dose was estimated dividing the collective doses by the number of patients included in the study (Table 3).

2.3. Estimation of radiation risk

The radiation risk was estimated using three different methods: the relative radiation level (RRL), estimation of the lifetime attributable risk for cancer incidence (LAR), the background equivalent radiation time (BERT) (Tables 2 and 3 respectively).

The individual LAR for cancer incidence was estimated for various ages of males and females using the BEIR VII preferred model Table 12D-1 [21] and represents the number of cancer cases per 100,000 persons which were exposed to a single dose of 0.1 Gy. The individual LAR for each child was calculated using linear interpolation of risk inside of the age interval and the effective dose for each exposure. The radiation risk was expressed only according to dental radiological examinations and the total individual risk for multiple exposures represents the sum of risks for each exposure.

Background equivalent radiation time (BERT) represents the amount of radiation received from a radiological procedure expressed in terms of number of days of background radiation [22]. It was calculated for the studied groups considering per caput dose for a certain radiological examination and a background radiation of 3 mSv/year (Table 3).

RRL was used to compare the amount of radiation given by the radiological examinations with a variable effective dose as follow:(☢) radiation dose < 30 μSv for ages under 18 or radiation dose < 100 μSv for ages over 18 years; (☢☢) radiation dose between 30 and 300 μSv for ages under 18 years [23].

2.4. Data analysis and statistics

In order to calculate the individual cumulative dose of dental radiological examinations, LabVIEW Professional for Windows v.2017 (NI, Austin, Texas, USA) was used for merging the effective doses of the radiological procedures based on the patient's name and date of birth. Median value, interquartile range and maximum values were calculated for the effective and cumulative doses. Statistical analysis of differences between CBCT group and 2D group of patients, was performed using Mann Whitney *U* test for the non-normally distributed data and p-values < 0.05 were considered statistically significant.

3. Results

3.1. Descriptive epidemiology

The cohort included 7150 children and young adults aged between 0 and 22 years. A total number of 12252 dental radiological examinations (4220 intraoral, 1324 cephalometric, 5284 panoramic radiographs and 1424 CBCTs) were performed on the selected pediatric population. Table 2 shows a summary of the distribution of cases according to age at exposure and studied group, the variation of the effective dose for the CBCT and conventional radiological examinations as well as the total individual cumulative doses for each group.

The CBCT group included 1009 children with a single CBCT exposure (71.4%) or multiple CBCTs (28,5%) from which only 2% underwent also a 2D radiological examination within the two years interval.

3.2. Radiation doses for the pediatric cohort

The median effective doses for 2D dental radiological exposures were lower than 20 μSv which represents the lowest range of RRL (☢) while a higher level of radiation (☢☢) was found for the CBCT examinations perform at ages under 18 (Table 2).

The individual cumulative dose in the CBCT group was found to be significantly higher for children aged between 11 and 14 years old than in other age groups ($p < 0.0001$). The cumulative dose for the repeated CBCTs was significantly higher than for a single CBCT (median is 121.2 ± IQR 118.2 μSv and 309.4 ± IQR 222.1 μSv respectively) ($p < 0.05$) and it exceed 1mSv in children with multiple CBCT exposures. There are no significant differences between the 2D and CBCT group in terms of the cumulative doses incurred by patients from 2D dental X-rays (Fig. 1).

Per caput collective dose was found to be increased for children exposed to CBCT compared to 2D group and it was statistically significantly higher for children exposed to CBCT at the ages between 11

Table 2
Distribution of the irradiated patients, effective doses and individual cumulative doses according to age and studied groups.

Age group (years)	Patients non-exposed to CBCT (2D group)						Patients exposed to CBCT (CBCT group)					
	N	2D Effective Dose (μSv)		Cumulative Dose (μSv)			N	CBCT Effective Dose (μSv)		Cumulative dose (μSv)		
		Q_2	IQR	Q_2	IQR	Max		Q_2	IQR	Q_2	IQR	Max
0–6	114	7.6☢	10.1	11.4	14.5	114.9	26	51.5☢☢	97.6	67.4	111.3	336.7
7–8	315	5.8☢	10.5	11.4	13.9	92.1	44	137.6☢☢	90.2	135.1	102.7	433.9
9–10	534	5.4☢	10.5	11.4	16.4	182.3	91	132.2☢☢	49.1	136.7	44.9	722.0
11–12	522	3.2☢	9.9	11.2	17.3	105.5	155	204.8☢☢	66.5	214.9*	145.7	1251
13–14	543	2.6☢	9.6	9.0	17.9	173.3	157	170.8☢☢	63.1	211.9*	216.2	1514
15–16	608	1.8☢	7.1	8.6	17.5	176.2	132	173.8☢☢	66.8	180.1	110.3	1412
17–18	745	3.2☢	9.5	7.5	14.7	177.6	98	141.1☢☢	88.0	119.2	138.2	678.1
19–20	956	2.1☢	9.5	5.7	12.1	167.2	125	78.9☢	56.4	91.7	90.7	542.9
21–22	1804	4.8☢	10.5	8.9	16.9	195.8	181	72.5☢	56.7	88.2	99.3	428.7
Total	6141	3.3	10.1	8.8	15.8	195.8	1009	127.2	98.5	156.5	144.8	1514

N – number of patients; *effective dose* – dose derived from dosimetric measurements on phantoms with scaling factors applied for age and exposure protocol; *cumulative dose*- represents the total individual dose provided by conventional x-rays and CBCT considering one year lag; Q_2–median effective dose, *IQR* – interquartile range; *Max* − maximum value of radiation dose, *μSv* – microsievert; *Relative Radiation Level*[23] and symbols were applied to effective dose as follow: ☢ for doses < 30 μSv in children under 18 year old and doses < 100 μSv for adults; ☢☢ for doses of children aged under 18 years that ranged between 30 and 300 μSv; * *Mann Whitney U* test $p < 0.05$.

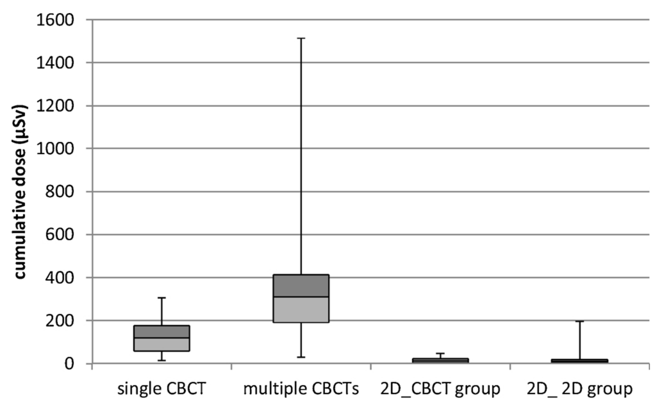

Fig. 1. Whisker-box-plots displays the distribution of the individual cumulative dose for dental radiological procedures in pediatric population: *single CBCT*: – dose for CBCT incurred by patients exposed to a single CBCT examination; *repeated CBCT*- dose for CBCT incurred by patients with multiple CBCTs within two years; *2D_CBCT group* – individual dose accumulated by a patient from CBCT group from conventional dental radiological exposures; *2D_2D group* – individual dose accumulated by a patient from 2D group within two years.

and 15 years ($p < 0.0001$) (Table 3).

The overall contribution of the CBCT examinations to the collective dose was 70% in two years even though the number of CBCT exposures was lower than other dental radiological examinations.

3.3. Radiation risk for pediatric cohort

A higher Life Attributable Risk (LAR) was found in the CBCT group compared to 2D group of pediatric population, for all age intervals. The overall variation of LAR showed an increased risk for children exposed to CBCT at ages under 15 years ($p < 0.05$) and the highest individual LAR was found for girls at the ages of 11–15 years (Table 3).

The background equivalent radiation time (BERT) for patients exposed to CBCT was higher than in the 2D group. The amount of radiation brought by a single CBCT examination was equivalent to 14.5 days of natural radiation on average and to 42.1 days for multiple CBCTs. The BERT for CBCT examination in the pediatric cohort was variable with age and the highest exposure equivalent time was found for ages between 11 and 15 years. The pediatric patients exposed only to conventional dental radiological examinations have a lower exposure equivalent time than for CBCT (1.5 days of natural radiation on average) which does not vary significantly with age (Table 3).

4. Discussion

4.1. Radiation doses for dental radiological exposures

An epidemiological study on CBCT radiation dose is challenging due to the heterogeneity of radiation exposure related to the radiological equipment, multiple combinations of exposure parameters, indications and patient characteristics. Currently, there are over 20 manufacturers providing more than 50 different CBCT units with different geometries

Table 3
Collective effective dose (μSv) and radiation risk for the studied groups.

Age group (years)	Per-caput collective dose (μSv)			Life attributable risk (LAR) of cancer incidence				*Background equivalent radiation time (BERT)* (days)		
	2D group	CBCT group	CBCT Contribution (%)	2D group		CBCT group		2D group	CBCT group	
				Female	Male	Female	Male		Single CBCT	Multiple CBCT
< 6	11.2	131.8	71	0.4	0.2	6.3	1.9	1.3	12.8	NA
6–10	13.8	145.1	59	0.4	0.2	5.1	2.8	1.6	12.6	30.5
11–15	14.5	279.8*	84	0.3	0.1	7.1	2.8	1.7	20.7	55.1
16–20	11.5	159.1	64	0.1	0.1	3.8	1.7	1.4	11.5	35.8
21–22	13.1	108.7	44	0.2	0.1	2.8	1.1	1.5	9.2	22.2
Overall	12.6	184.1	70%	0.4	0.2	6.1	2.9	1.4	14.5	42.1

Per caput collective dose – represents the total radiation dose incurred by children from dental radiological exposures truncated at one year lag divided by the number of exposed children; *CBCT Contribution*- represents the percent of the doses provided by CBCT for the total collective dose of the age groups; *Life Attributable Risk (LAR)* – mean number of cancers per 100,000 persons exposed to dental radiological examinations under clinical conditions; *Background Equivalent Radiation Time (BERT)* – mean days of exposure to natural background radiation (3mSv/year) equivalent to individual cumulative dose incurred from dental radiological exposures truncated at one year lag; **Mann Whitney U* test $p < 0.05$; *NA* – not applicable.

for scanning, collimators, filters and a large range of radiation dose per scan [24]. Moreover, most of these CBCT machines offer various protocols for exposures which considerably affect the radiation exposure including the FOV, milliampere x seconds (mAs), and kilovoltage (kV), which can be controlled by the technician according to patient size and the image quality requirements.

Therefore, any estimation of CBCT irradiation on a large population expressed in terms of effective dose could provide only average approximations. Limitations of the effective dose metric for medical exposures, i.e. uncertainty of measurement methodology, discrepancy between tissue weighting factors and actual radiation-induced detriment, as well as gender- and age-averaging of tissue weighting factors, all apply to the current study; however, the effective dose can still be considered as the most suitable index for risk assessment at a population level, especially when comparing between imaging modalities. At the time of writing, the debate regarding the most suitable dose index for CBCT, and its conversion to patient dose, it still on-going. Currently available dose indices for CBCT (e.g. dose-area product) serve many purposes, but cannot be used to directly compare the radiation risk between different units or protocols. Instead, the results were derived from direct measurements of effective dose in literature, revealing differences between the patients who underwent a CBCT examination and those irradiated only with conventional dental radiological techniques and highlighted the amount of cumulative doses for a single and multiple CBCTs in the pediatric population (Fig. 1).

To the best of our knowledge, our study is the first survey that compares doses for children and young adults exposed to CBCT and exposed only to 2D dental radiological modalities, in terms of current dental practice and taking age into account. The results clearly showed that CBCT exposures increased the individual cumulative dose for dental radiological exposures in children. However, the median effective dose for CBCT was lower than 0.3 mSv which placed this examination in the range of doses for mammography or pelvis radiography [23]. Also, the CBCT effective doses were much lower than the mean effective dose observed in children exposed to CT (1.06 mSv) [25].

On the other hand, a wide variation of the individual cumulative doses among ages was noted for children included in the CBCT group in contrast with the cumulative doses in the 2D group that do not vary significantly with age. The individual cumulative dose was significantly higher for children exposed to CBCT aged between 11 and 14 years compared to other ages (Mann Whitney *U* test $p < 0.05$). One explanation could be the high variability of the exposure protocols and frequency of CBCT examinations for children with dental anomalies or growth anomalies that may require repeated CBCTs. The CBCT examination in cleft patients is used for teeth assessment during mixed and permanent dentition. Moreover, during this age period, the CBCT evaluation of the bone defect volume provides technical details for graft procedures and it is also useful for establishing the thickness of the cortical bone and the possibility or the limits of orthodontic teeth movements. The young adults with ages between 19 and 22 years were included in the pediatric cohort in order to cover the CBCT exposures used for orthognatic surgery planning. However, the present study was a retrospective one and justification for the dental radiological examinations was therefore not assessed.

Recently, the International Commission on Radiological Protection (ICRP) stated that the estimation of collective dose in a population will not give a good indication of the health consequences and risks for the patient populations, due to the differences of age distributions of the patients undergoing medical ionizing exposures [26]. Our study also confirmed the importance of age related reporting of doses for a child population considering the significant contribution of CBCT exposures to the collective dose among all ages.

European Commission of Radiological Protection recommends the separation of the collective doses into various components, with an estimation of doses for different groups, reflecting the age and exposure characteristics as type of examinations, number of examinations for the selected population in a certain period of time [27]. In light of these new trends, our results emphasized the differences of the cumulative dose between the CBCT and 2D group and the significantly increased dose in the repeated CBCT exposures.

4.2. The radiation risk for pediatric cohort

Children could have a potentially higher risk for radiation-induced cancer occurrence due to their longer life span and their higher radiosensitivity compared with adults [28]. So far, several risk models have been developed in order to estimate the risk of cancer incidence after low-dose exposures [29].

The risk estimations in the present study rely on the linear non-threshold (LNT) model, which conservatively states that risks from high dose exposures can be linearly extrapolated to 0, taking into account a dose and dose rate effectiveness factor (DDREF). Both the validity of the LNT model and the value of DDREF used for low doses have been under scrutiny, as it is based on epidemiological data with a high level of uncertainty.

The individual LAR for dental radiological exposures was significantly higher for the CBCT group of patients and the highest LAR was found for girls of 11–15 year old. However, it remains uncertain whether a causality association between the CBCT exposure and an increased risk of cancer incidence exists for children. Ongoing research on radiobiological effects of low doses will lead to a reconsideration of the LNT, and possible even a replacement with another dose-effect model, which could completely reshape the concept of radiation protection of medical exposures.

Another way of estimating the radiation risk for low dose exposure is to compare the medical radiological exposure with the background radiation that represents the level of radiation to which the entire population is exposed daily from natural radioactive substances (3 mSv/year). The Background Equivalent Radiation Time (BERT) is a simple approach to express the potential risk for diagnostic radiological procedures. Our results showed that CBCT exposures increase the equivalent time of radiation compared to 2D group of patients but the equivalent risk remains much lower than for CT exposure (0.5 years for head CT) (22). BERT for CBCT was significantly higher for children exposed with multiple CBCTs between ages 11 and 15, being the age range for the highest dose per caput in the CBCT group (55.1 mean days equivalent time).

The American College of Radiology has established guidelines for defining the radiation dose, as a relative risk based on population medical exposure [23]. The Relative Radiation Level (RRL) classification allows for the comparison of the effective doses of medical exposures but the individual cumulative dose could be higher in children with multiple radiological examinations. The doses for 2D dental radiographies are equivalent with the radiation level for chest and hand radiographies while the CBCT examinations are placed in the range of doses for mammography and pelvis radiographies [23]. Nevertheless, in several cases with multiple CBCT exposures at ages under 16 years, the cumulative doses are much higher and can exceed 1mSv. Further research is still needed to describe the potential biomolecular effects for low dose exposure.

4.3. Limitation of the study

The limitations of the present study are mainly related to the small size of the epidemiological cohort, estimation of CBCT doses for various ages of children, and the uncertainties of linear no-threshold model for cancer risk estimation in low dose exposures. Our study includes only a limited size of population, that gives a low statistical power in dose and risk estimations.

For this retrospective analysis of irradiation in dental radiological exposures, the dosimetric measurements reported in the literature were considered. Future prospective studies on a larger number of CBCTs and exposure protocols are still necessary to describe the radiation doses and risk for children exposed in clinical condition. A well-reasoned justification of CBCT examinations based on selection criteria could reduce the number of dental radiological exposures in children. Optimization protocols by minimizing the field of view (FOV) could improve the radiation safety in CBCT exposures [30].

The limitations of risk models for low dose and the presence of the baseline risk of cancer incidence makes it difficult to conclude that an increasing of doses in the group of children exposed to CBCT could be directly associated with an excess risk of cancer incidence. However, our results showed that doses for CBCT exposures in current clinical conditions are higher than for other dental radiological exposures, placing the CBCT examination in a higher relative radiation risk level that has been considered before for pediatric dentistry.

In conclusion, our results revealed a wide variability of doses and risks of CBCT exposures in young patients that should be considered for reporting the dose-risk model in dentistry. Dentists should weigh the benefits of exposure according to age and pathological condition when considering indicating a CBCT or a conventional 2D radiography.

Authors contribution

All authors had the same contribution as the first author.

Conflict of interest statement

All authors declared no financial or personal relationship with other people or organisation, that could influenced this work.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ejrad.2018.04.021.

References

[1] European Commission, Radiation Protection 180, Medical Radiation Exposure for the European Population, Office for Official Publications of the European Communities, Luxembourg, 2014Available from: https://ec.europa.eu/energy/en/radiation-protection-publications.
[2] H.M. Alamri, M. Sadrameli, M.A. Alshalhoob, M. Sadrameli, M.A. Alshehri, Applications of CBCT in dental practice: a review of the literature, Gen. Dent. 60 (5) (2012) 390–400.
[3] European Commission, Radiation Protection 172. SEDENTEXCT Cone Beam CT for Dental and Maxillofacial Radiology: Evidence-based Guidelines, Office for Official Publications of the EuropeanCommunities, Luxembourg, 2012Available from: http://www.sedentexct.eu/files/radiation_protection_172.pdf.
[4] J.W. Casselman, K. Gieraerts, D. Volders, J. Delanote, K. Mermuys, B. De Foer, G. Swennen, Cone beam CT: non-dental applications, JBR-BTR 96 (6) (2013) 333–353.
[5] American Academy of Oral and Maxillofacial Radiology, Clinical recommendations regarding use of cone beam computed tomography in Orthodontics. Position statement by the American Academy of Oral and Maxillofacial Radiology, Oral. Surg. Oral Med. Oral Pathol. Oral Radiol. 116 (2) (2013) 238–257.
[6] R. Pauwels, J. Beinsberger, B. Collaert, C. Theodorakou, J. Rogers, A. Walker, L. Cockmartin, H. Bosmans, R. Jacobs, R. Bogaerts, K. Horner, SEDENTEXCT project consortium: effective dose range for dental cone beam computed tomography scanners, Eur. J. Radiol. 81 (2) (2012) 267–271.
[7] J.B. Ludlow, M. Ivanovic, Comparative dosimetry of dental CBCT devices and 64-slice CT for oral and maxillofacial radiology, Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod. 106 (2008) 106–114.
[8] A.C. Oenning, R. Jacobs, R. Pauwels, A. Stratis, M. Hedesiu, B. Salmon, Cone-beam CT in paediatric dentistry: DIMITRA project position statement, Pediatr. Radiol. (November) (2017).
[9] R. Pauwels, G. Zhang, C. Theodorakau, A. Walker, H. Bosman, R. Jacobs, K. Horner, R. Bogaerts, The SEDENTEXCT project consortium: effective radiation dose and eye lens dose in dental cone beam CT: effect of field of view and angle of rotation, Br. J. Radiol. 87 (2014) 20130654.
[10] J.A. Hidalgo-Rivas, C. Theodorakou, F. Carmichael, B. Murray, M. Payne, K. Horner, Use of cone beam CT in children and young people in three United Kingdom dental hospitals, Int. J. Paediatr. Dent. 24 (5) (2014) 336–348.
[11] J.B. Ludlow, R. Timothy, C. Walker, R. Hunter, E. Benavides, D.B. Samuelson, M.J. Scheske, Effective dose of dental CBCT-a meta analysis of published data and additional data for nine CBCT units, Dentomaxillofac. Radiol. 44 (1) (2015) 20140197.
[12] C.A. Raelson, K.M. Kanal, M.S. Vavilala, F.P. Rivara, L.J. Kim, B.K. Stewart, W.A. Cohen, Radiation dose and excess risk of cancer in children undergoing neuroangiography, AJR Am. J. Roentgenol. 193 (6) (2009) 1621–1628.
[13] R.T. Griffey, A. Sodickson, Cumulative radiation exposure and cancer risk estimates in emergency department patients undergoing repeat or multiple CT, AJR Am. J. Roentgenol. 192 (4) (2009) 887–892.
[14] B. Huang, J. Li, M.W. Law, J. Zhang, Y. Shen, P.L. Khong, Radiation dose and cancer risk in retrospectively and prospectively ECG-gated coronary angiography using 64-slice multidetector CT, Br. J. Radiol. 83 (986) (2010) 152–158.
[15] M. Loubele, R. Bogaerts, E. Van Dijck, R. Pauwels, S. Vanheusden, P. Suetens, G. Marchal, G. Sanderink, R. Jacobs, Comparison between effective radiation dose of CBCT and MSCT scanners for dentomaxillofacial applications, Eur. J. Radiol. 71 (3) (2009) 461–468.
[16] C. Theodorakou, A. Walker, K. Horner, R. Bogaerts, R. Jacobs, SEDENTEXCT project consortium: estimation of paediatric organ and effective doses from dental cone beam CT using anthropomorphic phantoms, Br. J. Radiol. 85 (1010) (2012) 153–160.
[17] X.M. Qu, G. Li, J.B. Ludlow, Z.Y. Zhang, X.C. Ma, Effective radiation dose of ProMax 3D cone-beam computerized tomography scanner with different dental protocols, Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod. 110 (2010) 770–776.
[18] J.B. Ludlow, L.E. Davies-Ludlow, S.C. White, Patient risk related to common dental radiographic examinations: the impact of 2007 International Commission on Radiological Protection recommendations regarding dose calculation, J. Am. Dent. Assoc. 139 (9) (2008) 1237–1243.
[19] F. Gijbels, R. Jacobs, R. Bogaerts, D. Debaveye, S. Verlinden, G. Sanderink, Dosimetry of digital panoramic imaging: part I: Patient exposure, Dentomaxillofac. Radiol. 34 (3) (2005) 145–149.
[20] A. Al-Okshi, A. M.Nilsson, M. Petersson, C. Wiese, Lindh using GafChromic film to estimate the effective dose from dental cone beam CT and panoramic radiography, Dentomaxillofac. Radiol. 42 (7) (2013) 20120343.
[21] National Research Council of the National Academies, Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII–Phase 2, The National Academy Press, 2006, Available from: https://www.nap.edu/read/11340/chapter/1.
[22] E.L. Nickoloff, Z.F. Lu, A.K. Dutta, J.C. So, Radiation dose descriptors: BERT, COD, DAP, and other strange creatures, Radiographics 28 (September–October (5)) (2008) 1439–1450.
[23] American College of Radiology ACR Appropriateness Criteria. Radiation Dose Assessment Introduction; 2011. Available at https://www.acr.org/-/media/ACR/Files/Appropriateness-Criteria/RadiationDoseAssessmentIntro.pdf.
[24] R. Pauwels, Cone beam CT for dental and maxillofacial imaging; dose matters, Radiat. Prot. Dosimetry 165 (1-4) (2015) 156–161.
[25] J. Aw-Zoretic, D. Seth, G. Katzman, S. Sammet, Estimation of effective dose and lifetime attributable risk from multiple head CT scans in ventriculoperitoneal shunted children, Eur. J. Radiol. 83 (10) (2014) 1920–1924.
[26] International Commission on Radiological Protection The 2007 Recommendations of the International Commission on Radiological Protection. ICRP Publication 103, 2007 Ann ICRP 37 (2-4). Available from: http://www.icrp.org/publication.asp?id=ICRP%20Publication%20103.
[27] European Commission on Radiological Protection Publication 154, 2008. European Guidance on Estimating Population Doses from Medical X- Ray Procedures. Available from: http://ddmed.eu/_media/background_of_ddm1:rp154.pdf.
[28] K.R. Kutanzi, A. Lumen, I. Koturbash, I.R. Miousse, Pediatric exposures to ionizing radiation: carcinogenic considerations, Int. J. Environ. Res. Public Health 13 (11) (2016) pii: E1057.
[29] M.P. Little, R. Wakeford, E.J. Tawn, S.D. Bouffler, A. Berrington de Gonzalez, Risks associated with low doses and low dose rates of ionizing radiation: why linearity may be (almost) the best we can do, Radiology 251 (1) (2009) 6–12.
[30] M.M. Rehani, R. Gupta, S. Bartling, G.C. Sharp, R. Pauwels, T. Berris, J.M. Boone, Radiological Protection in Cone Beam Computed Tomography (CBCT). ICRP Publication 129, Ann. ICRP 44 (1) (2015) Available from: http://www.icrp.org/publication.asp?id=ICRP%20Publication%20129.

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REVIEW ARTICLE

Artificial intelligence models for clinical usage in dentistry with a focus on dentomaxillofacial CBCT: a systematic review

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Abstract

This study aimed at performing a systematic review of the literature on the application of artificial intelligence (AI) in dental and maxillofacial cone beam computed tomography (CBCT) and providing comprehensive descriptions of current technical innovations to assist future researchers and dental professionals. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA) Statement was followed. The study's protocol was prospectively registered. Following databases were searched, based on MeSH and Emtree terms: PubMed/MEDLINE, Embase and Web of Science. The search strategy enrolled 1473 articles. 59 publications were included, which assessed the use of AI on CBCT images in dentistry. According to the PROBAST guidelines for study design, seven papers reported only external validation and 11 reported both model building and validation on an external dataset. 40 studies focused exclusively on model development. The AI models employed mainly used deep learning models (42 studies), while other 17 papers used conventional approaches, such as statistical-shape and active shape models, and traditional machine learning methods, such as thresholding-based methods, support vector machines, k-nearest neighbors, decision trees, and random forests. Supervised or semi-supervised learning was utilized in the majority (96.62%) of studies, and unsupervised learning was used in two (3.38%). 52 publications included studies had a high risk of bias (ROB), two papers had a low ROB, and four papers had an unclear rating. Applications based on AI have the potential to improve oral healthcare quality, promote personalized, predictive, preventative, and participatory dentistry, and expedite dental procedures.

Keywords Artificial intelligence · Deep learning · Cone beam computed tomography · Dentistry

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Abbreviations

AI	Artificial intelligence
ALADAIP	As low as diagnostically acceptable being indication-oriented and patient-specific
AME	Ameloblastoma
ASD	Average symmetrical surface distance
ASM	Active shape model
CBCT	Cone-beam computed tomography
CNN	Convolutional neural network
DICE	Dice similarity coefficient
DL	Deep learning
GAN	Generative adversarial network
HD	Hausdorff distance
IAN	Inferior alveolar nerve
IOS	Intra-oral scan
IOU	Intersection over union
ICP	Iterative closest point
KNN	K-nearest neighbors
ME	Mean error
MC	Mandibular canal
ML	Machine learning
MRE	Mean radial error
MSD	Mean surface distance
NN	Neural network
NPV	Negative predictive value
LOOCV	Leave one out cross-validation
PA	Periapical
PPV	Positive predictive value
PROBAST	Prediction risk of bias assessment tool
ReLU	Rectified linear unit
RMSE	Root mean squared error
RNN	Recurrent neural network
ROB	Risk of bias
Se	Sensitivity
SE	Surface error
Sp	Specificity
SVM	Support vector machine
TMJ	Temporomandibular joint
TMD	Temporomandibular disorder

Introduction

Artificial intelligence (AI) is a branch of computer science concerned with designing intelligent computer systems that exhibit characteristics associated with human intelligence [1]. AI has been used in all fields of dentistry for assisting with diagnostics and treatment planning, as well as for predicting certain treatment outcomes. It can be used as an auxiliary tool for increasing diagnostic accuracy, assisting junior or general dental practitioners, as well as for its time-saving capabilities [2].

Medical fields that rely on imaging data have benefited from the implementation of AI in recent years, as it can provide interpretation of complex features in an automated fashion [3]. The routine clinical acquisition of imaging data has led to the availability of large databases for training AI models. In the clinical practice of dentistry, 3D cone-beam computed tomography (CBCT) images are commonly acquired to assist in diagnosis, treatment planning, and surgery. Among all available options, CBCT imaging is the sole modality to provide comprehensive 3D volumetric information on complete teeth and alveolar bones [4]. CBCT provides high-quality images at a lower radiation dose than CT and a shorter scanning time. It has significantly added to the diagnostic efficiency and accuracy of dental diagnostic imaging and has positively impacted treatment outcomes [5].

Despite its many advantages, clinical interpretation of CBCT scans may suffer from low interobserver/intraobserver reliability, especially for less experienced practitioners [6]. Automation in dentistry, especially for CBCT segmentation and lesion detection, is highly needed. Integrating AI and CBCT could potentially streamline and expedite the dental workflow, eventually leading to better, more objective, reproducible radiology assessments and lessened workloads.

Machine learning (ML) is a subset of AI, which has been defined by Arthur Samuel as "the field of study that gives computers the ability to learn without being explicitly programmed". Based on the amount of human supervision received during the training phase, ML algorithms can be classified as supervised, unsupervised, semi-supervised and reinforcement learning. Supervised learning involves training an algorithm using labeled data, meaning data that contains the desired outcomes, whereas unsupervised learning uses data that is unlabeled [7]. Reinforcement learning arrives at a model trough complex mechanisms or rewards and punishments [8].

Recent developments in AI, particularly the field of deep learning (DL), have opened new doors for computer-aided clinical diagnosis [9]. These algorithms automatically learn discriminant features from data and can discover underlying patterns in classes of images and automatically work out the most descriptive features with respect to a specific class of object. The convolutional neural network (CNN) has achieved significant improvements in the field of computer vison [10]. The architecture of a CNN is composed of convolutional, pooling layers and fully connected layers. The convolutional layer extracts features from the input images. This is done using kernels, which are matrixes of values (weights) trained to detect specific features. To facilitate the learning of kernel weights, the convolution layer's output is then fed to a non-linear activation function, like a ReLU (Rectified

Linear Unit) function. The convolution layer is often followed by al pooling layer, which reduces dimensionality and speeds up the training process. These convolutional and pooling layers are repeated several times. Finally, the fully connected layers integrate the feature responses from the entire image and provide the final results [11].

To the best of our knowledge, there are no papers on the use of AI models for clinical usage in dentistry with a focus on CBCT. Therefore, the objective of the paper was to conduct a systematic review of the literature concerning the use of AI in dental and maxillofacial CBCT and provide detailed descriptions of recent technological advancements, in order to aid future researchers and dental practitioners.

Methods

The systematic review was performed following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA) Statement [12]. The study protocol was prospectively registered in the open science framework and can be found at the following address https://osf.io/r74ag.

The focused question used for the literature search was "What are the current clinical applications and diagnostic performance of AI algorithms in dental and maxillofacial CBCT?" The PICO framework is listed in Table 1.

Eligibility criteria

The inclusion criteria were represented by: original research (clinical trials, cohort studies, case–control, experimental studies) published in the English language; CBCT imaging-based studies using AI models for automatic diagnosis of disease, detection of abnormalities, measurements of pathological area/volume or identification of teeth and anatomical structures in the dental and maxillofacial region; articles which include mentions of datasets used to train, test, and validate the AI models, as well as quantifiable measures of AI performance.

The exclusion criteria were as follows: articles outside the area of interest, literature reviews, commentary, letter to the editor, editorials, case series, conference abstracts, grey literature and full-text not available or accessible.

Information sources

A structured electronic search was conducted in June 2022 in the following databases: PubMed/MEDLINE, Embase, and Web of Science. The last electronic search was performed on the 13th of June 2022.

The search strategy was based on MeSH and Emtree terms and the syntax was adapted to each database. The following keywords were used: CBCT, Cone-Beam Computed Tomography, Artificial Intelligence, Neural Networks, Machine Learning, Unsupervised Machine Learning, Supervised Machine Learning, Deep Learning, Support Vector Machine, Random Forest, Convolutional Neural Network. The detailed search strategies can be found in Supplementary Table S1. The publication period was restricted to the last 10 years (starting from 2012 to 2022).

Study selection

The study selection was performed using Rayyan AI [13], a web tool to assist in working on systematic reviews and scoping reviews. The publications were independently examined by two calibrated researchers (S.M. and O.A.), who evaluated the titles and abstracts for relevance and the presence of the eligibility criteria, followed by assessing the full text of the retrieved articles. In case of disagreement, a consensus was reached by discussion, and discrepancies were resolved by a third researcher (M.H.). References were managed using Mendeley Reference Manager v2.73.0 (Copyright© 2022 Mendeley Ltd) [14].

Data collection process

Two authors (S.M. and O.A.) similarly extracted the data from the articles using a standardized template. The principal summary outcomes were authors, year of publication, country, the field of dentistry, study design, aim, dataset, data augmentation, AI architecture, validation method,

Table 1 PICO elements for guiding the search strategy

What are the current clinical applications and diagnostic performance of AI algorithms in dental and maxillofacial CBCT?	
Patient or problem	Dental and maxillofacial CBCT scans
Intervention	Artificial Intelligence models for screening and diagnostics in dentistry
Comparison	Expert judgment, clinical/pathological examination
Outcome	Performance indicators, measurable or predictive outcomes (such as DICE, AUC, Se, Sp, Ac, Precision, AUC, mean difference from reference)

Table 2 Summary of included studies ($n = 59$)

Applications in endodontics									
Authors	Country	Objective	Study design	AI technique	Dataset	Data augmentation	Validation method	Reference standard/comparison (if any)	Outcome (best)
Benyó, B 2012 [21]	Hungary	Root canal identification	Development and validation	Decision tree	25 micro-CT and 36 CBCT scans (validation)	–	External validation	Expert assessment	Overall success rate 92.0% (micro-CT) 91.7% (CBCT)
Johari et al. 2016 [22]	Iran	Detection of Vertical Root Fractures	Development	Thresholding based algorithm	40 periapical (PA) and CBCT radiographs	–	–	Microscopic evaluation	Sp 99.02 ± 0.77 (CBCT); Sp 99.69 ± 0.22 (PA)
								Expert assessment	Se 79.54 to 100 (CBCT); Se 61.90 to 77.39 (PA)
Johari et al. 2017 [23]	Iran	Detection of vertical root fractures	Development	Probabilistic NN	240 radiographs of extracted teeth (CBCT and PA) 120 intact 120 fractured	–	threefold cross-validation	Microscopic evaluation (ground truth), a model trained on PA radiographs	CBCT (best) Accuracy 96.6 Se 93.3 Sp 100% PA Accuracy 70.0 Se 97.78 Sp 67.7%
Orhan et al. 2020 [24]	Turkey	Detection of periapical pathosis	Validation	Deep learning CNN Diagno-Cat	153 PA lesions from 109 patients (test)	–	External validation	Expert identification (ground truth)	AI system was able to detect 142 of 153 PA lesions (92.8% reliability) Recall 0.89 Precision 0.95 F-score 0.93
Setzer et al. 2020 [25]	USA	Periapical lesion detection	Development	Deep learning (CNN)	20 CBCT volumes (61 roots)	–	fivefold cross-validation	Expert assessment	Accuracy 0.93 Sp 0.88, PPV 0.87, NPV 0.93, Dice 0.67
Zheng et al. 2021 [26]	USA	Periapical lesion detection	Development	Deep learning	20 patients with periapical lesions	–	fourfold cross-validation	Expert assessment Other methods (Data-driven Dense U-Net)	Performance (best) Precision 0.9 Recall 0.84 Dice 0.741 (lesion)

Table 2 (continued)

Authors	Country	Objective	Study design	AI technique	Dataset	Data augmentation	Validation method	Reference standard/comparison (if any)	Outcome (best)
Applications in implantology									
Gerlach et al. 2014 [27]	Nether-lands	Mandibular canal segmentation	Development	Active shape model	2 CBCT scans (1 dentate 1 edentulous cadaver head)	–	–	Histological sections (ground truth)	Mean (SD) ranging up to 0.41 mm in the dentate jaw and 0.22 mm in the edentate jaw
				Active Appearance Model	13 CBCT scans			Manual segmentation	
Sorkhabi et al. 2019 [28]	Iran	Alveolar bone density classification	Development	Deep learning CNN	83 CBCT scans (207 surgery target areas) Training 110 Validation 54 Testing 43	Mirroring Translation Rotation	Split Sample Validation	Clinical measurements (surgeon tactile sensation during surgery, peak insertion torque, and fixture resonance frequency) -ground truth	Average Precision 84.63% (hexagonal prism) and 95.20% (cylindrical voxel)
								Other methods[29, 30]	Accuracy 95.2%
Jaskari et al. 2020 [31]	Finland, UK	Mandibular Canal Segmentation	Development	Deep learning (CNN)	637 CBCT scans Training 457 Validation 52 Test 128	–	Split sample validation	Expert evaluation (15 voxel-level annotations, 113 coarse annotations)	Mean curve distance 0.56 mm ASD 0.45 mm DICE 0.57 (left) 0.58 (right) HD 1.40 (left) 1.38 (right)
Kwak et al. 2020 [32]	China, South Korea, Finland	Segmentation of mandibular canal	Development	Deep learning CNN U-Net	102 CBCT scans (49,094 images) train:valid:test ratio 6:2:2	–	Split Sample Validation	Manual segmentation (ground truth), 3 CNNs	Global Accuracy 0.99 class Accuracy 0.96 mean IOU 0.577
Bayrakdar et al. 2021 [33]	Turkey	Dental implant planning	Validation	Deep Learning (CNN) DiagnoCat	75 CBCTs (508 edentulous regions)	–	External Validation	Expert assessment	95.3% missing tooth regions detected; AI system was unable to perform 80 bone height measurements and 15 bone thickness measurements

Table 2 (continued)

Authors	Country	Objective	Study design	AI technique	Dataset	Data augmentation	Validation method	Reference standard/comparison (if any)	Outcome (best)
Applications in implantology									
Lim et al. 2021 [34]	South Korea	Inferior Alveolar Nerve canal detection	Development and validation	Deep learning CNN U-Net	138 CBCT scans Internal dataset 98 (Train 68 patients Validation 15 Test 15) External dataset 40 (test)	–	Split sample validation	Manual segmentation (ground truth)	Dice 0.58 ± 0.08 (internal) Dice 0.49 ± 0.12 (external)
Roongruangsilp et al. 2021 [35]	Thailand	Dental implant planning	Development	Deep learning R-CNN	184 CBCT scans (316 implant position images-panoramic and cross-sectional) Training 300 Test 16	Blur, sharpen, color, crop, vertical flip, horizontal flip, rotate, noise	Split sample validation	Expert assessment (ground truth)	Detection 75.00% (panoramic); 75.00% (cross-sectional) Accuracy 100% (panoramic); 88.89% (cross-sectional)
Alsomali et al. 2022 [36]	Saudi Arabia	Localization of radiographic markers in implant sites	Development	Deep learning CNN	34 CBCT scans Training and validation 30 (16,272 images) Testing 4	–	Split sample validation	Manual identification	83% of markers correctly identified FPR (false positive rate) 2.8%
Cipriano et al. 2022 [20]	Italy	Inferior Alveolar Nerve canal detection	Development	Deep learning U-Net (CNN)	347 dental CBCT scans Primary dataset (dense and sparse annotations) 91 Training 68 Testing 15 Validation 8 Secondary dataset (sparse annotation) 256 scans (training)	–	Split sample validation	Other methods (Med3D)	Dice 0.69 IOU 0.54

Table 2 (continued)

Authors	Country	Objective	Study design	AI technique	Dataset	Data augmentation	Validation Method	Reference standard/comparison (if any)	Outcome (best)
Applications in Oral and Maxillofacial Surgery									
Chang et al. 2013 [37]	USA	Segmentation of maxilla	Development	Active Shape Model	19 CBCTs	–	LOOCV	Manual segmentation (ground truth) Other methods	MSD 0.25 ± 0.2 mm SE 0.25 ± 0.2
Wang et al. 2013 [38]	USA, China	Segmentation of mandible and maxilla	Development and validation	Atlas-based	30 spiral CT Testing 13 CBCT scans	–	Cross-validation External validation	Expert assessment (ground truth) Other methods	Dice 0.91 ± 0.02 (mandible) 0.87 ± 0.02 (maxilla) average distance error (ADE) 0.61 ± 0.17 (mandible) HD 0.92 ± 0.47 (mandible)
Wang et al. 2016 [39]	USA, South Korea, China	Segmentation of mandible and maxilla	Development and validation	Random forest	30 CBCT scans	–	LOOCV (internal) twofold cross-validation (external)	Manual segmentation (ground truth)	Dice 0.94 (mandible) and 0.91 (maxilla) ASD 0.42 ± 0.15 HD 0.74 ± 0.25 (internal)
					60 spiral MSCT scans (external validation)			Other methods	Dice 0.95 ± 0.02 (mandible) 0.92 ± 0.01 (maxilla) ASD 0.33 ± 0.11 HD 0.41 ± 0.20 (external)
Abdolali et al. 2017 [40]	Iran	Classification of maxillofacial cysts	Development	SVM, SDA (sparse discriminant analysis)	125 CBCT scans (20 000 axial images)	–	Threefold cross-validation	Classifiers with different feature extraction methods	Accuracy of 94.29% (SVM) and 96.48% (SDA)
Yilmaz et al. 2017 [41]	Turkey	Diagnosis of the periapical cyst and keratocystic odontogenic tumor	Development	SVM	50 dental CBCT scans	–	Tenfold cross-validation Split sample validation LOOCV	Expert identification Other classifiers (k-nearest neighbors (k-NN), naive Bayes, decision trees, random forest, neural network (NN)	Accuracy 100% F-score(F1) 100% (tenfold CV) Accuracy 96.00% F-score 96.00% (split sample) Accuracy 94.00% F-score 93.88% (LOOCV)

Table 2 (continued)

Authors	Country	Objective	Study design	AI technique	Dataset	Data augmentation	Validation Method	Reference standard/comparison (if any)	Outcome (best)
Applications in Oral and Maxillofacial Surgery									
de Dumast et al. 2018 [42]	USA	Diagnosis of temporomandibular joint osteoarthritis (TMJOA)	Development and validation	Deep learning	Dental and Craniofacial Bio network of Image Analysis database (DCBIA) CBCT images of 259 condyles (105 control subjects and 154 patients with diagnosis of TMJ OA) Testing 34	Perlin noise	Split sample validation	Expert assessment	91% close agreement between the clinician consensus and the classifier
Haghnegahdar et al. 2018 [43]	Iran	Diagnosis of TMJ disorders	Development	K-NN (k-nearest neighbor)	132 CBCT scans 66 patients (132 joints) with TMD and 66 normal cases (132 joints)	–	Tenfold cross-validation	Support Vector Machine, Naïve Bayes, Random Forest	Accuracy 0.9242 Se 0.9470 Sp 0.9015
Abdolali et al. 2019 [44]	Iran, Japan	Maxillofacial lesion detection for content-based image retrieval	Development	Knowledge-Based SVM, SDA	1145 CBCT scans	–	Split sample validation	Manual segmentation (ground truth) Other methods	mean Dice 0.89, 0.85, 0.92, and 0.87 (maxillary sinus perforation, radiolucent lesion, unerupted tooth, root fracture) HD 1.16 ± 0.19 1.35 ± 0.14 0.81 ± 0.21 1.27 ± 0.08 (maxillary sinus perforation, radiolucent lesion, unerupted tooth, root fracture) mean average retrieval accuracy 0.90 normalized discounted cumulative gain 0.92
Minnema et al. 2019 [45]	Netherlands, Germany	Bone segmentation	Development	Deep learning CNN	20 dental CBCT scans Training 18 Validation 2	–	twofold cross-validation	Expert assessment, other methods	average Dice 0.87 ± 0.06 Mean absolute deviation 0.44 mm ± 0.13 mm

Table 2 (continued)

Authors	Country	Objective	Study design	AI technique	Dataset	Data augmentation	Validation Method	Reference standard/comparison (if any)	Outcome (best)
Applications in Oral and Maxillofacial Surgery									
Lee et al. 2020 [46]	South Korea	Detection and diagnosis of odontogenic cystic lesions—odontogenic keratocysts, dentigerous cysts, and periapical cysts	Development	Deep learning CNN	2,126 images 1,140 panoramic and 986 CBCT images Training and validation 80% Testing 20%	Horizontal and vertical flipping Rotation (in the range of 20°) Width and height shifting (in the range of 0.2) Shearing (in the range of 0.5) Zooming	Split sample validation	Histopathological examination (ground truth) A model trained on panoramic images	AUC 0.914 Accuracy 91.4% Se 96.1% Sp 77.1% (CBCT)
Chai et al. 2021 [47]	China	Diagnosis of ameloblastoma (AME) and odontogenic keratocyst (OKC)	Development	Deep learning CNN	350 CBCT scans (178 AMEs and 172 OKCs) Training 272 Testing 78	–	Split sample validation	Histopathological examination (ground truth) Expert assessment	Se 87.2% Sp 82.1% Accuracy 84.6% F1-score 85.0%
Kim et al. 2021 [48]	South Korea	Segmentation of mandibular condyle and cortical thickness measurement	Development	Deep learning (CNN)	25 CBCT scans (12,800 images) Training 18 Validation 5 Test 2	–	Split sample validation Monte Carlo cross-validation	Manual segmentation	mean IOU 0.870 ± 0.023 (marrow bone) 0.734 ± 0.032 (cortical bone) mean HD 0.928 ± 0.166 mm (bone marrow) 1.247 ± 0.430 mm (cortical bone) ME approx. 1 mm
Lin et al. 2021 [49]	China	Diagnosis of oral and facial surgical diseases	Development	Deep learning (CNN)	680 CBCT scans Training: Validation:Test ratio 8:1:1	–	Split sample validation	Expert evaluation (ground truth) Other methods (semisupervised full CNN, spatial factorization, and ASNet)	IOU 0.906
Lo Giudice et al. 2021 [50]	Italy	Mandible segmentation	Development	Deep learning CNN	Pre-training MICCAI Head and Neck dataset[18] In-house dataset 45 CBCT scans Training 20 Validation 5 Testing 20	–	Split sample validation	Expert assessment (ground truth)	Dice 0.972 Surface deviation-matching percentage 89.23%

Table 2 (continued)

Applications in Oral and Maxillofacial Surgery									
Authors	Country	Objective	Study design	AI technique	Dataset	Data augmentation	Validation Method	Reference standard/comparison (if any)	Outcome (best)
Qiu et al. 2021 [51]	Nether-lands	Mandible segmentation	Development and validation	Deep learning CNN and recurrent SegUnet (RNN)	59 CBCT scans Training 38 Validation 1 Test 20 109 CT scans PDDCA dataset[19] 48 CT scans	–	Split sample validation External Validation	Expert assessment (ground truth), Other methods on two CT datasets	average Dice 95.31% ASD 1.2827 mm HD 3.1258 mm (CBCT dataset); average Dice 88.62% (±4.98) ASD 1.2582 (±0.4102) mm HD 4.9668 (±5.0592) mm (CT dataset); average Dice 94.57% (±1.21) HD 0.1252 (±0.0275) mm HD 1.1813 (±0.4028) mm (PDDCA dataset)
Qiu et al. 2021 [52]	Nether-lands	Mandible segmentation	Development and validation	Deep learning	59 CBCT scans Training 38 Validation 1 Testing 20 PDDCA dataset[19] 48 CT scans	–	Split sample validation External Validation	Expert assessment (ground truth) Other methods on CT dataset	average Dice 95.35% ASD 0.9908 mm HD 2.5723 mm (CBCT dataset) Dice 95.29% ASD 0.1353 mm HD 1.3054 mm (PDDCA dataset)
Ter Horst et al. 2021 [53]	Nether-lands	Soft tissue prediction	Development	Deep Learning	133 subjects (3D photographs and CBCT scans) Training 119 Testing 14	–	Split sample validation	Postoperative 3D photographs (ground truth), another model	Mean absolute error 1.0 ± 0.6 mm RMSE 1.2 ± 0.6 mm
Wang et al. 2021 [54]	China	Segmentation and Oral Lesion Detection	Validation	Deep learning (CNN)	90 CBCT scans	–	External Validation	Pathology (ground truth), Manual segmentation, a Thresholding algorithm	Accuracy 98.3%
Zhang et al. 2022 [55]	USA	Registration and quality assurance for 3D printed tissue engineering scaffolds	Development	Iterative closest point (ICP)	6 CBCT scans of 3D printed scaffolds	–	–	N/A	smallest RMSE 0.56 mm

Table 2 (continued)

Applications in Orthodontics

Authors	Country	Objective	Study design	AI technique	Dataset	Data augmentation	Validation Method	Reference standard/ comparison (if any)	Outcome (best)
Gupta et al. 2015 [56]	Germany	Cephalometric landmark detection	Validation	Knowledge-Based	30 CBCT scans (test)	–	External Validation	Expert localization	ME 2.01 mm SD 1.23 mm Overall landmark detection accuracy 64.67, 82.67, and 90.33% within 2-, 3- and 4-mm error
Gupta et al. 2016 [57]	Germany	Evaluation of 3D cephalometric measurements	Validation	Knowledge-Based	30 CBCT scans (test)	–	External Validation	Expert assessment	Highest ME 2.63 mm ± 2.46 (linear measurements), 2.12° ± 2.40 (angular measurements), 0.03 ± 0.02 (ratio measurements)
Zhang et al. 2016 [58]	USA	Cephalometric landmark detection	Development	Random forest	41 CBCT scans 30 MSCT scans	–	LOOCV fivefold cross-validation	Manual identification (expert assessment) other methods	Average Dice 0.89 ME 1.44 mm
Codari et al. 2017 [59]	Italy	Cephalometric landmark detection	Development	K-means clustering	18 CBCT scans (validation)	–	–	Expert evaluation (manual annotation)	median localization error 1.99 mm
Torosdagli et al. 2019 [60]	USA	Mandibular segmentation and landmark detection	Development and validation	Deep learning (deep NN + long short-term memory network (recurrent NN))	Training 50 CBCT scans External validation MICCAI Head-Neck Challenge 2015[18] 48 CT scans	–	fivefold cross-validation External validation	Expert evaluation Other methods (U-Net)	IOU 100 DICE 93.82 HD 5.47 DICE 93.86% (external validation)
Chen et al. 2020 [61]	China, USA	Cephalometric landmark detection and assessment of maxillary constriction	Validation	Random forest LINKS[16]	96 CBCT scans Training 30 Validation 6 Testing 60 (30 impacted canine 30 healthy)	–	Split sample validation	Expert assessment	average DICE 0.80

Table 2 (continued)

Applications in Orthodontics									
Authors	Country	Objective	Study design	AI technique	Dataset	Data augmentation	Validation Method	Reference standard/ comparison (if any)	Outcome (best)
Zhang et al. 2020 [62]	USA, China, South Korea	Craniomaxillofacial Bone Segmentation and Landmark Digitization	Development	Deep learning CNN	77 CBCT scans	–	fivefold cross-validation	Expert evaluation ground truth)	ME 1.10 ± 0.71 mm Midface Dice 93.19 ± 0.89 Se 92.82 ± 1.91 PPV 93.61 ± 1.40
					30 MSCT			Other methods (multi-atlas, random forest, sparse representation)	Mandible Dice 93.27 ± 0.97 Se 93.63 ± 1.37 PPV 92.93 ± 1.09
Huang et al. 2021 [63]	Germany	Cephalometric landmark detection and cephalogram synthesis from CBCT	Development	Deep learning GAN + CNN LeNet-5 and ResNet50	491 head CT scans[64] ISBI Challenge training data-set[17][17]	Patch Augmentation	Split Sample validation	Other methods [39][39][39] [39]	Cephalogram synthesis average peak signal-to-noise ratio (PSNR) 33.8 Landmark detection 93.0% successful detection rate (4 mm precision range)
Kim et al. 2021 [69]	South Korea, China, USA	Cephalometric landmark detection	Development	Deep learning (CNN)	430 CBCT scans Training 80% Testing 20%	Pixels shift Rotation	Split Sample validation	Manual identification (expert assessment)	average MRE 1.03 ± 1.29 mm Precision 87.13%, 91.19%, 93.52%, 96.59% (2.0 mm, 2.5 mm, 3.0 mm, and 4.0 mm)
Kim et al. 2021 [70]	South Korea, China, USA	Cephalometric landmark identification	Development	Deep learning CNN	430 posteroanterior cephalograms synthesized from CBCT scans Training 345 Test 85	–	Split sample validation	Expert identification (ground truth)	MRE 2.23 ± 2.02 mm SDR (successful detection rate) 60.88% (errors 2 mm or lower)

Table 2 (continued)

Applications in Orthodontics									
Authors	Country	Objective	Study design	AI technique	Dataset	Data augmentation	Validation Method	Reference standard/ comparison (if any)	Outcome (best)
Wang et al. 2021 [71]	Netherlands, China	Segmentation of jaws and teeth	Development	Deep Learning CNN	30 CBCT scans (9507 slices)	–	fourfold cross-validation	Expert assessment (ground truth)	Dice 0.934 ± 0.019 (jaw); 0.945 ± 0.021 (teeth)
								Other methods	Mean absolute deviations (MAD) 0.390 ± 0.093 mm (jaw); 0.204 ± 0.061 mm (teeth)
Zhang et al. 2021 [72]	China	Registration of lateral cephalogram with CBCT scan	Development	Deep learning CNN	220 CBCT scans Training 120 (CBCTs and synthetic lateral cephalograms LC) Testing 100 CBCTs, 2 LCs	Synthetic LCs	Split sample validation	Other methods	mean contour deviation 0.41 ± 0.12 mm (anterior cranial base) 0.48 ± 0.17 mm (mandible) 0.35 ± 0.08 (maxilla)
Chen et al. 2022 [73]	China	Cephalometric landmark detection	Development and validation	Deep learning RNN	89 CBCT scans (internal dataset)	-	threefold cross-validation	Expert assessment, other methods	MRE 1.64 mm; 74.28% of landmarks within the 2 mm clinically acceptable errors (internal)
					PDDCA dataset[19] 48 CT scans		External validation		MRE 2.37 mm; 56.36% of landmarks within the 2 mm clinically acceptable errors(external)

Table 2 (continued)

Other applications

Authors	Country	Objective	Study design	AI technique	Dataset	Data augmentation	Validation Method	Reference standard/comparison (if any)	Outcome (best)
Kim et al. 2016 [74]	South Korea	Classification of mandibular canal course	Development and validation	Cluster analysis	429 CBCT images	–	Silhouette analysis	N/A	ANOVA test showed each classified course was statistically distinct from the others
Pei et al. 2016 [75]	China	Tooth segmentation	Development	Random walks	20 CBCT scans	–	–	Expert assessment (ground truth), other methods	Average Dice 0.98 (anterior teeth and premolars) Average Dice 0.95 (molars)
Li et al. 2019 [76]	China, UK	Tooth segmentation	Development	Deep learning CNN	400 tooth CBCT images (100 incisors, 100 canines, 100 premolars, and 100 molars)	Rotation, gamma correction, noise injection, translation, scaling, random affine Transform	Split sample validation	Other methods	Accuracy 87.0%
Chung et al. 2020 [77]	South Korea	Tooth segmentation	Development	Deep learning CNN	175 CBCT scans Training 150 Testing 25	Cutout augmentation	Split sample validation	Expert assessment (ground truth) Other methods	F1 score 0.93; aggregated Jaccard index 0.86; Precision 0.93; Se 0.93; HD 1.59 mm; ASD 0.20 mm
Lee et al. 2020 [78]	South Korea	Tooth segmentation	Development	Deep learning (CNN)	102 CBCT scans Training 69 Validation 1 Testing 32	Translation (±5%) Resize (±30%) Vertical flip Horizontal flip	Split Sample validation	Other methods [79, 79] Ablation study	Dice 0.912 Recall 0.945 Precision 0.881
Li et al. 2020 [81]	China	Segmentation of tooth roots	Development	Deep learning CNN(U-Net) and RNN	29 CBCT scans Training 24 Testing 5	–	Split Sample validation	Manual segmentation Other methods (CNN, classic U-Net)	IOU 0.914 DICE 0.955 average precision 95.8%, average Recall 95.3% and ASD 0.145 mm
Ezhov et al. 2021 [82]	Cyprus, Turkey	Dental diagnostics	Validation	Deep learning Diagnocat (CNN)	1346 CBCT scans (705,017 samples consisting of 28,745 teeth and 25 conditions)	–	k-fold cross validation Split Sample validation	Expert evaluation	Se 0.9239 Sp 0.9899

Table 2 (continued)

Other applications									
Authors	Country	Objective	Study design	AI technique	Dataset	Data augmentation	Validation Method	Reference standard/comparison (if any)	Outcome (best)
Kats et al. 2021 [83]	Israel	Detection of image sharpening	Development	Deep learning (CNN)	4290 CBCT slices (original and with sharpening filter)	Horizontal flip Vertical flip	Split sample validation	Expert assessment	Se 53%, 93.33%, 93%
					Training 80% Validation 20%	Rotation Zoom			Sp 72.33%, 84%, 85.33%
					Testing 1200 images (with and without filter)	Height Width shift			Accuracy 62.17%, 88.67%, 89% (for three levels of image sharpening—1, 2, 3)
Lahoud et al. 2021 [84]	Belgium, Brazil, Sweden	Tooth segmentation	Development	Deep learning (CNN)	314 CBCT scans (2924 slice images of teeth)	Data augmentation	Split sample validation	Semiautomated (manual) segmentation (clinical reference)	Mean IOU 0.87 (±0.03) and 0.88 (±0.03) MSD 9.96 mm (±59.33 μ) and 7.85 mm (±69.55μ)
					Training 71.6% Optimization 17.2% Validation 11.2%			Other methods fully automated segmentation, refined AI-driven segmentation	Average Dice 0.93 (±0.02) and 0.94 (±0.02)
Cui et al. 2022 [85]	China	Tooth and alveolar bone segmentation	Development and validation	Deep Learning	Internal dataset 4938 CBCT scans	–	Split Sample Validation	Expert assessment (ground truth)	Internal testing set—average Dice 94.1% (tooth) and 94.5% (bone), average Se 93.9% (tooth), average ASD error 0.17 mm (tooth) and 0.33 mm (bone)
					Training and validation 70% Testing 30% External dataset 407 CBCTs		External Validation	Other methods	External testing set—average Dice 92.54% (tooth) and 93.8% (bone), Se 92.1% (tooth) and 93.5% (bone), ASD error 0.21 mm (tooth) and 0.40 mm (bone)

Table 2 (continued)

Authors	Country	Objective	Study design	AI technique	Dataset	Data augmentation	Validation Method	Reference standard/comparison (if any)	Outcome (best)
Other applications									
Deferm et al. 2022 [86]	Netherlands	Registration of IOS (intra-oral scans) with CBCT scans	Development	Iterative Closest Point	22 IOS and CBCT scans Patient groups 8-dentate 14 edentulous	–	Split sample validation	–	RMSE 0.49 ± 0.26 mm (dentate) RMSE 0.16 ± 0.08 mm (palate edentulous); 0.16 ± 0.05 mm (alveolar crest edentulous)

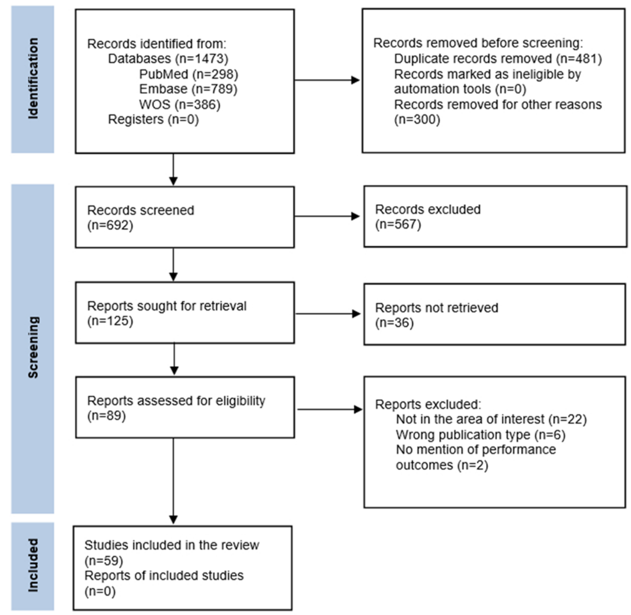

Fig. 1 PRISMA flowchart illustrating the study selection

comparison, and outcome. These data are presented in Table 2.

Risk of bias assessment

The methodological quality of the included studies was evaluated by two reviewers using adapted criteria based on the Prediction Model Risk of Bias Assessment Tool (PROBAST) [15]. PROBAST is a tool designed to assess studies developing, validating, or updating diagnostic and prognostic prediction models. Studies were rated on a 3-point scale, reflecting concerns about applicability and risk of bias was low, high, or unclear. The risk of bias assessment according to the Prediction Risk of Bias Assessment Tool (PROBAST) is presented in Supplementary Table S2.

Results

Study selection

A total of 1473 articles were enrolled after applying the search strategy. After the elimination of the duplicates, 692 articles were considered for screening. During the initial phase, the included studies were selected based on their title and abstracts' relationship to the research question. The screening process generated 125 publications for retrieval. A total of 89 articles were retrieved in full text and assessed for eligibility. These were evaluated based on the inclusion

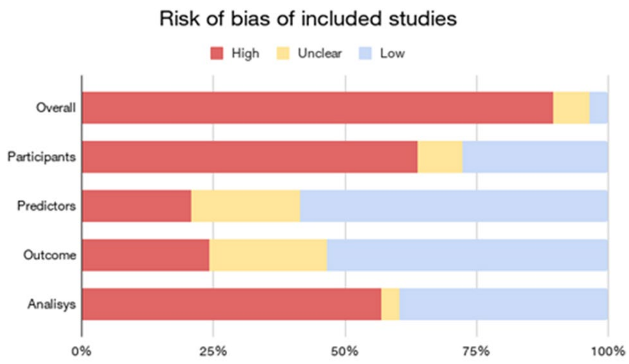

Fig. 2 Risk of bias (ROB) of included studies ($n=59$)

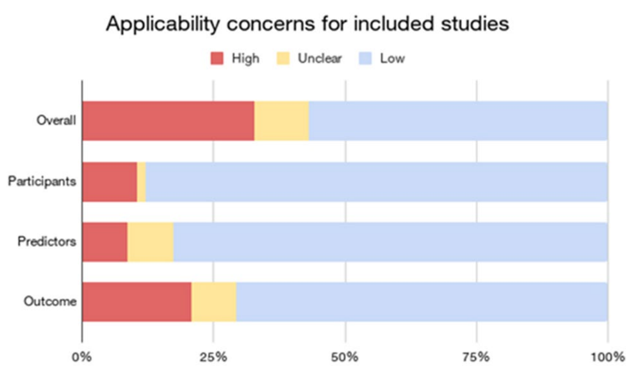

Fig. 3 Applicability concerns for included studies ($n=59$)

criteria. Finally, a total of 59 publications were included in this review. The study selection process is shown in Fig. 1.

Study characteristics

Fifty-nine studies evaluated applications of AI on CBCT images in dentistry. The included studies were published between the years 2012–2022. Out of these studies, 18 came from the field of oral and maxillofacial surgery, eight from implantology, 13 from orthodontics, and six from endodontics. Studies that did not match any of the fields were labeled as “other”. The general characteristics of included studies are summarized in Table 2.

In terms of study design, according to the PROBAST guidelines, studies performed external validation, with seven being validation-only studies and 11 reporting both model development and validation on an external dataset. 40 studies only dealt with model development [15].

Regarding the applications of the AI models, 10 studies reported cephalometric landmark detection, seven articles dealt with the diagnosis of tumors, cysts, and other oral lesions, four publications with dental implant planning, two dealt with the diagnosis of temporomandibular joint disorders, three focused on the diagnosis of periapical pathology, one with the detection of vertical root fractures, one with the prediction of soft tissue changes after orthognathic surgery, and one with the diagnosis of multiple dental pathologies. A total of 24 papers described the segmentation of teeth and other anatomical structures (mandibular canal, alveolar bone, root canals, jaw bones, mandibular condyles), three papers described registration tasks, and one was concerned with detecting the use of image sharpening filters (Figs. 2, 3).

The AI models used consisted mostly of deep learning models (42 studies), while the remaining 17 studies employed traditional techniques, such as statistical-shape and active shape models, as well as classic machine learning techniques, including thresholding-based methods (1), support vector machines (3), k-nearest neighbors (1), decision trees (1) knowledge-based methods (3), and random forests (4). Only two studies (3.38%) used unsupervised learning, and the rest (96.62%) used supervised or semi-supervised learning.

A few studies (8) made use of publicly available datasets for training or validation, in addition to in-house ones, and in terms of data augmentation, 12 studies used various techniques (like rotation, noise, flipping, cutout) to enhance the size of their training datasets. The publicly available datasets consisted of the ISBI Challenge training datasets [16, 17], the MICCAI Head-Neck Challenge dataset [18], the PDDCA dataset [19] and, the IAN 3D dataset [20].

Validation methods included split sample validation (30 studies), k-fold cross validation (16 studies), leave-one-out cross-validation (LOOCV, four studies), and Silhouette analysis for unsupervised learning (one study). Eighteen studies validated their results on external datasets.

Risk of bias in the included studies

According to the PROBAST assessment tool, out of the 59 included studies, 52 papers were at high risk of bias (ROB), two papers were rated as low ROB, and four papers as unclear. For this study, only the AI models recommended by the authors were assessed for bias. Overall, the major contributors to the high ROB were the participants (37 studies) and analysis (33 studies) domains. The predictors domain yielded 12 studies at high ROB, while another 12 were unclear, and for the outcome domain, there were 14 high ROB studies and 12 unclear. A detailed breakdown of included studies is available in Supplementary file 2.

Discussion

This systematic review aimed to assess the current clinical applications of AI in dental and maxillofacial CBCT imaging. There have been many reviews published on the topic of AI in dentistry, but as far as we are aware, this review is the first to deal strictly with the applications related to CBCT imaging.

The advantages of CBCT are evident in tasks involving surgical planning, dental implant planning [21, 22], or apical pathology detection [23]. Even fields such as orthodontics, which traditionally make use of two-dimensional imaging methods, can further benefit from CBCT, by way of making up for the limitations of 2D imaging (for example magnification, distortion, or imperfect overlaps of anatomical structures) [24]. However, there are concerns about potential health risks caused by radiation doses, considering the ALADAIP (As Low as Diagnostically Acceptable being Indication-oriented and Patient-specific) principle [25, 26]. Children have a potentially higher risk for radiation-induced cancer occurrence, owing to their longer life span and their higher radiosensitivity [27]. CBCT exposure in children had a higher median effective dose (127.2 µSv) and cumulative dose (156.5 µSv) with a significant increase in the cumulative dose between the ages of 11 and 14 [25].

Some of the AI architectures included in the literature consisted of traditional techniques such as statistical-shape and active shape models, as well as classic machine learning techniques (including thresholding-based methods, regression-based methods, support vector machines, decision trees, random forests etc.). These methods, while yielding some promising results and having the advantage of transparency, require a lot of expert analysis and lengthy processes of feature extraction [28]. Most of the studies employed deep learning-based methods, which offer better performance than other methods.

Deep learning (DL), a subfield of machine learning concerned with algorithms inspired by the structure and function of the brain [29], has gained prominence in recent years for applications in biomedical research, due to the increase in size and complexity of available data for training, enhanced computing power and its capacity to explore more complex patterns in the data [30]. It is frequently used for image analysis, as imaging data is naturally high-dimensional [30, 31]. While DL can indeed produce better results than traditional methods, it does so at the cost of large amounts of computing power (which calls into question its environmental sustainability [32]), needs exponentially more data, and raises the problem of a lack of transparency (black-box medicine [33]).

Applications in endodontics

In the field of endodontics, AI can be used for diagnosing cases of apical periodontitis, as well as for identifying elusive vertical root fractures [34]. Setzer et al. [35] trained a U-Net [36] based model for tooth, alveolar bone and periapical lesion segmentation, obtaining a DICE score of only 0.52 for the lesion label. Zheng et al. [37] similarly sought to segment periapical lesions, using an approach which integrated oral anatomical knowledge, therefore requiring less images for training. Their method outperformed the non-anatomically constrained Dense-Net [38]. Orhan et al. [39] performed external validation on a clinically available DL-based model (Diagnocat Inc., San Francisco, CA, USA), which showed high reliability (92.8%) of correctly detecting periapical lesions. In the case of vertical root fractures, the studies showed that applying AI on CBCT scans yields better accuracy than on periapical radiographs [40, 41]. However, both studies only used single-rooted, non-endodontically treated teeth, therefore further studies on multi-rooted teeth, in the presence of endodontic fillings, need to be conducted.

Applications in implantology

Dental implant planning relies on accurate evaluations of the quantity and quality of the alveolar bone. Roongruangsilp et al. [42], in a preliminary study using the faster R-CNN algorithm [43], developed an approach for implant planning based on the quantity of the alveolar bone. The Diagnocat system was also evaluated for this purpose [22]. It correctly identified 95.3% of edentulous regions, but unable to perform 80 bone height measurements and 15 bone thickness measurements. Sorkhabi et al. [44] proposed a 3D deep CNN for a qualitative evaluation of the alveolar bone, which outperformed other state-of-the art approaches.

The identification of the inferior alveolar nerve canal (IAN) is crucial for avoiding nerve damage during implant placement. Earlier methods employing Active-Shape [45] or Statistical-Shape models [46] were deemed unsuitable for clinical use. Cipriano et al. [20] published a fully annotated, public dataset of mandibular images, and their U-Net based DL model achieved a higher DICE score (0.69) than other methods [47, 48]. Lim et al. [49] also developed and validated a DL semi-supervised approach, which achieved a DICE score of 0.58, but found that the accuracy of manual segmentation was higher than that of automatic segmentation.

Applications in oral and maxillofacial surgery

Early research in maxillofacial surgery focused on the identification of intraosseous lesions, such as periapical cysts or keratocystic odontogenic tumors [50, 51], using SVMs, sparse discriminant analysis and random forests. Abdolali et al. [52] incorporated their knowledge-based model into a medical content-based image retrieval system, with the goal of assisting clinicians by retrieving the most similar cases to a given query image. Chai et al. [53] compared the accuracy of the DL Inception v3 algorithm with oral and maxillofacial surgeons, in the diagnosis ameloblastoma (AME), showing that the AI was able to better differentiate between AME and odontogenic keratocysts. Lin et al. [54] also showed that their semisupervised adversarial collaborative network can assist practitioners in patient diagnosis, lesion localization, and surgical planning. The advantage of this network is the fact that it can be trained with limited annotated data and large amounts of unlabeled data.

Furthermore, there has been interest in the computer aided diagnosis of temporomandibular joint (TMJ) diseases. Haghnegahdar et al. [55] used ML in the diagnostic assessment of TMD. They compared the results obtained using K-nearest neighbors (K-NN) with SVM, Naïve Bayesian and Random Forest classifiers and concluded that the K-nearest neighbor classifier achieved the highest accuracy (0.92). On the other hand, de Dumast et al. [56] used a deep neural network classifier of 3D condylar morphology, providing a neural network based classification of temporomandibular joint osteoarthritis.

Maxillary and mandible segmentation has also been the focus of several studies, with early attempts using atlas-based [57] and statistical shape models [58]. A recent review on automated mandibular segmentation [59] concluded that while such methods performed well, advances in DL now provide better accuracy. The authors also found that CT-imaging was the most frequent imaging modality used, however, CBCT is valuable due to its lower radiation dose. Qiu et al. [60] proposed an approach based on 3D CNN and a recurrent neural network (SegNet [61]) for automatic segmentation using images affected by metallic artefacts. It showed better results than other state-of-the-art models evaluated using the same datasets (average DICE 95.31%).

Other related articles centered on the prediction of soft tissue profiles after orthognathic surgery [62], using an Iterative Closest Point (ICP) algorithm and an autoencoder-inspired neural network. Another study by Zhang et al. [63] used an ICP algorithm for assessing the quality of 3D printed scaffolds for tissue engineering, showed that the scaffold quality can be quantified on a sub-voxel scale.

Applications in orthodontics

Cephalometric analysis has started to move from 2D radiographs towards 3D imaging [64]. This has been facilitated by the fact that CBCT imaging allows for 3D visualization of anatomical landmarks without superimpositions [65]. In 2017, Codari et al. [66] proposed a cluster-based segmentation and an intensity-based registration of an annotated reference volume onto a patient's CBCT scan. This approach only produces an estimation of the landmark location and needs further refining by a clinician. Torosdagli et al. [67] developed a deep geodesic learning framework for fully automated cephalometric analysis, achieving state-of-the-art performance in both mandible segmentation and landmark digitization. Huang et al. [68] synthesized cephalograms from CBCT projections using a generative adversarial network and used a combination of LeNet-5 and ResNet50 for automatic landmark detection. Chen et al. [69] recently introduced a Long Short-Term Memory Network to detect 3D cephalometric landmarks from the CBCT volume, outperforming other methods on an in-house skull CBCT dataset and a public CT dataset.

Other applications

Tooth segmentation had been studied extensively over the years, as it constitutes a necessity in numerous digital dentistry applications. It represents an essential step in generating 3D models for the diagnosis and treatment planning of maxillofacial deformities [70], and is typically performed manually. Manual segmentation is a labor-intensive task that is dependent on the skill and experience of the operator [71]. Challenges for CBCT segmentation include limited contrast resolution, inaccurate density, noise [72], lower signal-to-noise ratio, similar intensities of neighboring structures, and image artifacts [70] and difficulties arising from dental anatomy and maximum intercuspation [73].

In terms of methodology, traditional level-set based methods have shown promising results, but they require selection manual of a seed point for each tooth [74]. In recent years, a shift towards fully automated segmentation has occurred, with the development of fully convolutional networks and U-Net [75]. Just this year, Cui et al. [76] validated their model on a large dataset, comparing it with other state-of-the-art algorithms (ToothNet24 [77], MWTNet27 [78], CGDNet28 [79]), and achieved very good results.

Other applications included Kim et al. [71] use of cluster analysis to obtain a classification of the mandibular canal (MC) course. The MC courses were automatically classified as three types and showed that unsupervised ML can enable an unbiased classification of anatomical structures. Kats et al. [80] attempted to verify the effectiveness of using a neural networking to automatically determine use of the sharpening filter in X-ray images, to prevent errors in the diagnostic process. Finally, Deferm et al.'s [81] study evaluated a novel soft tissue-based method to register an intraoral scan (IOS) with a CBCT scan. The high accuracy of this registration method may aid in optimizing the digital dental workflow, especially in cases of edentulism.

Addressing the shortage of high quality labeled data

In general, DL algorithms need a large amount of labeled data to achieve high accuracy. However, in many healthcare applications, high-quality labeled data are limited due to the availability and cost of clinical experts, as well as the complexity of the problem domain. To address this label data shortage, some of the included studies exploited different mechanisms such as transfer learning [53, 80, 82, 83] and data augmentation [42, 44, 56, 68, 80, 82, 84–87]. Data augmentation refers to techniques employed to increase the size of existing datasets used to train DL algorithms, intending to increase the generalizability of the data and avoid overfitting. These include image rotation, flipping, noise injection, width and height shifting, shearing, zooming, or gamma correction. A study by Khan et al. [88] found a 10% increase in the accuracy of DL classifiers trained on augmented dental radiology datasets. Other studies found the utility of these techniques questionable [42]. Transfer learning has been found to achieve better performance in computer-aided diagnostics applications [89].

Limitations and implications for practice and future research

The strength of the study relies on the focus solely on the applications related to CBCT imaging out of the many reviews that have been published about AI in dentistry. However, several limitations are also present. First, the quality assessment of the literature suggests that many of the included studies are at high ROB. Overall, the main contributors to the high ROB were insufficient sample size and incomplete reporting. Efforts must be made to create more high-quality annotated datasets, as well as additional validation on external datasets, for these models to become viable for clinical practice. Second, even in the field of dental diagnostic imaging, applications were ample, with large heterogeneity in terms of AI techniques, collection and analysis of the datasets, and performance metrics, making comparisons difficult. AI in dentistry faces both technical and ethical challenges, and further research is in need of standards [90] concerning adequate reporting, concepts and terminology, performance testing, and overall transparency and reproducibility.

Conclusions

AI-based applications have the potential to streamline dental care, increase the quality of oral healthcare, and facilitate personalized, predictive, preventive and participatory dentistry. More research and validation need to be conducted before these models are viable for clinical practice, particularly to tackle the challenges of limited data availability, insufficient standards in development and reporting, as well as ethical challenges.

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Declarations

Conflict of interest The authors have no conflicts of interest or competing interests.

Human and ethical approval This article does not contain any studies with human or animal subjects performed by the any of the authors.

References

1. Hung K, Yeung AWK, Tanaka R, Bornstein MM. Current applications, opportunities and limitations of AI for 3D imaging in dental research and practice. Int J Environ Res Public Health. 2020;17:1–18. https://doi.org/10.3390/ijerph17124424.
2. Khanagar SB, Al-ehaideb A, Maganur PC, Vishwanathaiah S, Patil S, Baeshen HA, et al. Developments, application, and performance of artificial intelligence in dentistry—a systematic review. J Dent Sci. 2021;16:508–22. https://doi.org/10.1016/j.jds.2020.06.019.
3. Hosny A, Parmar C, Quackenbush J, Schwartz LH, Aerts HJWL. Artificial intelligence in radiology. Nat Rev Cancer. 2018;18:500. https://doi.org/10.1038/S41568-018-0016-5.
4. Hung K, Montalvao C, Tanaka R, Kawai T, Bornstein MM. The use and performance of artificial intelligence applications in dental and maxillofacial radiology: a systematic review. Dentomaxillofac Radiol. 2020. https://doi.org/10.1259/DMFR.20190107.
5. Scarfe WC, Angelopoulos C. Maxillofacial cone beam computed tomography: principles, techniques and clinical applications. Springer International Publishing; 2018. https://doi.org/10.1007/978-3-319-62061-9/COVER.
6. Parker JM, Mol A, Rivera EM, Tawil PZ. Cone-beam computed tomography uses in clinical endodontics: observer variability in detecting periapical lesions. J Endod. 2017;43:184–7. https://doi.org/10.1016/J.JOEN.2016.10.007.
7. Géron A. Hands-on machine learning with scikit-learn, keras, and tensorflow. Concepts, tools, and techniques to build intelligent systems. 2nd ed. O'Reilly Media; 2019.

8. Deo RC. Machine learning in medicine. Circulation. 2015;132:1920–30. https://doi.org/10.1161/CIRCULATIONAHA.115.001593.
9. Katsumata A, Fujita H. Progress of computer-aided detection/diagnosis (CAD) in dentistry. Jpn Dent Sci Rev. 2014;50:63–8. https://doi.org/10.1016/J.JDSR.2014.03.002.
10. Lee JG, Jun S, Cho YW, Lee H, Kim GB, Seo JB, et al. Deep learning in medical imaging: general overview. Korean J Radiol. 2017;18:570–84. https://doi.org/10.3348/KJR.2017.18.4.570.
11. O'Shea K, Nash R. An introduction to convolutional neural networks. arXiv preprint. 2015. https://doi.org/10.48550/arxiv.1511.08458.
12. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, The PRISMA, et al. Statement: an updated guideline for reporting systematic reviews. BMJ. 2020;2021:372. https://doi.org/10.1136/BMJ.N71.
13. Rayyan – Intelligent Systematic Review - n.d. https://www.rayyan.ai/. Accessed 24 Jun 2022.
14. Introduction | Mendeley n.d. https://www.mendeley.com/release-notes-reference-manager/. Accessed 24 Jun 2022.
15. Moons KGM, Wolff RF, Riley RD, Penny WF, Westwood M, et al. PROBAST: a tool to assess risk of bias and applicability of prediction model studies: explanation and elaboration. Ann Intern Med. 2019;170:1–33. https://doi.org/10.7326/M18-1377.
16. Wang L, Gao Y, Shi F, Li G, Gilmore JH, Lin W, et al. LINKS: learning-based multi-source IntegratioN frameworK for Segmentation of infant brain images. Neuroimage. 2015;108:160–72. https://doi.org/10.1016/J.NEUROIMAGE.2014.12.042.
17. Wang CW, Huang CT, Lee JH, Li CH, Chang SW, Siao MJ, et al. A benchmark for comparison of dental radiography analysis algorithms. Med Image Anal. 2016;31:63–76. https://doi.org/10.1016/J.MEDIA.2016.02.004.
18. 2015 MICCAI Challenge - Imageng n.d. http://www.imagenglab.com/wiki/mediawiki/index.php?title=2015_MICCAI_Challenge. Accessed 23 Jun 2022.
19. Raudaschl PF, Zaffino P, Sharp GC, Spadea MF, Chen A, Dawant BM, et al. Evaluation of segmentation methods on head and neck CT: Auto-segmentation challenge 2015. Med Phys. 2017;44:2020–36. https://doi.org/10.1002/MP.12197.
20. Cipriano M, Allegretti S, Bolelli F, Di Bartolomeo M, Pollastri F, Pellacani A, et al. Deep segmentation of the mandibular canal: a new 3D annotated dataset of CBCT volumes. IEEE Access. 2022;10:11500–10. https://doi.org/10.1109/ACCESS.2022.3144840.
21. Suomalainen A, Vehmas T, Kortesniemi M, Robinson S, Peltola J. Accuracy of linear measurements using dental cone beam and conventional multislice computed tomography. Dentomaxillofac Radiol. 2008;37:10–7. https://doi.org/10.1259/DMFR/14140281.
22. Bayrakdar SK, Orhan K, Bayrakdar IS, Bilgir E, Ezhov M, Gusarev M, et al. A deep learning approach for dental implant planning in cone-beam computed tomography images. BMC Med Imaging. 2021. https://doi.org/10.1186/S12880-021-00618-Z.
23. Saidi A, Naaman A, Zogheib C. Accuracy of cone-beam computed tomography and periapical radiography in endodontically treated teeth evaluation: a five-year retrospective study. J Int Oral Heal JIOH. 2015;7:15.
24. Gupta A, Kharbanda OP, Sardana V, Balachandran R, Sardana HK. Accuracy of 3D cephalometric measurements based on an automatic knowledge-based landmark detection algorithm. Int J Comput Assist Radiol Surg. 2016;11:1297–309. https://doi.org/10.1007/S11548-015-1334-7.
25. Mihaela H, Maria M, Benjamin S, Ruben P, Caroline OA, Oana A, et al. Irradiation provided by dental radiological procedures in a pediatric population. Eur J Radiol. 2018;103:112–7. https://doi.org/10.1016/J.EJRAD.2018.04.021.
26. Oenning AC, Jacobs R, Pauwels R, Stratis A, Hedesiu M, Salmon B. Cone-beam CT in paediatric dentistry: DIMITRA project position statement. Pediatr Radiol. 2018;48:308–16. https://doi.org/10.1007/S00247-017-4012-9.
27. Oenning AC, Pauwels R, Stratis A, De Faria VK, Tijskens E, De Grauwe A, et al. Halve the dose while maintaining image quality in paediatric cone beam CT. Sci Reports. 2019;9:1–9. https://doi.org/10.1038/s41598-019-41949-w.
28. O'Mahony N, Campbell S, Carvalho A, Harapanahalli S. Deep Learning vs. Traditional computer vision. CVC 2019. Computer Vision and Pattern Recognition. https://doi.org/10.48550/arXiv.1910.13796
29. Goodfellow I, Bengio Y, Courville A. Deep learning (adaptive computation and machine learning series). The MIT Press; 2016.
30. Jiang F, Jiang Y, Zhi H, Dong Y, Li H, Ma S, et al. Artificial intelligence in healthcare: past, present and future. Stroke Vasc Neurol. 2017;2:230–43. https://doi.org/10.1136/SVN-2017-000101.
31. Pisano ED, Garnett LR. Big data and radiology research. J Am Coll Radiol. 2019;16:1347–50. https://doi.org/10.1016/j.jacr.2019.06.003.
32. Weygandt JJ, Kimmel PD, Kieso DE, Aly IM, Steenkamp JBEM, Tatum P, et al. Energy and policy considerations for deep learning in NLP. J Int Mark. 2019;53:3645–50. https://doi.org/10.48550/arxiv.1906.02243.
33. Poon AIF, Sung JJY. Opening the black box of AI-Medicine. J Gastroenterol Hepatol. 2021;36:581–4. https://doi.org/10.1111/JGH.15384.
34. Liao WC, Chen CH, Pan YH, Chang MC, Jeng JH. Vertical root fracture in non-endodontically and endodontically treated teeth: current understanding and future challenge. J Pers Med. 2021. https://doi.org/10.3390/JPM11121375.
35. Setzer FC, Shi KJ, Zhang Z, Yan H, Yoon H, Mupparapu M, et al. Artificial intelligence for the computer-aided detection of periapical lesions in cone-beam computed tomographic images. J Endod. 2020;46:987–93. https://doi.org/10.1016/j.joen.2020.03.025.
36. Weng W, Zhu X. U-Net: convolutional networks for biomedical image segmentation. IEEE Access. 2015;9:16591–603. https://doi.org/10.48550/arxiv.1505.04597.
37. Zheng Z, Yan H, Setzer FC, Shi KJ, Mupparapu M, Li J. Anatomically constrained deep learning for automating dental CBCT segmentation and lesion detection. IEEE Trans Autom Sci Eng. 2021;18:603–14. https://doi.org/10.1109/TASE.2020.3025871.
38. Jegou S, Drozdzal M, Vazquez D, Romero A, Bengio Y. The one hundred layers tiramisu: fully convolutional densenets for semantic segmentation. IEEE Comput Soc Conf Comput Vis Pattern Recognit Work 2016. 2017. https://doi.org/10.48550/arxiv.1611.09326.
39. Orhan K, Bayrakdar IS, Ezhov M, Kravtsov A, Özyürek T. Evaluation of artificial intelligence for detecting periapical pathosis on cone-beam computed tomography scans. Int Endod J. 2020;53:680–9. https://doi.org/10.1111/iej.13265.
40. Johari M, Esmaeili F, Andalib A, Garjani S, Saberkari H. Detection of vertical root fractures in intact and endodontically treated premolar teeth by designing a probabilistic neural network: an ex vivo study. 2017. Dentomaxillofac Radiol. .
41. Johari M, Esmaeili F, Andalib A, Garjani S, Saberkari H. A novel thresholding based algorithm for detection of vertical root fracture in nonendodontically treated premolar teeth. J Med Signals Sens. 2016;6:81–90. https://doi.org/10.4103/2228-7477.181027.
42. Roongruangsilp P, Khongkhunthian P. The learning curve of artificial intelligence for dental implant treatment planning: a descriptive study. Appl Sci. 2021;11:10159. https://doi.org/10.3390/APP112110159.
43. Ren S, He K, Girshick R, Sun J. Faster R-CNN: towards real-time object detection with region proposal networks. IEEE Trans

Pattern Anal Mach Intell. 2017;39:1137–49. https://doi.org/10.1109/TPAMI.2016.2577031.
44. Sorkhabi MM, Saadat KM. Classification of alveolar bone density using 3-D deep convolutional neural network in the cone-beam CT images: a 6-month clinical study. Measurement. 2019;148:106945. https://doi.org/10.1016/J.MEASUREMENT.2019.106945.
45. Gerlach NL, Meijer GJ, Kroon D-J, Bronkhorst EM, Bergé SJ, Maal TJJ. Evaluation of the potential of automatic segmentation of the mandibular canal using cone-beam computed tomography. Br J Oral Maxillofac Surg. 2014;52:838–44. https://doi.org/10.1016/j.bjoms.2014.07.253.
46. Abdolali F, Zoroofi RA, Abdolali M, Yokota F, Otake Y, Sato Y. Automatic segmentation of mandibular canal in cone beam CT images using conditional statistical shape model and fast marching. Int J Comput Assist Radiol Surg. 2017;12:581–93. https://doi.org/10.1007/S11548-016-1484-2.
47. Jaskari J, Sahlsten J, Järnstedt J, Mehtonen H, Karhu K, Sundqvist O, et al. Deep learning method for mandibular canal segmentation in dental cone beam computed tomography volumes. Sci Rep. 2020;10:5842. https://doi.org/10.1038/s41598-020-62321-3.
48. Chen S, Ma K, Zheng Y. Med3D: transfer learning for 3D medical image analysis . ArXiv Abs/190400625 2019. Computer Vision and Pattern Recognition. https://doi.org/10.48550/arXiv.1904.00625
49. Lim H-K, Jung S-K, Kim S-H, Cho Y, Song I-S. Deep semi-supervised learning for automatic segmentation of inferior alveolar nerve using a convolutional neural network. BMC Oral Health. 2021;21:630. https://doi.org/10.1186/s12903-021-01983-5.
50. Abdolali F, Zoroofi RA, Otake Y, Sato Y. Automated classification of maxillofacial cysts in cone beam CT images using contourlet transformation and spherical harmonics. Comput Methods Programs Biomed. 2017;139:197–207. https://doi.org/10.1016/j.cmpb.2016.10.024.
51. Yilmaz E, Kayikcioglu T, Kayipmaz S. Computer-aided diagnosis of periapical cyst and keratocystic odontogenic tumor on cone beam computed tomography. Comput Methods Programs Biomed. 2017;146:91–100. https://doi.org/10.1016/j.cmpb.2017.05.012.
52. Abdolali F, Zoroofi RA, Otake Y, Sato Y. A novel image-based retrieval system for characterization of maxillofacial lesions in cone beam CT images. Int J Comput Assist Radiol Surg. 2019. https://doi.org/10.1007/s11548-019-01946-w.
53. Chai Z-K, Mao L, Chen H, Sun T-G, Shen X-M, Liu J, et al. Improved diagnostic accuracy of ameloblastoma and odontogenic keratocyst on cone-beam CT by artificial intelligence. Front Oncol. 2021;11:793417. https://doi.org/10.3389/fonc.2021.793417.
54. Lin Y, He M. Deep learning-based three-dimensional oral conical beam computed tomography for diagnosis. J Healthc Eng. 2021;2021:1–7. https://doi.org/10.1155/2021/4676316.
55. Haghnegahdar AA, Kolahi S, Khojastepour L, Tajeripour F. Diagnosis of tempromandibular disorders using local binary patterns. J Biomed Phys Eng. 2018. https://doi.org/10.22086/jbpe.v0i0.577.
56. de Dumast P, Mirabel C, Cevidanes L, Ruellas A, Yatabe M, Ioshida M, et al. A web-based system for neural network based classification in temporomandibular joint osteoarthritis. Comput Med Imaging Graph. 2018;67:45–54. https://doi.org/10.1016/j.compmedimag.2018.04.009.
57. Wang L, Chen KC, Shi F, Liao S, Li G, Gao Y, et al. Automated segmentation of CBCT image using spiral CT atlases and convex optimization. Med Image Comput Comput Assist Interv. 2013;16:251–8.
58. Chang YB, Xia JJ, Yuan P, Kuo TH, Xiong Z, Gateno J, et al. 3D segmentation of maxilla in cone-beam computed tomography imaging using base invariant wavelet active shape model on customized two-manifold topology. J Xray Sci Technol. 2013;21:251–82.
59. Qiu B, Der Wel HV, Kraeima J, Glas HH, Guo J, Borra RJH, et al. Automatic segmentation of mandible from conventional methods to deep learning-a review. J Pers Med. 2021. https://doi.org/10.3390/jpm11070629.
60. Qiu B, Wel H, Kraeima J, Glas HH, Guo J, Borra RJH, et al. Mandible segmentation of dental cbct scans affected by metal artifacts using coarse-to-fine learning model. J Pers Med. 2021. https://doi.org/10.3390/jpm11060560.
61. Badrinarayanan V, Kendall A, Cipolla R. SegNet: a deep convolutional encoder-decoder architecture for image segmentation. IEEE Trans Pattern Anal Mach Intell. 2017;39:2481–95. https://doi.org/10.1109/TPAMI.2016.2644615.
62. ter Horst R, van Weert H, Loonen T, Bergé S, Vinayahalingam S, Baan F, et al. Three-dimensional virtual planning in mandibular advancement surgery: soft tissue prediction based on deep learning. J Cranio-Maxillofacial Surg. 2021;49:775–82. https://doi.org/10.1016/j.jcms.2021.04.001.
63. Zhang N, Singh S, Liu S, Zbijewski W, Grayson WL. A robust, autonomous, volumetric quality assurance method for 3D printed porous scaffolds. 3D Print Med. 2022. https://doi.org/10.1186/s41205-022-00135-x.
64. Pittayapat P, Limchaichana-Bolstad N, Willems G, Jacobs R. Three-dimensional cephalometric analysis in orthodontics: a systematic review. Orthod Craniofac Res. 2014;17:69–91. https://doi.org/10.1111/OCR.12034.
65. Waugh RL. Use of cone beam computerized tomography (CBCT) in orthodontic diagnosis and treatment planning in the presence of a palatally-impacted canine. Orthod Fr. 2014;85:355–61. https://doi.org/10.1051/ORTHODFR/2014021.
66. Codari M, Caffini M, Tartaglia GM, Sforza C, Baselli G. Computer-aided cephalometric landmark annotation for CBCT data. Int J Comput Assist Radiol Surg. 2017;12:113–21. https://doi.org/10.1007/s11548-016-1453-9.
67. Torosdagli N, Liberton DK, Verma P, Sincan M, Lee JS, Bagci U. Deep geodesic learning for segmentation and anatomical landmarking. IEEE Trans Med Imaging. 2019;38:919–31. https://doi.org/10.1109/TMI.2018.2875814.
68. Huang Y, Fan F, Syben C, Roser P, Mill L, Maier A. Cephalogram synthesis and landmark detection in dental cone-beam CT systems. Med Image Anal. 2021. https://doi.org/10.1016/j.media.2021.102028.
69. Chen R, Ma Y, Chen N, Liu L, Cui Z, Lin Y, et al. Structure-aware long short-term memory network for 3D cephalometric landmark detection. IEEE Trans Med Imaging. 2022. https://doi.org/10.1109/TMI.2022.3149281.
70. Wang L, Gao Y, Shi F, Li G, Chen KC, Tang Z, et al. Automated segmentation of dental CBCT image with prior-guided sequential random forests. Med Phys. 2016;43:336–46. https://doi.org/10.1118/1.4938267.
71. Kim YH, Jeon KJ, Lee C, Choi YJ, Jung HI, Han SS. Analysis of the mandibular canal course using unsupervised machine learning algorithm. PLoS ONE. 2021. https://doi.org/10.1371/JOURNAL.PONE.0260194.
72. Pauwels R, Jacobs R, Singer SR, Mupparapu M. CBCT-based bone quality assessment: are Hounsfield units applicable? Dentomaxillofac Radiol. 2015. https://doi.org/10.1259/DMFR.20140238.
73. Chung M, Lee M, Hong J, Park S, Lee J, Lee J, et al. Pose-aware instance segmentation framework from cone beam CT images for tooth segmentation. Comput Biol Med. 2020. https://doi.org/10.1016/j.compbiomed.2020.103720.
74. Gao H, Chae O. Individual tooth segmentation from CT images using level set method with shape and intensity prior. Pattern Recognit. 2010;43:2406–17. https://doi.org/10.1016/J.PATCOG.2010.01.010.
75. Ronneberger O, Fischer P, Brox T. U-net: convolutional networks for biomedical image segmentation. Lect Notes Comput Sci (Including Subser

Lect Notes Artif Intell Lect Notes Bioinformatics). 2015;9351:234–41. https://doi.org/10.1007/978-3-319-24574-4_28/COVER/.
76. Cui Z, Fang Y, Mei L, Zhang B, Yu B, Liu J, et al. A fully automatic AI system for tooth and alveolar bone segmentation from cone-beam CT images. Nat Commun. 2022;13:2096. https://doi.org/10.1038/s41467-022-29637-2.
77. Cui Z, Li C, Wang W. Toothnet: automatic tooth instance segmentation and identification from cone beam ct images. Proc IEEE Comput Soc Conf Comput Vis Pattern Recognit. 2019;63:61–70. https://doi.org/10.1109/CVPR.2019.00653.
78. Chen Y, Du H, Yun Z, Yang S, Dai Z, Zhong L, et al. Automatic segmentation of individual tooth in dental CBCT images from tooth surface map by a multi-task FCN. IEEE Access. 2020;8:97296–309. https://doi.org/10.1109/ACCESS.2020.2991799.
79. Wu X, Chen H, Huang Y, Guo H, Qiu T, Wang L. Center-sensitive and boundary-aware tooth instance segmentation and classification from cone-beam CT. Proc—Int Symp Biomed Imaging. 2020. https://doi.org/10.1109/ISBI45749.2020.9098542.
80. Kats L, Goldman Y, Kahn A. Automatic detection of image sharpening in maxillofacial radiology. BMC Oral Health. 2021;21:1–8. https://doi.org/10.1186/S12903-021-01777-9/FIGURES/4.
81. Deferm JT, Nijsink J, Baan F, Verhamme L, Meijer G, Maal T. Soft tissue-based registration of intraoral scan with cone beam computed tomography scan. Int J Oral Maxillofac Surg. 2022;51:263–8. https://doi.org/10.1016/j.ijom.2021.04.004.
82. Lee J-H, Kim D-H, Jeong S-N. Diagnosis of cystic lesions using panoramic and cone beam computed tomographic images based on deep learning neural network. Oral Dis. 2020;26:152–8. https://doi.org/10.1111/odi.13223.
83. Lo Giudice A, Ronsivalle V, Spampinato C, Leonardi R. Fully automatic segmentation of the mandible based on convolutional neural networks (CNNs). Orthod Craniofac Res. 2021;24(Suppl 2):100–7. https://doi.org/10.1111/OCR.12536.
84. Kim M-J, Liu Y, Oh SH, Ahn H-W, Kim S-H, Nelson G. Automatic cephalometric landmark identification system based on the multi-stage convolutional neural networks with CBCT combination images. Sensors (Basel). 2021. https://doi.org/10.3390/s21020505.
85. Li Z, Wang SH, Fan RR, Cao G, Zhang YD, Guo T. Teeth category classification via seven-layer deep convolutional neural network with max pooling and global average pooling. Int J Imaging Syst Technol. 2019;29:577–83. https://doi.org/10.1002/IMA.22337.
86. Lahoud P, EzEldeen M, Beznik T, Willems H, Leite A, Van Gerven A, et al. Artificial intelligence for fast and accurate 3-dimensional tooth segmentation on cone-beam computed tomography. J Endod. 2021;47:827–35. https://doi.org/10.1016/J.JOEN.2020.12.020.
87. Zhang Y, Qin H, Li P, Pei Y, Guo Y, Xu T, et al. Deformable registration of lateral cephalogram and cone-beam computed tomography image. Med Phys. 2021;48:6901–15. https://doi.org/10.1002/mp.15214.
88. Khan S, Mukati A, Zulfikar S, Bhutto A. Dataset augmentation for machine learning applications of dental radiography. Int J Adv Comput Sci Appl. 2020. https://doi.org/10.14569/IJACSA.2020.0110258.
89. Shin HC, Roth HR, Gao M, Lu L, Xu Z, Nogues I, et al. Deep convolutional neural networks for computer-aided detection: CNN architectures, dataset characteristics and transfer learning. IEEE Trans Med Imaging. 2016;35:1285. https://doi.org/10.1109/TMI.2016.2528162.
90. U.S. LEADERSHIP IN AI: A Plan for Federal Engagement in Developing Technical Standards and Related Tools. 2019. Available at: https://www.nist.gov/system/files/documents/2019/08/10/ai_standards_fedengagement_plan_9aug2019.pdf

Journal of *Personalized Medicine*

Review

Blood Cell Count Inflammatory Markers as Prognostic Indicators of Periodontitis: A Systematic Review and Meta-Analysis

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Abstract: (1) Background: Our study aimed to assess the association between the neutrophil to lymphocyte ratio (NLR), platelet to leukocyte ratio (PLR), lymphocyte to monocyte ratio (LMR), red cell distribution width (RDW), and systemic immune inflammation index (SII) and periodontitis. (2) Methods: We searched PubMed, Embase, Scopus, Web of Science, and LILACS databases, identifying observational studies. The Newcastle Ottawa scale was used to evaluate the quality of the included studies. The principal summary outcome measure in our random effects meta-analysis was the mean difference (MD). (3) Results: After screening 682 search results, a total of 10 studies including 3164 subjects were selected for quantitative assessment. We found a higher mean NLR, PLR, and LMR in the periodontitis group compared to the control group (0.41 (95% CI 0.12–0.7), $p = 0.006$; 7.43 (95% CI 0.31–14.54), $p = 0.04$; 2.05 (95% CI 0.27–3.83), $p = 0.024$). No differences were observed for RDW. (4) Conclusions: We found an association between NLR, LMR, and PLR and periodontitis, which might be thought of as emerging blood cell count inflammatory biomarkers that could shed light on the link between periodontitis and systemic disbalances, as well as for periodontitis prognosis and grading.

Keywords: inflammatory biomarkers; systemic inflammation; blood cells; gingival aggressive periodontitis; periodontitis prognosis

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1. Introduction

Periodontitis represents a group of chronic diseases that affect the supporting tissues of the teeth and are characterized by the destruction of periodontal tissues, the alveolar bone, and the supporting tissues of teeth. Inflammatory cells cause an immune response in the periodontal tissues [1]. The inflammatory mediators from the periodontal tissues can activate the immune system and initiate a systemic acute phase response [2]. In addition, many chronic diseases are linked to periodontitis, including cardiovascular disease, diabetes, cerebrovascular disease, neurodegenerative disease, and cancer [3]. Analyzing systemic circulatory markers, such as neutrophils [4,5], the neutrophil to lymphocyte ratio (NLR) [1], platelets [6], the platelet to leukocyte ratio (PLR) [7], and erythrocyte counts [8], could offer relevant data regarding systemic and periodontal infection.

The white blood cell count and absolute neutrophil count seem to be among the additional markers that could also help predict infection [9]. The amount of peripheral white blood cells has been reported to rise as the severity of periodontitis increases [10]. Despite the fact that these indicators are not specific to periodontitis, there may be a link between them.

In 2017, a new classification scheme for periodontitis was adopted [11]. The new periodontal disease categorization replaced the previous one [12], which uses a single term, “periodontitis”, for all earlier forms of the disease defined as “chronic” or “aggressive”.

To the best of our knowledge, there is no systematic review focusing on the relation between blood cell count inflammatory markers and periodontitis. Therefore, the objectives of this research were to carry out a systematic review and meta-analysis to investigate the association between the neutrophil to lymphocyte ratio (NLR), platelet to leukocyte ratio (PLR), lymphocyte to monocyte ratio (LMR), red cell distribution width (RDW), and systemic immune inflammation index (SII) and periodontitis.

2. Materials and Methods

This systematic review was performed in accordance with the recommendations of the “Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA) Statement” [13].

2.1. Eligibility Criteria

We included in our review all the studies on periodontitis subjects assessing inflammation status using blood cell count ratios or the red cell distribution width. We excluded case reports, mechanistic articles, animal studies, reviews, editorials, and conference abstracts.

2.2. Information Sources

A structured electronic search was conducted in March 2022 of the following databases: PubMed, Scopus, Embase, Web of Science, and LILACS. MeSH and Emtree terms were used, where applicable. The last electronic search was performed on all databases on 15 April 2022.

2.3. Search Strategy

The search strategy included the terms “neutrophils”, “platelets”, “lymphocytes”, “ratio”, “systemic immune inflammation index”, “red cell distribution width”, and “periodontitis” as free text words, along with MeSH or Emtree terms (where possible), synonyms, singular as well as plural forms, and abbreviations (NLR, PLR, LMR, SII, RDW). The complete strategies adapted for each database are presented in Supplementary Table S1.

2.4. Selection Process

The exported lists of results from all the databases were imported in the Clarivate EndNoteTM online version [14], where the duplicates were removed by the software. Next, the remaining results were exported to an Excel spreadsheet file (Microsoft Office 365, MS, Redmond, WA, USA), which served as a selection, extraction, and quality assessment electronic form. All references were managed with Zotero software version 6.0.6 (Roy Rosenzweig Center for History and New Media, Fairfax, Virginia, USA) [15]. Two authors (A.O., L.D.C.) independently screened the titles and abstracts of all the articles manually, and, when in doubt, debated whether the paper should be considered. The selected articles were retrieved in full-text and assessed for inclusion by the same authors independently, with differences in opinion resolved by discussion. For each excluded article, the exclusion motive was recorded. For one article for which we could not locate a full-text version, we contacted the corresponding author, and he provided us with the document we needed.

2.5. Data Collection Process

Two reviewers extracted data from the articles in the standardized Excel form file.

2.6. Data Items

Data were extracted using a standardized form, which included the following information: (1) author names and year of publication; (2) title; (3) abstract; (4) publication title; (5) keywords; (6) study selection; (7) screening; (8) inclusion criteria; (9) exclusion criteria; (10) population; (11) exposure; (12) age; (13) gender; (14) other characteristics; (15) outcomes (NLR, PLR, LMR, RDW), i.e., mean and standard deviations; and (16) studies' quality assessment.

2.7. Study Risk of Bias Assessment

All the selected articles were independently assessed regarding their methodological quality by two reviewers, and differences in assessment were resolved by discussion. The Newcastle Ottawa Scale [16] for case-control studies was used to identify the sources of bias.

2.8. Effect Measures

For all the outcomes, the mean difference was used as an effect measure, along with its confidence interval.

2.9. Synthesis Methods

If we could not identify the mean and standard deviation for the outcomes we were interested in and only found medians, we used the formula supplied by Hozo SP et al. to convert the range and number of participants [17]. Although some papers lacked the needed numbers, we were able to identify them in their charts. We extracted the numerical values from the figures using WebPlotDigitizer [18].

All meta-analyses were performed with the random effects model using the method of restricted maximum likelihood to estimate the heterogeneity variance, as we anticipated a clinical heterogenicity between studies. The X2-based Q-test and I2 were used to assess between-study heterogeneity, according to the Cochrane Handbook's recommendations [19]

Meta-analyses were carried out in the R environment for statistical computing and graphics, version 4.1.2 [20], using the meta R package [21]. The leave-one-out sensitivity analyses, performed in case of important heterogeneity meta-analyses, as well as meta-analysis diagnostics to identify influential studies were carried out with the dmetar package [22]. No subgroup analyses were performed.

2.10. Reporting Bias Assessment

Since the number of selected studies was low, publication bias assessment is underpowered. Nevertheless, we computed the Egger test and plotted funnel plots to assess the presence of publication bias.

3. Results

3.1. Study Selection

A description of the search process and selection is presented in a PRISMA flow diagram (Figure 1). A total of 682 publications were found in the initial search (PubMed n = 135, EMBASE n = 107, Scopus n = 373, Web of Science n = 60, LILACS n = 7). After being identified as duplicates, a total of 149 studies were deleted. Following the removal of duplicates, 533 articles were subjected to a preliminary screening that included a review of the title and abstract for compliance with the inclusion and exclusion criteria. Then, 110 articles were eliminated during the screening process. There were 460 irrelevant articles and 22 wrong study types, and 35 duplicate records. We looked for the complete text of 16 articles, and for one article, we contacted the authors through email, and finally, we managed to collect all the necessary files. We read and evaluated the whole text thoroughly in order to determine the remaining articles' eligibility. Six of these articles were eliminated for the following reasons: outcome not reported (*n* = 5) or wrong study type, i.e., review (*n* = 1). As a result, the qualitative and quantitative synthesis included 10 articles.

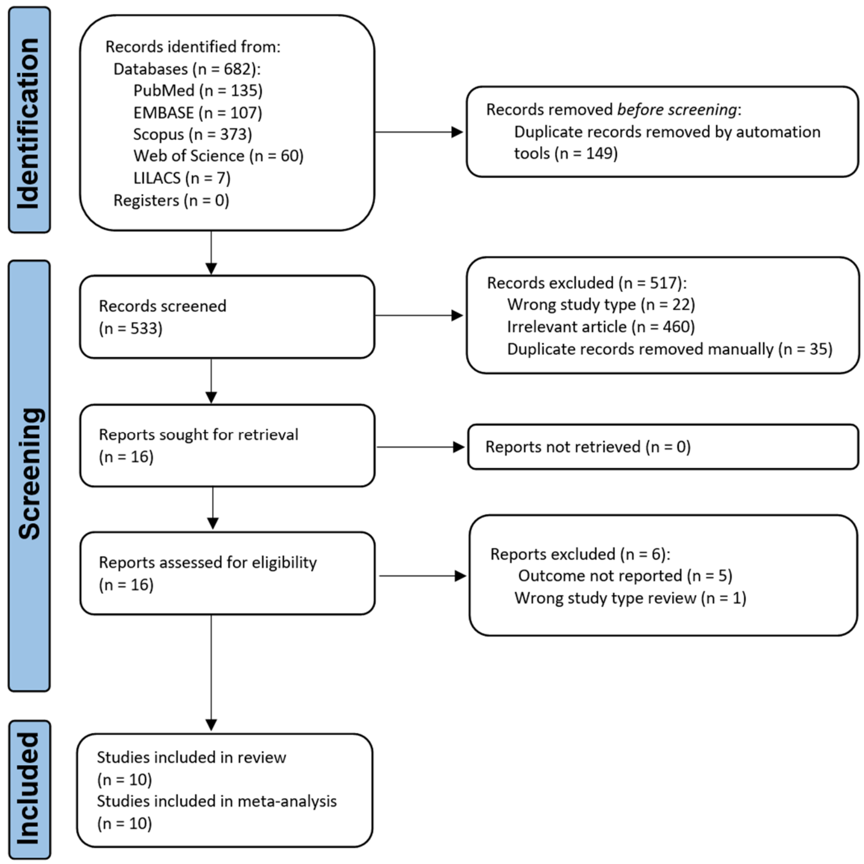

Figure 1. Flow diagram of the literature search and selection criteria adapted for PRISMA 2020.

3.2. Study Characteristics

Table 1 and Supplementary Table S2 summarizes the basic characteristics of the studies that were included. A total of 3164 subjects were included in this systematic review and meta-analysis.

Table 1. Characteristics of the included studies.

Author, Year of Publication	Country	Region	Study Design	Study Population	Age (Years): Mean ± (SD) /(Range) Case vs. Control	Female (%) Case vs. Control	Outcome Parameters	Periodontitis Classification
Acharya AB, 2019 [7]	India	Asia	PC	CP vs. H	39.6 ± 0.96 vs. 39.6 ± 0.96	50% vs. 50%	NLR, PLR	NCS
Anand PS, 2014 [23]	India	Asia	CS	GAP vs. H	32.80 ± 7.21 vs. 30.40 ± 7.60	50% vs. 43%	RDW	ICWP 1999
Çetin Özdemir E, 2022 [1]	Turkey	Asia	CS	CP vs. H	38.36 ± 7.02 vs. 35.3 ± 9.88	36% vs. 73%	NLR	WWC 2017
Dogan B, 2015 [24]	Turkey	Asia	CS	CP vs. H	NR	32%	NLR	NCS
Lu RF, 2021 [25]	China	Asia	CC	GAP vs. H	27.50 ± 5.24 vs. 26.77 ± 5.05	59% vs. 60%	NLR, PLR	WWC 1999
Mishra S, 2022 [26]	India	Asia	CC	CP vs. H	30.67 ± 4.89 vs. 30.67 ± 4.89	45% vs. 48%	NLR, PLR, LMR	WWC 2017
Sridharan S, 2021 [27]	India	Asia	CS	CP vs. H	50.8 ± 10 vs. 41.6 ± 3.4	65% vs. 65%	RDW	WWC 2017
Temelli B, 2018 [28]	Turkey	Asia	CS	CP vs. H	50 (42–71) vs. 49 (33–65)	33% vs. 63%	NLR, RDW	WWC 1999
Torrungruang K, 2018 [29]	Thailand	Asia	CS	CP vs. H	48.0 ± 5.0	28%	NLR, PLR	CDC/AAP 2007
Ustaoglu G, 2020 [2]	Turkey	Asia	CS	CP vs. H	37.4 ± 7.0 vs. 35.6 ± 7.0	44% vs. 54.3%	RDW	WWC 2017

PC-prospective cohort; CS-cross-sectional; CC-case-control; CP-chronic periodontitis; GAP-gingival aggressive periodontitis; H-healthy; ICWP-International Workshop for Classification of Periodontal Disease and Conditions; WWC-World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions; CDC/AAP-Centers for Disease Control and Prevention (CDC), American Academy of Periodontology (AAP); NLR-neutrophil to lymphocyte ratio; PLR-platelet to leukocyte ratio; LMR-lymphocyte to monocyte ratio; RDW-red cell distribution width; NR-not reported; NCS-no classification system.

Eight studies used a cross-sectional study design, and two used a case-control study design. All investigations were conducted in Asia (Turkey $n = 4$, India $n = 4$, Thailand $n = 1$, China $n = 1$). Two articles assessed gingival aggressive periodontitis and eight articles observed chronic periodontitis as a case group; all articles compared them to healthy controls. The periodontitis classification differed between articles, with seven using World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions (1999 or 2017 versions); one used the Centers for Disease Control and Prevention, American Academy of Periodontology classification; and two did not stipulate any classification system. Six studies had a mean age of subjects between 26 and 40, three studies had a mean age of around 50, and one study did not report the age range. Most studies reported a similar distribution of gender between the groups. Concerning outcomes, seven studies reported NLR, four reported PLR and RDW, one reported LMR, and no article was identified to report SII.

3.3. Results of Syntheses

3.3.1. Neutrophil to Lymphocyte Ratio

The meta-analysis of seven studies found that the mean NLR was higher by 0.41 (95% CI 0.12–0.7), $p = 0.006$, in the periodontitis group compared to the control group (Figure 2). There was a statistically significant heterogeneity, measured with I2 = 86.8% (95% CI 74.9–93%), $p = < 0.001$. To assess the robustness of the result, we performed a leave-one-out sensitivity analysis (Supplementary Figure S1). The result remained statistically significant after excluding each of the articles included in the meta-analysis. The influence analysis indicated the Torrungruang [29] study to be influential. When removing the Torrungruang study [29], the heterogeneity was the lowest, dropping to 62%, as assessed by I2, while with the removal of any other study, the heterogeneity was greater than or equal to 81%.

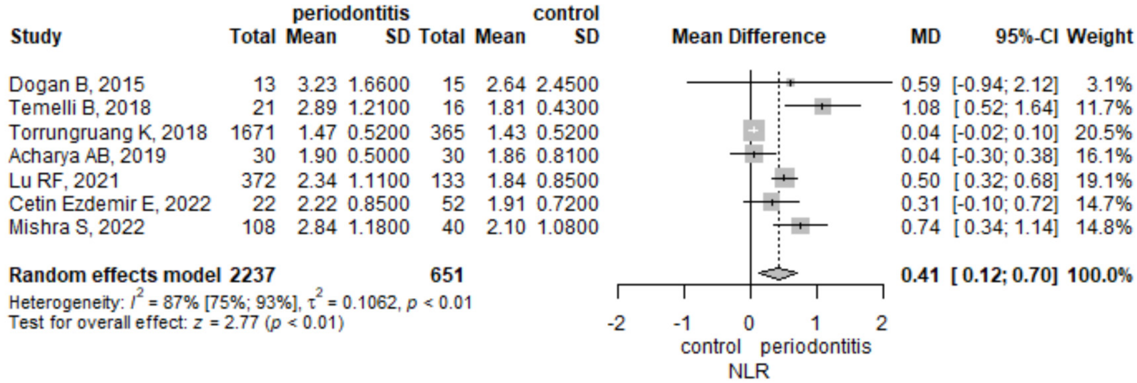

Figure 2. Neutrophile to lymphocyte ratio-mean difference between periodontitis and control subjects.

3.3.2. Platelet to Leucocyte Ratio

Four studies analyzed the values of PLR. The meta-analysis found a mean PLR higher by 1.83 (95% CI −9.38–13.04) in the periodontitis group compared to the control group, but the result was not statistically significant, p = 0.749 (Figure 3). There was a statistically significant heterogeneity, measured with I2 = 83.1% (95% CI 56.9–93.4%), p = < 0.001. To assess the robustness of the result, we performed a leave-one-out sensitivity analysis (Supplementary Figure S2). The influence analysis indicated the Torrungruang study [29] to be influential. When removing the Torrungruang study [29], the result became statistically significant, and the heterogeneity dropped to 0%, as assessed by I2. When removing any other study, the pooled estimate did not reach statistical significance.

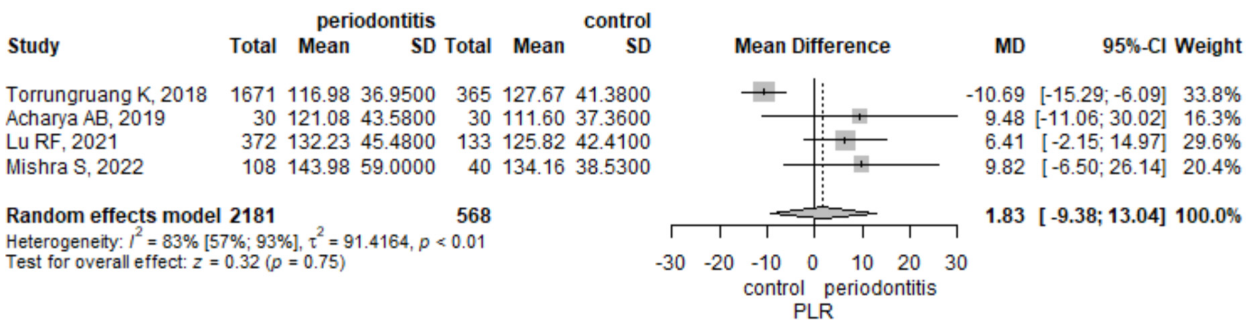

Figure 3. Platelet to leucocyte ratio-mean difference between periodontitis and control subjects.

3.3.3. Lymphocyte to Monocyte Ratio

The mean LMR was lower in the periodontitis group compared to the control group (mean difference of 2.05 (95% CI 0.27–3.83), p = 0.024, as observed in one study, Mishra et al. [26]) (Figure 4).

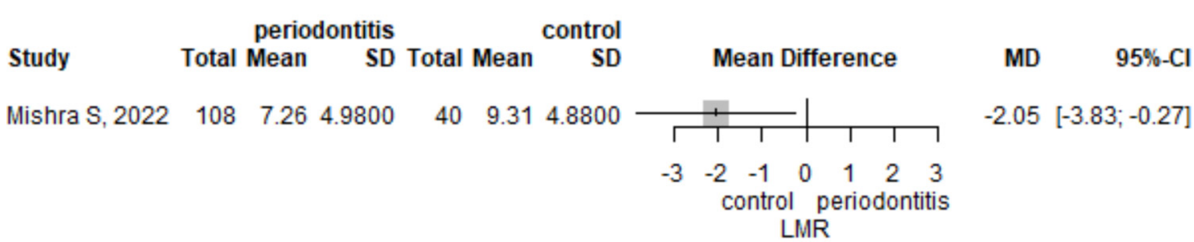

Figure 4. Lymphocyte to monocyte ratio -mean difference between periodontitis and control subjects.

3.3.4. Red Cell Distribution Width

The meta-analysis of four studies that assessed RDW observed that its mean values were higher by 0.1 (95% CI −0.63–0.84) in the periodontitis group compared to the control group, but the result was not significant, p = 0.782 (Figure 5). There was a statistically significant heterogeneity, measured with I2 = 78.1% (95% CI 40.9–91.9%), p = 0.003. To assess the robustness of the result, we performed a leave-one-out sensitivity analysis (Supplementary Figure S3). The influence analysis indicated the Temelli B et al. study [28] to be influential. When removing the Temelli study [28], the result did not reach the significance level, although the heterogeneity dropped to 30%. In the case of any other study removal, the heterogeneity was greater than or equal to 81%.

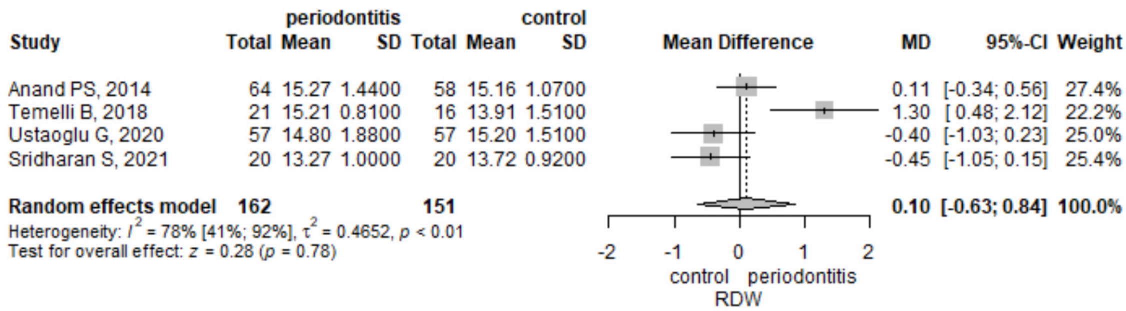

Figure 5. Red cell distribution width-mean difference between periodontitis and control subjects.

3.4. Risk of Bias in Studies

We used the Newcastle Ottawa scale (NOS) [16] to assess the methodological quality of the included studies (Table 2). For the objective of our review, we used the case-control subsection of the NOS.

Table 2. Newcastle Ottawa Scale quality assessment of the selected articles.

Author and Year of Publication	Cases DA	Cases R	Controls S	Controls D	Cases and Controls C †	EA	Cases and Controls A ††	NRR
Acharya AB, 2019 [7]	*			*	#	*	*	*
Anand PS, 2014 [23]	*	*	?	*	#	*	*	*
Çetin Özdemir E, 2022 [1]	*		?	*	#	*	*	*
Dogan B, 2015 [24]	*		*	*	#	*	*	*
Lu RF, 2021 [25]	*		?	*	#	*	*	*
Mishra S, 2022 [26]	*		?	*	#	*	*	*
Sridharan S, 2021 [27]	*			*	^ (age, gender)	*	*	*
Temelli, B, 2018 [28]	*	*	*	*	#	*	*	*
Torrungruang K, 2018 [29]	*		?	*	#	*	*	*
Ustaoglu G, 2020 [2]	*		?	*	#	*	*	*

DA-definition adequacy; R-representativeness; D-definition; EA-exposure ascertainment; A-ascertainment; †-according to design or analysis; ††-same method; ^-matched for the variables in the brackets; NRR-non-response rate; *-fulfilled criteria; ?-unclear criteria; #-extensive exclusion criteria.

Regarding the selection section of the NOS scale, all the studies used pre-defined, transparent criteria to identify the presence of the disease (chronic periodontitis or aggressive periodontitis) and controls; thus, the case and control definitions were adequate. Nevertheless, the authors of the studies used different criteria to identify the disease according to official classifications (Periodontal Disease Classification, American Association of Periodontology 1999-three studies [23,25,28]; Classification of Periodontal and Peri-Implant Diseases and Conditions 2017-four studies [1,2,26,27]; Center of Disease Control and

Prevention, American Academy of Periodontology Periodontal Disease Classification CDC/AAP-one study [29]), or no specified classification [7,24]. Only two studies (20%) out of ten had clear representativeness of the cases [23,28]. Two studies had a poor selection of controls [7,27], and two studies had a correct selection of controls. For the other six, it might be difficult to assess if the selection of controls was correct. Half of the studies enrolled subjects from the department of periodontology [1,2,7,23,26]; the other studies enrolled subjects from the internal medicine [28] or cardiology departments [24], or from an electrical company [29], and in two studies, the population was not stated [25,27].

Concerning comparability, only one study used matching for age and gender [27], and all the other studies performed a simple comparison between cases and controls. Nevertheless, all the studies used extensive exclusion criteria for systemic diseases, which help in group comparability. A problem in comparability might be the smoking status, as four studies had a percentage under 25% of smokers or occasional smokers [25,27,28].

All research can be regarded as bias-free when it comes to assessing blood parameters since the laboratory methods used were reliable, the same methods for cases and controls were used, and there was no non-response rate.

The biggest issue in the methodology of these studies is the representativeness of the cases. The possible problem with control selection, as well as the comparability of the groups, appears to be less affected.

3.5. Reporting Biases

Since the number of studies in each meta-analysis was below ten, publication bias could not be reliably assessed. Nevertheless, the *p*-values for the Egger test for assessing publication bias were greater than the level of significance.

4. Discussion

This is the first systematic review and meta-analysis, to our knowledge, investigating the association between blood cell count inflammatory biomarkers and periodontitis. Periodontitis was found to have a statistically significant relationship with NLR and LMR, a debatable association with PLR, and RDW did not approach the significance level.

The neutrophil to lymphocyte ratio and platelet to lymphocyte ratio are two biomarkers of systemic inflammation that have increasingly gained interest in the diagnosis of a variety of cardiovascular diseases [30–32], diabetes [33–35], inflammatory diseases [36,37], and malignancies [38,39]. In our review, we found higher mean values of NLR in periodontitis patients compared to healthy controls. Although there was an important heterogeneity, the result was robust even when performing the leave-one-out sensitivity analyses. Furthermore, a prospective study by Acharya et al. [7] objectivated the reduction of NLR and PLR levels after scaling and root planing.

Concerning PLR, the initial analysis did not reach statistical significance, but after the removal of the statistically influential study of Torrungruang et al. [29], the result became statistically significant and without heterogeneity. Twenty-five percent of the subjects in this study were with impaired glucose tolerance or diabetes, while all the other studies that reported PLR were free of systemic diseases; thus, this exclusion is likely to be warranted.

Little is known-and remains unknown-about the association between LMR and periodontitis, which could serve as a possible marker of systemic inflammation as well as aid in diagnosing and predicting the prognosis of periodontitis. Only one study reported the association between periodontitis and LMR, and it proved to be statistically significant, with higher values being observed in the periodontitis group.

Several studies found a link between periodontal disorders and low erythrocyte count, implying that periodontal diseases could be linked to chronic anemia [40,41]. RDW has also been linked to inflammatory markers, including erythrocyte sedimentation rate and high-sensitivity C-reactive protein, which have both been linked to periodontitis [42]. In our meta-analysis, we could not objectivate a statistically significant association between RDW and periodontitis, the results being heterogeneous, with studies showing conflicting results concerning the direction of the association.

Leite et al., in a systematic review and meta-regression, studied the effect of smoking on periodontitis and showed that periodontitis is aggravated by smoking [43]. Larvin et al. used a unique artificial intelligence-based network analysis to identify systemic multimorbidity clusters in subjects with periodontitis and analyzed factors that may influence the severity of those clusters. The authors stated that hypertension, arthritis, and obesity had the largest impact on multimorbidity clusters in subjects with periodontitis, and diabetes was more prevalent in those who had experienced a greater degree of clinical attachment loss. they also showed that in adults with severe periodontitis, smoking status influenced the clustering pattern of diabetes and cancer [44]. The authors of the chosen studies from our systematic review and meta-analysis evaluated the smoking status in different ways: the authors Acharya AB et al. [7] and Lu RF et al. [25] did not discuss smoking. Çetin Özdemir E et al. [1], Mishra S et al. [26], and Ustaoglu G et al. [2] studied non-smoking subjects; thus smoking was excluded as a confounder. In the study of Dogan B et al. [24], almost the entire population consisted of non-smokers, and therefore, the results were interpreted as independent of the effects of smoking. The authors Anand PS et al. [23] discussed smoking, and they performed a logistic regression model adjusted for age, gender, smoking, and body mass index. Sridharan S et al. [27] and Temelli B at al. [28] discussed smoking and found no significant differences between smokers and non-smokers. Torrungruang K et al. [29] discussed the smoking status and did not show the relation between periodontitis and the biomarkers of interest.

Michaud et al., in a review, showed that periodontitis is common in adults, and it worsens with age [45]. Ciesielska et al., in a narrative review, showed that menopausal women have a higher risk of periodontal disease [46]. In the publications selected in our review and meta-analysis, the authors Çetin Özdemir et al. [1] showed that the mean age of the individuals in the periodontitis group was higher than the other groups, and gender was significantly different. Dogan B et al. revealed a higher proportion of females in the risk factor groups and a higher age [24]. Sridharan S et al. showed that age was significantly related to red cell distribution width, but not gender [27]. Temelli B et al. found only age differences among groups [28]. No significant differences in age and gender distribution between the groups were found by Lu RF et al. [25], Mishra S et al. [26], Torrungruang K et al. [29], or Ustaoglu G et al. [2].

Our pooled results ring a bell, paving the way for future studies that could identify viable strategies for evaluating blood cell count inflammatory biomarkers for diagnostic, prognostic, and therapeutic management. Moreover, this study emphasizes that periodontitis has a repercussive potential upon systemic inflammation, being a response to bacterial infection.

4.1. Limitations and Strengths

There are several limitations of our study as well as of the included studies. The observational nature of the studies precludes any cause and effect relationship affirmations. This is further limited by the fact many of the studies were cross-sectional, a design that cannot assess the directional relation between the inflammatory biomarkers and periodontitis. Only one study assessed the effects of periodontal treatment on NLR and PLR that significantly lowered their values. There was a high heterogeneity between the results of the studies. To check the robustness of our results, we performed leave-one-out sensitivity analyses, and NLR results resisted. Furthermore, PLR became statistically significant after the removal of one study that had other comorbidities, and the heterogeneity dropped to 0. Nevertheless, for RDW, the heterogeneity remained important. For several of the outcomes, we found only a few studies to support our meta-analyses since the literature is still emerging on this topic. Concerning the methodological quality, the selected studies had two more relevant drawbacks: the representativeness of the cases was problematic since many studies did not report if all the cases in the accessible population were included in their research, and the reporting of the selection of controls, whether derived from the same population as the cases, was lacking in several studies. Nevertheless, the other quality criteria were fulfilled. Although the majority of the studies reported the classification system used to diagnose periodontitis, there was some heterogeneity between them regarding the type or the year of classification. Nevertheless, the systems used are from trusted authorities on the subject.

4.2. Study Strengths

The study's key strength is that it primarily assessed four commonly viable non-invasive biomarkers that may be easily used in a clinical context. To the best of our knowledge, this is the first systematic review and meta-analysis on this emerging topic. Our search technique was thorough and included many medical databases, allowing us to explore the link in a systematic manner across a wide range of populations, resulting in more generalizable findings. Furthermore, the review has a robust methodology and uses a solid approach that includes sensitivity analyses and quality assessments of the selected publications.

4.3. Implications for Practice and Future Research

These inflammatory markers could be included as potential parameters to assess the impact of periodontitis on systemic health, adding to the burden of other inflammation-generating diseases. Furthermore, they could be used as prognostic markers for the evolution of the disease and the treatment efficiency assessment on a systemic level. Moreover, it would be possible to employ the inflammatory markers in a way that uses standardized values to allow for consistent periodontal disease diagnosis and severity grading. Through the creation and utilization of biological instruments to make a diagnosis and evaluate treatment outcomes, this method will serve as a key step toward the medicalization of periodontics and dentistry [47].

To gain evidence in these directions, future prospective designed studies should be endeavored.

If their role is confirmed, clinicians could better classify and monitor the disease progression and treatment efficiency with these inflammatory markers.

5. Conclusions

Our systematic review and meta-analysis found an association between NLR, LMR, and PLR and periodontitis, but not for RDW. Thus, these ratios might be thought of as emerging blood cell count inflammatory biomarkers that could shed light on the link between periodontitis and systemic disbalances, as well as for periodontitis prognosis and grading. However, because the methodological quality of the evaluated research is imperfect, the results should be used with care. Further prospective design studies are warranted.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jpm12060992/s1, Figure S1: Leave-one-out sensitivity analysis for neutrophils to lymphocyte ratio; Figure S2: Leave-one-out sensitivity analysis for platelet to leucocyte ratio; Figure S3: Leave-one-out sensitivity analysis for red cell distribution width; Table S1: Search strategies for each database; Table S2: Inclusion and exclusion criteria of the subjects within the original articles.

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References

1. Çetin Özdemir, E.; Bilen, E.; Yazar, F.M. Can the Delta Neutrophil Index Be Used as a Preliminary Biomarker In the Evaluation of Periodontal Disease: A Pilot Study. *J. Appl. Oral Sci.* **2022**, *30*, e20210555. https://doi.org/10.1590/1678-7757-2021-0555.
2. Ustaoglu, G.; Erdal, E.; İnanır, M. Does Periodontitis Affect Mean Platelet Volume(MPV) and Plateletcrit (PCT) Levels in Healthy Adults? *Rev. Assoc. Med. Bras.* **2020**, *66*, 133–138. https://doi.org/10.1590/1806-9282.66.2.133.
3. Cecoro, G.; Annunziata, M.; Iuorio, M.T.; Nastri, L.; Guida, L. Periodontitis, Low-Grade Inflammation and Systemic Health: A Scoping Review. *Medicina* **2020**, *56*, 272. https://doi.org/10.3390/medicina56060272.
4. Brum, R.S.; Duarte, P.M.; Canto, G.D.L.; Flores-Mir, C.; Benfatti, C.A.M.; Porporatti, A.L.; Zimmermann, G.S. Biomarkers in Biological Fluids in Adults with Periodontitis and/or Obesity: A Meta-Analysis. *J. Indian Soc. Periodontol.* **2020**, *24*, 191–215. https://doi.org/10.4103/jisp.jisp_512_19.
5. Shi, D.; Meng, H.; Xu, L.; Zhang, L.; Chen, Z.; Feng, X.; Lu, R.; Sun, X.; Ren, X. Systemic Inflammation Markers in Patients With Aggressive Periodontitis: A Pilot Study. *J. Periodontol.* **2008**, *79*, 2340–2346. https://doi.org/10.1902/jop.2008.080192.
6. Papapanagiotou, D.; Nicu, E.A.; Bizzarro, S.; Gerdes, V.E.A.; Meijers, J.C.; Nieuwland, R.; van der Velden, U.; Loos, B.G. Periodontitis Is Associated with Platelet Activation. *Atherosclerosis* **2009**, *202*, 605–611. https://doi.org/10.1016/j.atherosclerosis.2008.05.035.
7. Acharya, A.B.; Shetty, I.P.; Jain, S.; Padakannaya, I.; Acharya, S.; Shettar, L.; Thakur, S. Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio in Chronic Periodontitis before and after Nonsurgical Therapy. *J. Indian Soc. Periodontol.* **2019**, *23*, 419–423. https://doi.org/10.4103/jisp.jisp_622_18.
8. Yamamoto, T.; Tsuneishi, M.; Furuta, M.; Ekuni, D.; Morita, M.; Hirata, Y. Relationship between Decrease of Erythrocyte Count and Progression of Periodontal Disease in a Rural Japanese Population. *J. Periodontol.* **2011**, *82*, 106–113. https://doi.org/10.1902/jop.2010.100211.
9. Park, S.; Lee, S.J.; Shin, B.; Lee, S.J.; Kim, S.-H.; Kwon, W.C.; Kim, J.; Lee, M.K. The Association of Delta Neutrophil Index with the Prognosis of Acute Exacerbation of Chronic Obstructive Pulmonary Disease. *BMC Pulm Med.* **2020**, *20*, 47. https://doi.org/10.1186/s12890-020-1083-4.
10. Loos, B.G.; Craandijk, J.; Hoek, F.J.; Wertheim-van Dillen, P.M.; van der Velden, U. Elevation of Systemic Markers Related to Cardiovascular Diseases in the Peripheral Blood of Periodontitis Patients. *J. Periodontol.* **2000**, *71*, 1528–1534. https://doi.org/10.1902/jop.2000.71.10.1528.
11. Papapanou, P.N.; Sanz, M.; Buduneli, N.; Dietrich, T.; Feres, M.; Fine, D.H.; Flemmig, T.F.; Garcia, R.; Giannobile, W.V.; Graziani, F.; et al. Periodontitis: Consensus Report of Workgroup 2 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. *J. Periodontol.* **2018**, *89* (Suppl. 1), S173–S182. https://doi.org/10.1002/JPER.17-0721.
12. Armitage, G.C. Development of a Classification System for Periodontal Diseases and Conditions. *Ann. Periodontol.* **1999**, *4*, 1–6. https://doi.org/10.1902/annals.1999.4.1.1.
13. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews. *BMJ* **2021**, *372*, n71. https://doi.org/10.1136/bmj.n71.
14. EndNote. Available online: https://access.clarivate.com/login?app=endnote (accessed on 29 April 2022).
15. *Zotero*; Corporation for Digital Scholarship. Available online: https://www.zotero.org/ (accessed on 5 May 2022).
16. Wells, G.; Shea, B.; O'Connell, D.; Peterson, J.; Welch, V.; Losos, M.; Tugwell, P. Ottawa Hospital Research Institute Available online: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed on 29 April 2022).
17. Hozo, S.P.; Djulbegovic, B.; Hozo, I. Estimating the Mean and Variance from the Median, Range, and the Size of a Sample. *BMC Med. Res. Methodol.* **2005**, *5*, 13. https://doi.org/10.1186/1471-2288-5-13.
18. Rohatgi, A. WebPlotDigitizer. Available online: https://apps.automeris.io/wpd/ (accessed on 29 April 2022).
19. Higgins, J.; Thomas, J.; Chandler, J.; Cumpston, M.; Li, T.; Page, M.; Welch, V. *Cochrane Handbook for Systematic Reviews of Interventions*, 2nd ed.; John Wiley & Sons: Chichester, UK, 2019.
20. R Core Team *A Language and Environment for Statistical Computing*; R Foundation for Statistical Computing: Austria, Vienna, 2021;
21. Balduzzi, S.; Rücker, G.; Schwarzer, G. How to Perform a Meta-Analysis with R: A Practical Tutorial. *Evid.-Based Ment. Health* **2019**, *22*, 153–160. https://doi.org/10.1136/ebmental-2019-300117.

22. Harrer, M.; Pim, C.; Toshi, F.; David Daniel, E. *Companion R Package For The Guide 'Doing Meta-Analysis in R*; Taylor & Francis Group: Boca Ranton, FL, USA, 2019.
23. Anand, P.S.; Sagar, D.K.; Ashok, S.; Kamath, K.P. Association of Aggressive Periodontitis with Reduced Erythrocyte Counts and Reduced Hemoglobin Levels. *J. Periodont. Res.* **2014**, *49*, 719–728. https://doi.org/10.1111/jre.12154.
24. Doğan, B.; Fentoğlu, Ö.; Kırzıoğlu, F.Y.; Kemer, E.S.; Köroğlu, B.K.; Aksu, O.; Çarsancaklı, S.A.; Orhan, H. Lipoxin A4 and Neutrophil/Lymphocyte Ratio: A Possible Indicator in Achieved Systemic Risk Factors for Periodontitis. *Med. Sci. Monit.* **2015**, *21*, 2485–2493. https://doi.org/10.12659/MSM.895115.
25. Lu, R.; Li, W.; Wang, X.; Shi, D.; Meng, H. Elevated Neutrophil-to-Lymphocyte Ratio but Not Platelet-to-Lymphocyte Ratio Is Associated with Generalized Aggressive Periodontitis in a Chinese Population. *J. Periodontol.* **2021**, *92*, 507–513. https://doi.org/10.1002/JPER.20-0282.
26. Mishra, S.; Gazala, M.P.; Rahman, W. Clinical and Diagnostic Significance of Blood Leukocyte Ratios in Young Patients with Stage III Grade C Periodontitis. *Acta Odontol. Scand.* **2022**, *80*, 161–168. https://doi.org/10.1080/00016357.2021.1969035.
27. Sridharan, S.; Sravani, P.; Rao, R.J. Coefficient of Variation of Red Cell Distribution Width Has Correlations to Periodontal Inflamed Surface Area in Non-Obese Hypertensive Patients. *J. Int. Acad. Periodontol.* **2021**, *23*, 106–114.
28. Temelli, B.; Yetkin Ay, Z.; Aksoy, F.; Büyükbayram, H.İ.; Kumbul Doğuç, D.; Uskun, E.; Varol, E. Platelet Indices (Mean Platelet Volume and Platelet Distribution Width) Have Correlations with Periodontal Inflamed Surface Area in Coronary Artery Disease Patients: A Pilot Study. *J. Periodontol.* **2018**, *89*, 1203–1212. https://doi.org/10.1002/JPER.17-0684.
29. Torrungruang, K.; Ongphiphadhanakul, B.; Jitpakdeebordin, S.; Sarujikumjornwatana, S. Mediation Analysis of Systemic Inflammation on the Association between Periodontitis and Glycaemic Status. *J. Clin. Periodontol.* **2018**, *45*, 548–556. https://doi.org/10.1111/jcpe.12884.
30. Larmann, J.; Handke, J.; Scholz, A.S.; Dehne, S.; Arens, C.; Gillmann, H.-J.; Uhle, F.; Motsch, J.; Weigand, M.A.; Janssen, H. Preoperative Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio Are Associated with Major Adverse Cardiovascular and Cerebrovascular Events in Coronary Heart Disease Patients Undergoing Non-Cardiac Surgery. *BMC Cardiovasc. Disord.* **2020**, *20*, 230. https://doi.org/10.1186/s12872-020-01500-6.
31. Lee, C.D.; Folsom, A.R.; Nieto, F.J.; Chambless, L.E.; Shahar, E.; Wolfe, D.A. White Blood Cell Count and Incidence of Coronary Heart Disease and Ischemic Stroke and Mortality from Cardiovascular Disease in African-American and White Men and Women: Atherosclerosis Risk in Communities Study. *Am. J. Epidemiol.* **2001**, *154*, 758–764. https://doi.org/10.1093/aje/154.8.758.
32. Zhang, S.; Diao, J.; Qi, C.; Jin, J.; Li, L.; Gao, X.; Gong, L.; Wu, W. Predictive Value of Neutrophil to Lymphocyte Ratio in Patients with Acute ST Segment Elevation Myocardial Infarction after Percutaneous Coronary Intervention: A Meta-Analysis. *BMC Cardiovasc. Disord.* **2018**, *18*, 75. https://doi.org/10.1186/s12872-018-0812-6.
33. Gkrania-Klotsas, E.; Ye, Z.; Cooper, A.J.; Sharp, S.J.; Luben, R.; Biggs, M.L.; Chen, L.-K.; Gokulakrishnan, K.; Hanefeld, M.; Ingelsson, E.; et al. Differential White Blood Cell Count and Type 2 Diabetes: Systematic Review and Meta-Analysis of Cross-Sectional and Prospective Studies. *PLoS ONE* **2010**, *5*, e13405. https://doi.org/10.1371/journal.pone.0013405.
34. Wan, H.; Wang, Y.; Fang, S.; Chen, Y.; Zhang, W.; Xia, F.; Wang, N.; Lu, Y. Associations between the Neutrophil-to-Lymphocyte Ratio and Diabetic Complications in Adults with Diabetes: A Cross-Sectional Study. *J. Diabetes Res.* **2020**, *2020*, 6219545. https://doi.org/10.1155/2020/6219545.
35. Wang, S.-Y.; Shen, T.-T.; Xi, B.-L.; Shen, Z.; Zhang, X. Vitamin D Affects the Neutrophil-to-Lymphocyte Ratio in Patients with Type 2 Diabetes Mellitus. *J. Diabetes Investig.* **2021**, *12*, 254–265. https://doi.org/10.1111/jdi.13338.
36. Kuplay, H.; Erdoğan, S.B.; Bastopcu, M.; Arslanhan, G.; Baykan, D.B.; Orhan, G. The Neutrophil-Lymphocyte Ratio and the Platelet-Lymphocyte Ratio Correlate with Thrombus Burden in Deep Venous Thrombosis. *J. Vasc. Surg. Venous. Lymphat. Disord.* **2020**, *8*, 360–364. https://doi.org/10.1016/j.jvsv.2019.05.007.
37. Isaac, V.; Wu, C.-Y.; Huang, C.-T.; Baune, B.T.; Tseng, C.-L.; McLachlan, C.S. Elevated Neutrophil to Lymphocyte Ratio Predicts Mortality in Medical Inpatients with Multiple Chronic Conditions. *Medicine* **2016**, *95*, e3832. https://doi.org/10.1097/MD.0000000000003832.
38. Stefaniuk, P.; Szymczyk, A.; Podhorecka, M. The Neutrophil to Lymphocyte and Lymphocyte to Monocyte Ratios as New Prognostic Factors in Hematological Malignancies - A Narrative Review. *Cancer Manag. Res.* **2020**, *12*, 2961–2977. https://doi.org/10.2147/CMAR.S245928.
39. Mleko, M.; Pitynski, K.; Pluta, E.; Czerw, A.; Sygit, K.; Karakiewicz, B.; Banas, T. Role of Systemic Inflammatory Reaction in Female Genital Organ Malignancies - State of the Art. *Cancer Manag. Res.* **2021**, *13*, 5491–5508. https://doi.org/10.2147/CMAR.S312828.
40. Musalaiah, S.V.V.S.; Anupama, M.; Nagasree, M.; Krishna, C.M.; Kumar, A.; Kumar, P.M. Evaluation of Nonsurgical Periodontal Therapy in Chronic Periodontitis Patients with Anemia by Estimating Hematological Parameters and High-Sensitivity C-Reactive Protein Levels. *J. Pharm. Bioallied Sci.* **2014**, *6*, S64–S69. https://doi.org/10.4103/0975-7406.137390.
41. Naik, V.; Acharya, A.; Deshmukh, V.L.; Shetty, S.; Shirhatti, R. Generalized, Severe, Chronic Periodontitis Is Associated with Anemia of Chronic Disease: A Pilot Study in Urban, Indian Males. *J. Investig. Clin. Dent.* **2010**, *1*, 139–143. https://doi.org/10.1111/j.2041-1626.2010.00028.x.
42. Lappé, J.M.; Horne, B.D.; Shah, S.H.; May, H.T.; Muhlestein, J.B.; Lappé, D.L.; Kfoury, A.G.; Carlquist, J.F.; Budge, D.; Alharethi, R.; et al. Red Cell Distribution Width, C-Reactive Protein, the Complete Blood Count, and Mortality in Patients with Coronary Disease and a Normal Comparison Population. *Clin. Chim. Acta* **2011**, *412*, 2094–2099. https://doi.org/10.1016/j.cca.2011.07.018.

43. Leite, F.R.M.; Nascimento, G.G.; Scheutz, F.; López, R. Effect of Smoking on Periodontitis: A Systematic Review and Meta-Regression. *Am. J. Prev. Med.* **2018**, *54*, 831–841. https://doi.org/10.1016/j.amepre.2018.02.014.
44. Larvin, H.; Kang, J.; Aggarwal, V.R.; Pavitt, S.; Wu, J. Systemic Multimorbidity Clusters in People with Periodontitis. *J. Dent. Res.* **2022**, 220345221098910. https://doi.org/10.1177/00220345221098910.
45. Michaud, D.S.; Fu, Z.; Shi, J.; Chung, M. Periodontal Disease, Tooth Loss, and Cancer Risk. *Epidemiol. Rev.* **2017**, *39*, 49–58. https://doi.org/10.1093/epirev/mxx006.
46. Ciesielska, A.; Kusiak, A.; Ossowska, A.; Grzybowska, M.E. Changes in the Oral Cavity in Menopausal Women—A Narrative Review. *IJERPH* **2021**, *19*, 253. https://doi.org/10.3390/ijerph19010253.
47. Khoury, W.; Glogauer, J.; Tenenbaum, H.C.; Glogauer, M. Oral Inflammatory Load: Neutrophils as Oral Health Biomarkers. *J Periodontal Res.* **2020**, *55*, 594–601. https://doi.org/10.1111/jre.12758.

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Article

Recovery following Orthognathic Surgery Procedures—A Pilot Study

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Abstract: This study aims at evaluating and categorizing patients' objective and subjective postoperative recovery symptoms after bimaxillary orthognathic surgery assigning the healing process. The patients were monitored throughout the recovery process, and their symptoms were managed. A prospective, observational study was performed. Patients with Class II and III malocclusion (aged 18 to 35) were evaluated and monitored preoperatively, and postoperatively at 48 h, 2 weeks, 1 month, and 3 months postsurgery. A questionnaire was used to assess pain and anesthesia/hypoesthesia. The most common objective and subjective signs that were correlated with the healing process were edema, hematoma, trismus, pain, and anesthesia/hypoesthesia. Edema peaked at 48–72 h postoperatively (distance between eye's external canthus and gonion, mean difference = 4.53, between tragus and cheilion, mean difference = 7, between tragus and gnathion, mean difference = 4.65, $p < 0.001$); mouth opening amplitude was significantly decreased during the first two weeks postsurgery (class II, mean difference = 32.42, $p = 0.006$, class III, mean difference = 44.57, $p < 0.001$), but it steadily and considerably improved over three months. The nose tended to widen postsurgery. The most severe pain experienced by patients was of medium intensity in the mandibular body, described as pressure, and usually did not spread. Patients were most severely and persistently impacted by anesthesia/hypoesthesia.

Keywords: orthognathic surgery; edema; trismus; pain; anesthesia; hypoesthesia; recovery after surgery

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1. Introduction

Anomalies of the craniomaxillofacial complex are the expression of changes occurring in the growth and development of various segments of the neurocranium or viscerocranium during the intrauterine period and throughout the entire somatic development. They can be visible at birth due to the suffering of the embryo during intrauterine life, but they can also appear during life through the action of different etiological factors, whereas dental anomalies are defined by any form of interruption of the eruption process of a tooth germ from its initial position of development in the alveolar bone into its functional position, of the oral cavity [1]. Individuals with extensive malocclusion have much worse mastication function, aesthetics, general oral health, periodontal disease, and general self-esteem, all of which can be treated through orthognathic surgery and consecutive specific treatments [2]. By properly planning and carrying out precise orthodontic planning, intraoperative surgical procedures, and postoperative procedures, long-term three-dimensionally stable occlusion results can be attained [3].

The correct repositioning of the maxilla, mandible, or even both can be accomplished through orthognathic surgery [4]. The most common surgical procedure in the maxilla is the LeFort I osteotomy (a low horizontal maxillary osteotomy). It allows for 3D movements of the maxilla, including translational and rotational displacements, and even transversal deficit correction when multisegmental osteotomies are employed [5,6]. Often, it is indicated in conjunction with the bilateral sagittal split osteotomy (BSSO), the most used orthognathic technique in the mandible for correcting Class II or III malocclusion and other discrepancies. The BSSO osteotomy splits the ramus and the posterior body of the mandible sagittaly, which allows for the complex movement of the mandible [7].

Orthognathic surgery may be the best option for treating significant hyperdivergent Class II skeletal malocclusions in mature individuals [8]. The lower-jaw strategy has replaced the maxilla-first technique in some situations as the preferred method of therapy for bimaxillary orthognathic surgery due to the development of robust screw stabilization and the need to avoid any potential inaccuracies that can occur throughout the initial occlusal recording [9]. After Class II and III surgical orthognathic procedures, considerable intended vertically mandible alterations are accomplished. Some degree of relapse was observed from a vertical point of view with these patients over the long term [10].

Congenital and acquired dentofacial abnormalities are routinely treated with orthognathic surgery; hence, the appearance of every facial feature, such as the nose, is impacted through any surgical intervention performed to alter or restore facial characteristics [11]. Since orthognathic surgery procedures are accompanied by swelling, pain, and peripheral nerve abnormalities following orthognathic surgery, low-level laser therapy was helpful in reducing discomfort, edema, and neurosensory disturbances involving the inferior alveolar nerve [12]. Although it had no effect on peripheral nerve abnormalities, supplying corticosteroids after orthognathic surgery enhanced the reduction in face edema [13]. Hilotherapy, which involves using a face mask to apply cool pressure at a controlled temperature, was linked with considerable decreases in postoperative facial pain and edema [14]. In lowering postsurgical edema after mandible orthognathic surgery, photobiomodulation treatment was the most beneficial addition to oral nonsteroidal anti-inflammatory drugs [15].

This study aims at evaluating and classifying the patient's objective and subjective postoperative recovery symptoms after bimaxillary orthognathic surgery into stabilizing parameters and assigning the healing process, monitoring parameters over time during checkup visits for persistence, amplification, or symptom relief, observing changes throughout the course of the recovery process, classifying relevant data into predicable categories that enable patients' symptoms to be better understood in terms of their nature, severity, and duration, determining if there is a correlation between the severity of remission symptoms and signs evolving over time in patients who presented with a Class II or III malocclusion, and observing changes in the recovery process. This information is extremely valuable to practitioners because it allows for them to not only provide more accurate data to their patients, but also to develop strategies aimed at reducing their patients' discomfort.

2. Materials and Methods

A prospective, observational study was performed between July and September 2021. The study was approved by the ethics committee of the University of Medicine and Pharmacy in Cluj-Napoca (approval number 248/30.06.2021). A three-month study was conducted. Each patient was informed on the study protocol, the procedures for collecting the necessary data for the study, the time frame for completion, and the number of assessments the evaluator was required to complete. By filling out and signing the legal paperwork addressing the acquisition, processing, storage, and privacy protection of personal data, patients gave their informed consent to participate in the study. For each patient, a file was created with the qualitative data provided by the patient and recorded in their evaluation form before surgery at 48 h, 2 weeks, and 1 and 3 months after surgery combined with the objective information determined by the evaluator at the following time intervals: preoperatively, and postoperatively at 48 h, 2 weeks, 1 month, and 3 months.

Patients needing bimaxillary orthognathic surgery (LeFort I and BSSO—Epker Technique) were included in the present study. Patients with malocclusions that did not involve orthognathic surgery and those who had only undergone monomaxillary or segmental surgery were excluded.

Five parameters were evaluated: three objective and two subjective. The three main objective parameters that were evaluated were edema, mouth opening amplitude, and nose width, whereas pain and anesthesia/hypoesthesia were the two subjective evaluated parameters. A digital caliper and ruler were used as the measuring tools to ascertain and quantify the objective data, and all the results were recorded in millimeters. Subjective data were collected using a nonvalidated operator-assisted survey that included questions on all relevant parameters of interest.

The objective parameter of edema was defined as the distance between the external canthus, gonion, tragus, cheilion, and gnathion of the eye, and was measured with a flexible ruler. Three distances were established between these points: distance AB (between the eye's external canthus and gonion), distance CD (between tragus and cheilion), and distance CE ((between tragus and gnathion) (Figure 1).

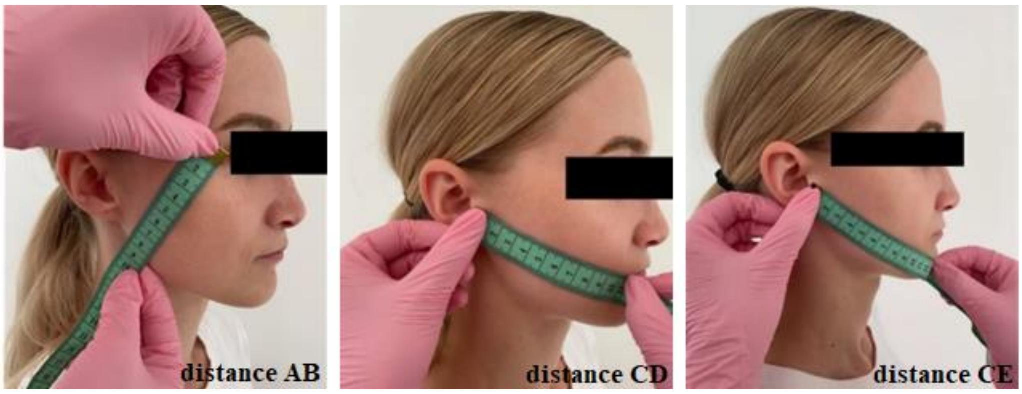

Figure 1. Edema measurement. Distance AB (between the eye's external canthus and gonion), distance CD (between tragus and cheilion), and distance CE (between tragus and gnathion).

The mouth's opening was measured with a digital caliper, and the quantitative value (length) of the mandibular path was calculated. At the maximal opening, the distance between the right central upper incisor's incisal edge and a tangent to the lower right central incisor's incisal edge was measured (Figure 2).

Figure 2. Mouth opening measurement.

The nose's width indicates soft-tissue changes after the surgery. It was examined with the use of the digital caliper. Anthropometric points alare, the most external point of the nose's wings, the distance between the insertions of the nasal fins, and the diameter of the left and right nostrils were all measured (Figure 3).

Figure 3. Nose width measurement.

A self-developed, nonvalidated questionnaire based on previous research was used to assess pain [16,17]. The survey inquired about the affected region, the degree of pain as judged by the patient using a numerical rating scale ranging from 0 to 10 (where 0 represented no pain and 10 represented pains felt to the greatest extent possible), the type of pain (which was classified as pressure, pulsating, stabbing, flashing, tingling, or twitching), and whether pain extended to other structures.

Anesthesia/hypoesthesia was investigated because the elongation of the inferior alveolar nerve branches occurs during the BSSO via bone segment manipulation. It was graded on a scale from 1 to 5, where 1 represented an unmodified tactile experience, 2 slightly modified, 3 moderate sensation, 4 almost absent, and 5 was the absence of tactile sensation. Statistical analysis was performed using GraphPad Prism software, version 8. The Shapiro–Wilk test was used to determine the normality of the data distribution for continuous quantitative data; a *p*-value of <0.05 suggested a normal distribution. The variables were investigated according to how they fluctuated over time (both before surgery and at different postoperative intervals); consequently, they were considered to be dependent variables. The ANOVA test was employed for the analysis of more than two groups in accordance with a single independent variable (the time variable). The Bonferroni post hoc test was used for comparison between pairs of groups. A two-way ANOVA test was used for the study of more than two groups with two independent variables (time variable and skeletal class). The Tukey test was used to compare the group means when there was a statistically significant association between the time variable and the continuous dependent variable. The between-group analysis of ordinal and nominal quantitative variables was conducted using the Friedman test. When comparing groups, Dunn's mean rank test was used if the test had statistical significance. The tests were considered to be statistically significant with an error threshold of 5% (p-value < 0.05).

3. Results

A total of 13 patients were examined (five males and eight females). Patients ranged in age from 18 to 35 years old, were of both sexes, and had dentomaxillary Class II and III malocclusion types (Table 1).

All continuous variables considered for the objective parameter edema were considered to be normally distributed (Shapiro–Wilk $p > 0.05$), and there were statistically significant differences between time intervals for all dimensions measured. The ANOVA test yielded a $p < 0.001$ value between the AB points (eye's external canthus and gonion), and the assessment among groups revealed a statistically significant difference between the preoperative and 48 h postoperative groups ($p < 0.001$, mean difference = 4.53), 48 h postoperative and 2 weeks postoperative ($p < 0.001$, mean difference = 3.77), 48 h and 1 month postoperative ($p < 0.001$, mean difference = 4.46), and between 48 h and 3 months postoperative ($p < 0.001$, mean difference = 4.46) (Figure 4).

Table 1. Patient characteristics.

Number	Age	Sex	Skeletal Class
1	18	Female	III
2	29	Female	III
3	29	Female	II
4	27	Female	II
5	24	Male	II
6	22	Male	III
7	28	Female	II
8	22	Male	III
9	30	Female	II
10	25	Female	II
11	29	Male	III
12	21	Female	III
13	35	Male	III

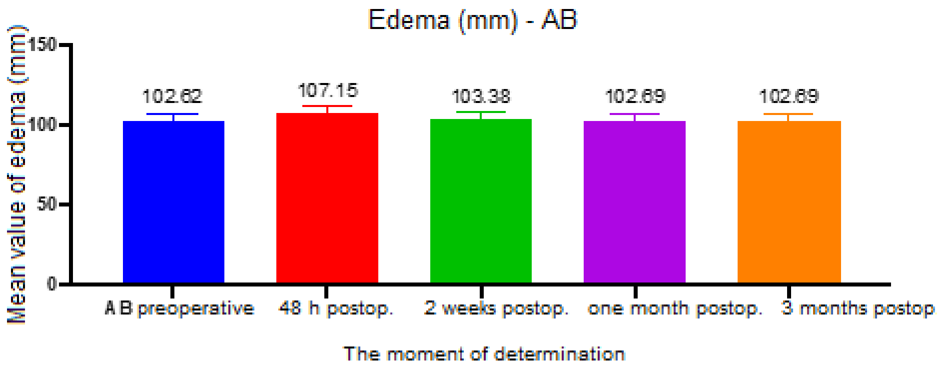

Figure 4. Edema assessment, AB distance.

For the CD distance (between tragus and cheilion), the ANOVA test had a value of $p = 0.008$, and the analysis between groups revealed a statistically significant difference between the preoperative and 48 h postoperative groups ($p < 0.001$, mean difference = 7), 48 h postoperative and 2 weeks postoperative ($p = 0.002$, mean difference = 3.76), 48 h and 1 month postoperative ($p = 0.006$, mean difference = 5.61) and between 48 h and 3 months postoperative ($p = 0.006$, mean difference = 6.15) (Figure 5).

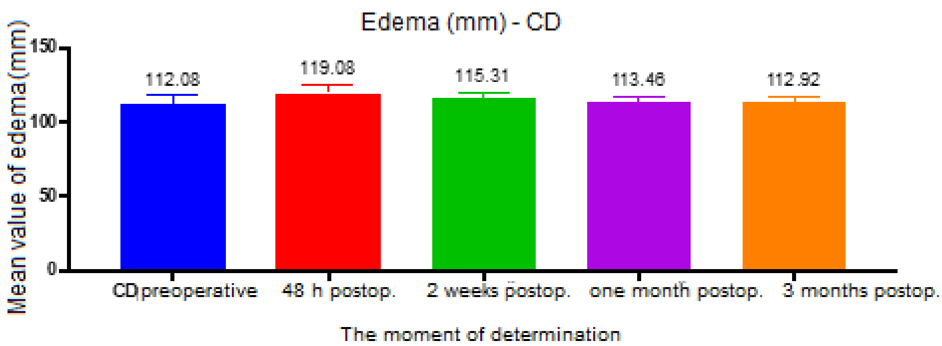

Figure 5. Edema assessment, CD distance.

For the CE distance (between tragus and gnathion), the ANOVA test had a value of $p = 0.003$, and the analysis between groups revealed a statistically significant difference between the preoperative and 48 h postoperative groups ($p < 0.001$, mean difference = 8.23), 48 h and 2 weeks postoperative ($p < 0.001$, mean difference = 4.65), 48 h postoperative and 1 month postoperative ($p < 0.001$, mean difference = 5.07), between 48 h and 3 months postoperative ($p < 0.001$, difference means = 6.53), and between 2 weeks and 3 months postoperative ($p = 0.02$, mean difference = 1.88) (Figure 6).

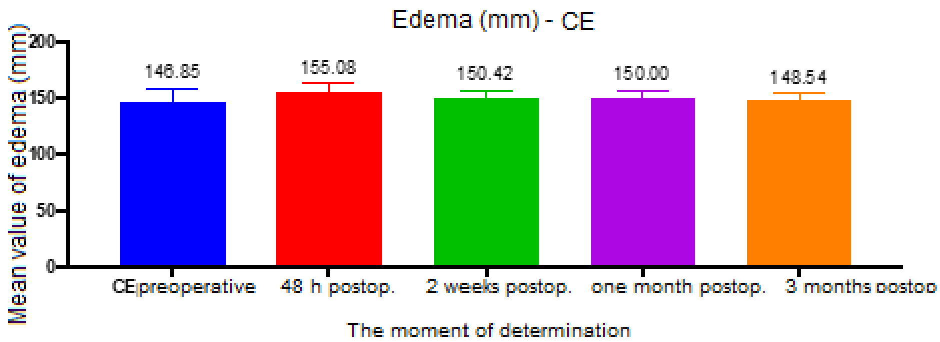

Figure 6. Edema assessment, CE distance.

A two-way ANOVA test was used to analyze the mouth opening amplitude data that included, in addition to the moment of determination, the skeletal class (II or III). Taking the time variable into account, skeletal class had no effect on the amplitude of the mouth opening ($p = 0.44$). The time of determination had a significant impact on the results, with a statistically significant difference between the groups ($p < 0.001$). The test between groups was performed for each skeletal class individually. For Class II, there were statistically significant differences between preoperative and 2 weeks postoperative ($p = 0.006$, mean difference = 32.42), preoperative and 4 weeks postoperative ($p = 0.02$, mean difference = 21.75), 2 weeks postoperative and 3 months postoperative ($p = 0.01$, mean difference = 24.58) and between 4 weeks postoperative and 3 months postoperative ($p = 0.02$, mean difference = 13.92). For Class III, there were also statistically significant differences between all groups. Between preoperative and: 2 weeks postoperative ($p < 0.001$, mean difference = 44.57), 4 weeks postoperative ($p < 0.001$, mean difference = 28.43) and 3 months postoperative ($p = 0.006$, mean difference = 11.43). Between 2 weeks and 4 weeks postoperative ($p < 0.001$, mean difference = 16.14) and 3 months postoperative ($p < 0.001$, mean difference = 33.14) and between 4 weeks and 3 months postoperative ($p < 0.001$, mean difference = 17) (Figure 7).

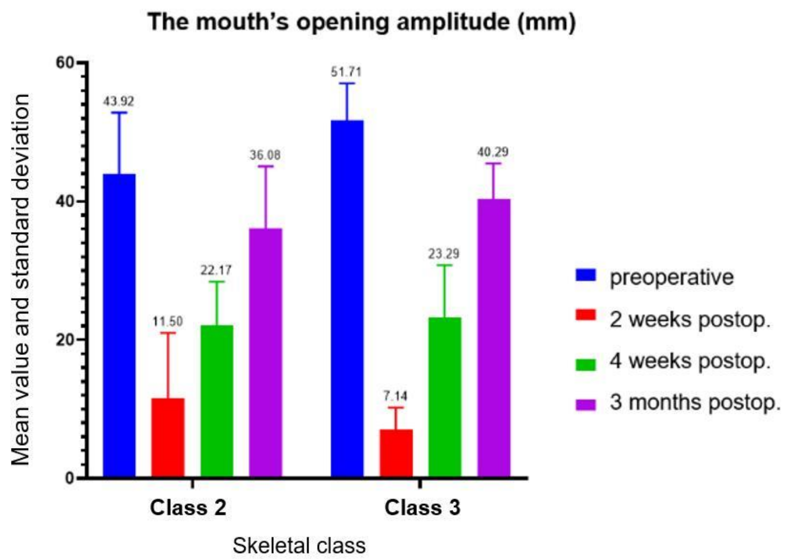

Figure 7. Mouth's opening amplitude.

In terms of nose width, for the Alare–Alare distance, both the skeletal class ($p = 0.03$) and the time of determination had an influence. When comparing classes, no statistically significant difference was detected between preoperative and 3 months postoperative ($p = 0.08$ for skeletal class II and $p = 0.28$ for skeletal class III). However, when the skeletal class was not considered, there was a difference between preoperative and 3 months postoperative (*t*-test $p = 0.02$, difference in means = 1). There was also a statistically significant difference (p = 0.04) of 4 mm in the preoperative moment between Skeletal Classes II and III (Figure 8).

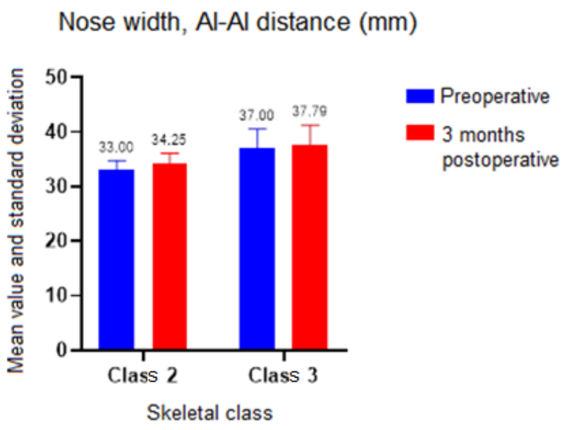

Figure 8. Nose width assessment.

The time of determination (p = 0.91) and skeletal class (p = 0.11) had no statistically significant influence on the values for the distance between the insertions of the nasal fins. As a result, the group tests were no longer used (Figure 9).

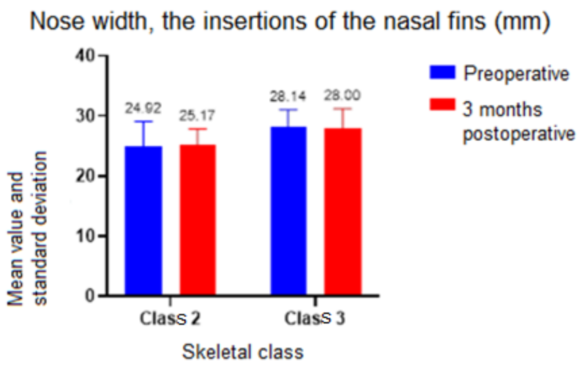

Figure 9. Nose width assessment, insertions of the nasal fins.

In the case of the width of the nose, for the left nostril, the moment of determination (p = 0.58) and the skeletal class (p = 0.98) and for the right nostril, class (p = 0.49) and time of determination (p = 0.48) did not have a statistically significant influence on the values (Figure 10). Therefore, the group tests were not used.

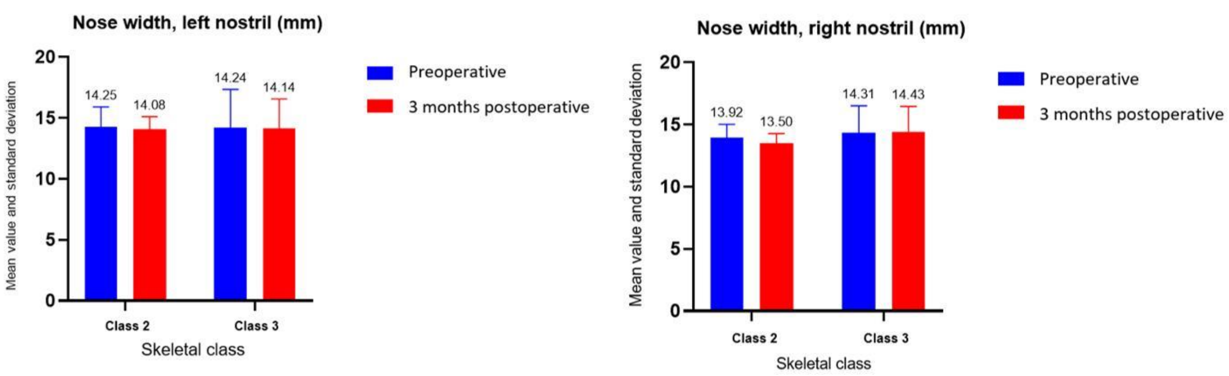

Figure 10. Nose width assessment, right and left nostrils.

The information gathered for pain evaluation revealed the following data about the affected area: at 48 h, the following areas were the most affected, in descending order: pain in the temporomandibular joint—1 patient, toothache—1 patient, and pain of the mandibular angle—1 patient. One month after surgery, seven patients reported no pain, three patients reported pain in the temporomandibular joint, two patients pain in the chin, and one patient pain in the cheeks. On a scale of 1 to 10, the patients rated the intensity of their pain as follows: 4 patients gave it a score of, 3 patients gave it a 6, 3 patients gave it a 4, one patient gave it a 5, and 2 did not present pain. One month after surgery, the intensity score for 3 patients was 2, 5 for 2 patients, 3 for 1 patient, and 0 for the remaining 6 patients. The Friedman test revealed that the distribution of pain intensity differed significantly between groups ($p = 0.02$). Dunn's test revealed a statistically significant difference in pain intensity between 48 h and 1 month ($p = 0.049$) (Figure 11).

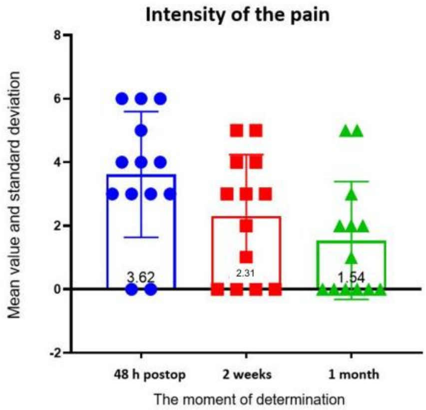

Figure 11. Pain intensity assessment.

The codes observed for the type of pain at 48 h were pressure for 9 of the patients, pulsating pain for 2 patients, throbbing pain for 1 patient, and no pain for 1 other patient. At the one-month assessment, three patients described their pain as pulsing, two as tingling, one as pressure, and one as stabbing. Attempting to assess whether pain extended to other structures, it was possible to quantify that, at 48 h, only three people reported pain extending to other areas, and at one month postoperative, only one person reported pain extending to other regions. There were no statistically significant differences between groups (Figure 12).

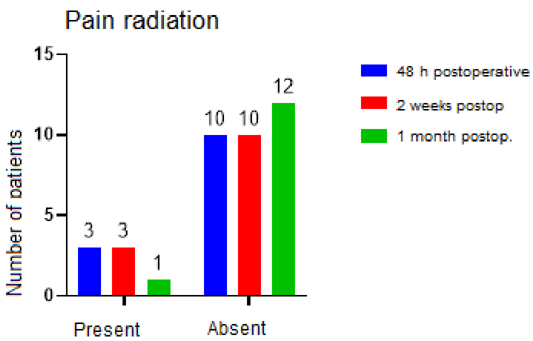

Figure 12. Pain radiation.

In the Friedman test, there was a statistically significant difference between the average values of the ranks of the groups' values in the presence of anesthesia/hypoesthesia ($p = 0.006$). However, Dunn's test for group comparison revealed no statistically significant difference between any time points (Figure 13).

We tested the correlation between edema CD and pain intensity at 48 h, 2 weeks. and 1 month using the Spearman rank correlation test. There were no significant correlations between the variables at any time point. The correlation coefficient (r) was r = 0.41 at 48 h ($p = 0.16$), r = 0.34 at 2 weeks ($p = 0.25$), and r = 0.33 at 1 month ($p = 0.25$).

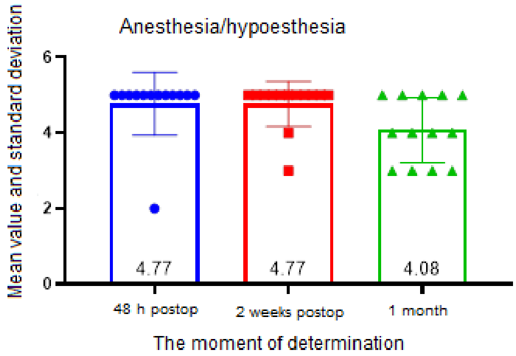

Figure 13. Anesthesia, hypoesthesia assessment.

4. Discussion

The present study determined and assessed the most common symptoms associated with bimaxillary orthognathic surgery. We also found several correlations between the initial values and the values at different time intervals, the type of dentomaxillary anomaly and the tendency of changes of the monitored parameters. All three objective parameters assessed at the facial level showed significant differences in edema between the initial preoperative values and the postoperative values at 48 h. These differences were obvious and clinically confirmed during the patient's examination by the noticeable increase in soft-tissue volume. Additionally, there were notable changes between the 48 h postoperative clinical assessment and the assessments at 2 weeks, 1 month, and 3 months, as clinically reflected by the remission of the inflammatory phenomena from one clinical control to the next. The edema was minimal at the 3-month postoperative follow-up, close to the initial values. Kwon et al. found that, at 6 and 21 months following surgery, no considerable alterations were seen, indicating that postponed soft-tissue modifications do not take place in patient populations who have undergone surgical procedures after surgically related facial swelling and edema had subsided, and the hard tissue beneath the soft tissue had healed [18].

Van der Vlis et al. assessed the volumetric analysis of postoperative edema after orthognathic surgery interventions, quantifying postoperative inflammatory changes and showed that postoperative edema decreased by 50% of the initial one after the 3rd week, and after 3 months, only 20% of the initial edema remained. The authors concluded that the rapid resolution of facial edema occurred in the first three postoperative weeks, but also its resolution continued between 6 and 12 months postoperatively [19], which we also encountered.

In the current study, the results were similar to those mentioned above. This study evaluated edema as the distance between the external canthus, gonion, tragus, cheilion, and gnathion of the eye. Postoperative edema decreased considerably from one clinical visit to the next, its value being maximal at the evaluation at 48 h postoperative and minimal at 3 months. These results are in concordance with the ones reported by Reategui et al., who revealed that the majority of facial edema disappeared within the initial month, with a considerable decline in edema occurring within 6 and 12 months later in patients following double jaw surgery [20].

Given the noticeable differences in postoperative edema severity among patients despite relatively similar treatments, it is indisputable that each patient's unique reactivity has a considerable influence on this criterion. Furthermore, contrary to expectation, there was no relationship between the patient's pain and the degree of edema. The insufficiency of the relationship between objective and subjective variables highlights the significance of each patient's unique perception of pain, which varies while receiving the same treatment and is thereby not closely associated with any objective parameter assessed.

In terms of mouth opening amplitude, in our study, statistically significant differences were found between the values measured at the various established clinical controls. The skeletal class had no effect on the amplitude of mouth opening when the time variable was considered; however, the time of determination had a significant impact on the results.

Clinically, there was a significant decrease in mouth opening amplitude at 2 weeks postoperative compared to the preoperative value, and a significant increase in mouth opening amplitude at subsequent clinical assessments. This parameter underlines the importance of physiotherapy after orthognathic surgery for temporomandibular joint rehabilitation and for overall patient comfort. Patients reported significant improvements in masticatory function beginning at two weeks after surgery and continuing for three months. All these patients underwent a period of presurgical orthodontic treatment aiming to decompensate the dental anomaly, which translates into poorer-than-before occlusion and masticatory function. The removal of the surgical splint was performed one month after surgery, which coincided with a high increase in patient comfort, oral hygiene possibilities, and masticatory function.

Bai et al. showed that short-term craniofacial function impairment in Skeletal Class III patients could be caused by orthognathic surgery, and individuals' mouth openings were less than they had been preoperatively; however, over time, orthognathic surgery lead to more stable and symmetrical orofacial functions [21]. Meneses-Santos et al. showed the beneficial effects of low-level laser therapy in maximal mouth opening following orthognathic surgery [22]. Additionally, Joachim et al. observed a reduction in mouth opening amplitude. The majority of patients' concerns following orthognathic surgery were nasal aspect and mouth openness [23]. The small amount of research with which our findings may be compared shows how little information there is in the literature evaluating opening amplitude. As a result, it might be regarded as an original feature of the current study.

Alyahya et al. reviewed the literature, and found that pre-emptive analgesics and low-level laser treatment significantly reduced pain within the first 48 h after orthognathic surgery, [24]. Opioid use was lower than what was anticipated following the orthognathic operation, however to prevent prescribing narcotics, prudence is required [25].

In this study, both the skeletal class and the time of determination influenced the width of the nose. Neither the time of determination nor the skeletal class had a significant influence on the values for the distance measured between the insertions of the nasal fins and the nostril diameter. Clinical examination, and a comparison of preoperative and postoperative photographs at 3 months revealed a widening of the interalar diameter.

Khamashta-Ledezma et al. reviewed the literature to assess nose modifications following maxillary orthognathic surgery, and demonstrated the broadening of the nares and the widening of the alar base after nearly all maxillary osteotomies. The nose width showed postoperative changes concerning the width of the nose, the exposure of the nostrils, the orientation of the columella, and the nasolabial angle [26]. van Loon et al. showed that the anterior translation of the maxilla and its clockwise inclination resulted in a significant increase in the volume of the upper lip and in the width of the alar portion [27].

The findings of this study confirm the existence of postoperative alterations at the level of the nose, particularly an increase in its width. These modifications are comparable to those observed in the previously described studies. A proper surgical strategy must be adopted if a nose widening is not necessary from a functional or aesthetical point of view. This might include strategically placed suture points after maxilla repositioning or even osteotomies at the level of the piriform aperture.

Regarding pain, in our study, the distribution of its intensity differed significantly between the moments of determination, particularly between the evaluations at 48 h and 1 month postoperative. There were no significant differences in pain radiation between the groups, and at the end of the study, at the 3-month postoperative evaluation, only 1 patient out of the 13 confirmed the presence of pain radiation. Except for one patient who described the pain as moderate, the patients at the 3-month postoperative follow-up showed minimal values on the intensity scale. Most patients described their pain as a constant pressure in the affected areas.

After the bimaxillary orthognathic procedure, Dadmehr et al. reported that the introduction of oral tizanidine was successful in lowering postoperative soreness [28]. Following orthognathic surgery, acute chronic postoperatively pain can be predicted using the pain catastrophizing scale and presurgical conditioned pain modulation [29]. In the current study, at the 48 h postoperative evaluation of the intensity rating scale, the highest value was 6, and at the 3-month follow-up, the presence of pain and intensity was minimal (below 3 on the intensity scale) except for one patient who scored the felt value as 5 on the intensity scale.

When analyzing the presence of anesthesia/hypoesthesia, there were significant differences between the average values of the ranks of the groups' values, but no significant differences between the moments of determination. The statistical difference between the Friedman test, which found a statistically significant difference between the mean values of the ranks of the group values, and the Dunn test, which found no statistically significant difference at any time of the determination, is explained by the type of nonparametric tests used and an insufficient number of patients. Clinically, no patient reported a complete resolution of the neurosensorial phenomenon at the end of the study, with anesthesia/hypoesthesia present to varying degrees in each patient. Degala et al. showed that, following orthognathic surgery, the occurrence of a neurosensory impairment of the lower lip and chin was substantial, this being correlated with the operative expertise and intraoperative nerve contact, nevertheless, and the frequency of sensory return increased during the course of the follow-up period [30].

Kim et al. assessed the natural recovery of neurological damage after orthognathic surgery on the basis of subjective neurological assessment, and showed that sensory changes occurred in proportions of 55.7% at the chin level and 27.3% at the lip level. The altered neurosensorial sensation that may develop after orthognathic surgery is an unavoidable complication, but, with time, this may resolve spontaneously. In patients who also underwent a simultaneous genioplasty, the incidence of altered sensation was high, but not significantly associated with the patient's age or with performing simultaneous maxillary surgery [31].

Yamamoto et al. evaluated tactile restoration following sagittal split ramus osteotomy, and explored the association between the degree of neurosensory disturbance and mandible migration length. They found that the occurrence of a neurosensory disruption in regards to tactile sensation may be higher in the category with more mandible advancement immediately postoperative [32].

Schlund et al. described a customized mandibular bilateral sagittal split osteotomy that protects the mandible lower margin, which causes a neurosensory disruption of the inferior alveolar nerve, which reduces the likelihood of postoperative hypoesthesia [33].

Hanfesh et al. showed that three months was a sufficient healing duration to fully re-establish neurological feeling after bilateral sagittal split osteotomy [34].

Thiem et al. observed that long-term difficulties after orthognathic surgery arose when they assessed intraoperative and early postoperative consequences, delayed outcomes, and patients' average contentment, with hypoesthesia of the lower lip being an encountered side effect [35]. However, Ahmad et al. described that following mandible orthognathic surgery, individuals who experienced lower lip neuropathy showed no negative effects on their comfort or quality of life [36].

As far as we are aware, no other investigations have simultaneously followed all the research parameters that were assessed in this research. Even if a similar study has been performed, the findings from our study are still highly significant and important because every surgical team has its own treatment regimen and surgical approach, and diverse populations respond differently to the same surgical procedure.

The current study was carried out in a clinic that treats a sizable number of orthognathic patients annually. Consequently, the team has a richness of experience. The parameters that were assessed throughout this pilot study and their values may be used to compare the recovery of patients treated using this protocol with those treated using other protocols, allowing for the authors and readers from other centers to modify their surgical approaches for better outcomes, particularly in terms of patient comfort.

4.1. Limitations and Strengths

The small sample, brief follow-up period, and reliance on the examiner's objectivity for the accurate measurements of the monitored parameters were the study's limitations.

4.2. Implications for Future Research

Given the extensive tissue manipulation involved in these surgical procedures, our research indicates that the recovery time following surgical interventions to treat dental–maxillary anomalies should receive special attention. This is because the recovery process is complicated and prolonged and incorporates a number of the patients' objective and subjective signs. The healing process must be monitored and evaluated to promote proper and harmonious healing, the remission of inflammatory, nervous, and painful phenomena, and the avoidance of further complications. The recovery time directly affects the patient's quality of life. To increase the power of this clinical trial, it would be necessary to enroll a larger number of patients in the study, and the monitored parameters need to be followed for a longer period.

5. Conclusions

The complexity and extent of orthognathic surgery requires an increased awareness of patients regarding everything that this type of surgery entails, from the aesthetic, functional, and social implications to the extent of the treatment and postoperative care. The recovery period after orthognathic surgery can last up to six months. During the recovery period, the most frequently associated objective and subjective signs are edema, hematoma, mouth opening limitations, pain, anesthesia/hypoesthesia, with edema being maximal at 48–72 h postoperatively. At the three-month postoperative follow-up, the patients showed minimal values of pain on the intensity scale, with the most common type of pain being the feeling of continuous pressure. The resolution of the neurosensorial phenomenon was incomplete at three months after surgery, and present in all patients in different degrees. After bimaxillary orthognathic surgery, soft-tissue changes occurred with a direct influence on facial aesthetics. These findings provide valuable insight into the field, helping practitioners in better developing their intra- and postoperative strategies to obtain the best results and minimize patients' discomfort.

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References

1. Roslan, A.A.; Rahman, N.A.; Alam, M.K. Dental Anomalies and Their Treatment Modalities/Planning in Orthodontic Patients. *J. Orthod. Sci.* **2018**, *7*, 16. [CrossRef] [PubMed]
2. Wiechens, B.; Quast, A.; Klenke, D.; Brockmeyer, P.; Schliephake, H.; Meyer-Marcotty, P. Evaluation of Occlusal Function during Orthognathic Therapy: A Prospective Clinical Trial Using a Digital Registration Method. *J. Orofac. Orthop. Fortschr. Kieferorthopädie*, 2022; *epub ahead of print*. [CrossRef]
3. Arnett, G.W.; D'Agostino, A.; Grendene, E.; McLaughlin, R.P.; Trevisiol, L. Combined Orthodontic and Surgical Open Bite Correction: Principles for Success. Part 2. *Angle Orthod.* **2022**, *92*, 431–445. [CrossRef] [PubMed]
4. Daluz, A.D.J.; da Silva, T.V.S.; Tôrres, B.O.; Costa, D.F.N.; Santos, L.A.D.M. Long-Term Airway Evolution after Orthognathic Surgery: Systematic Review. *J. Stomatol. Oral Maxillofac. Surg.* **2022**, *123*, 191–198. [CrossRef]
5. Applied Facial Anatomy—ClinicalKey. Available online: https://www.clinicalkey.com/#!/content/book/3-s2.0-B9780323358767000029?scrollTo=%23hl0000165 (accessed on 2 October 2022).
6. Moorhead, A.; Serra, M. *Le Fort Osteotomy*; StatPearls Publishing: Treasure Island, FL, USA, 2022.
7. Monson, L. Bilateral Sagittal Split Osteotomy. *Semin. Plast. Surg.* **2013**, *27*, 145–148. [CrossRef]
8. Lu, Y.; Zhang, W.; Zhao, B.; Liu, Y. Vertical Control of a Severe Hyperdivergent Skeletal Class II Malocclusion with Steep Posterior Occlusal Plane in a Camouflage Case. *Medicina* **2022**, *58*, 1217. [CrossRef] [PubMed]
9. Hamdy Mahmoud, M.; Ismail Elfaramawi, T. Maxillary Stability in Patients with Skeletal Class III Malocclusion Treated by Bimaxillary Orthognathic Surgery: Comparison of Mandible-First and Maxilla-First Approaches in a Randomised Controlled Study. *Br. J. Oral Maxillofac. Surg.* **2022**, *60*, 761–766. [CrossRef]
10. Woods, M.G. An Assessment of Surgical and 10-Year Follow-up Vertical Changes after Contemporary Class II and III Orthognathic Surgery. *Am. J. Orthod. Dentofac. Orthop.* **2022**, *161*, e380–e389. [CrossRef]
11. Altman, J.I.; Oeltjen, J.C. Nasal Deformities Associated with Orthognathic Surgery: Analysis, Prevention, and Correction. *J. Craniofac. Surg.* **2007**, *18*, 734–739. [CrossRef]
12. Barbosa, L.M.; de Luna Gomes, J.M.; Laureano Filho, J.R.; do Egito Vasconcelos, B.C.; Dantas Moraes, S.L.; Pellizzer, E.P. Does the Use of Low-Level Light Therapy Postoperatively Reduce Pain, Oedema, and Neurosensory Disorders Following Orthognathic Surgery? A Systematic Review. *Int. J. Oral Maxillofac. Surg.* **2022**, *51*, 355–365. [CrossRef]
13. De Lima, V.N.; Lemos, C.A.A.; Faverani, L.P.; Santiago Júnior, J.F.; Pellizzer, E.P. Effectiveness of Corticoid Administration in Orthognathic Surgery for Edema and Neurosensorial Disturbance: A Systematic Literature Review. *J. Oral Maxillofac. Surg.* **2017**, *75*, 1528.e1–1528.e8. [CrossRef]
14. Glass, G.E.; Waterhouse, N.; Shakib, K. Hilotherapy for the Management of Perioperative Pain and Swelling in Facial Surgery: A Systematic Review and Meta-Analysis. *Br. J. Oral Maxillofac. Surg.* **2016**, *54*, 851–856. [CrossRef] [PubMed]
15. Domínguez Camacho, A.; Velásquez, S.A.; Benjumea Marulanda, N.J.; Moreno, M. Photobiomodulation as Oedema Adjuvant in Post-Orthognathic Surgery Patients: A Randomized Clinical Trial. *Int. Orthod.* **2020**, *18*, 69–78. [CrossRef] [PubMed]
16. Sirintawat, N.; Sawang, K.; Chaiyasamut, T.; Wongsirichat, N. Pain Measurement in Oral and Maxillofacial Surgery. *J. Dent. Anesth. Pain Med.* **2017**, *17*, 253. [CrossRef] [PubMed]
17. Agbaje, J.; Luyten, J.; Politis, C. Pain Complaints in Patients Undergoing Orthognathic Surgery. *Pain Res. Manag.* **2018**, *2018*, 4235025. [CrossRef] [PubMed]
18. Kwon, J.-J.; Kang, Y.-H.; Hwang, D.-S. Delayed Soft Tissue Changes after Clockwise Rotation of the Maxillo-Mandibular Complex. *J. Craniofac. Surg.* **2022**, *33*, 2041–2044. [CrossRef]
19. van der Vlis, M.; Dentino, K.M.; Vervloet, B.; Padwa, B.L. Postoperative Swelling After Orthognathic Surgery: A Prospective Volumetric Analysis. *J. Oral Maxillofac. Surg.* **2014**, *72*, 2241–2247. [CrossRef] [PubMed]
20. Reategui, A.; Phillips, S.; Dinis, J.; Junn, A.; Parsaei, Y.; Yang, J.; Lopez, J.; Steinbacher, D.M. Postoperative Edema Resolution Post-Orthognathic Triple Jaw Surgery: A Three-Dimensional Volumetric Analysis. *J. Craniofac. Surg.* **2022**, *33*, 512–516. [CrossRef]
21. Bai, Y.; Tang, Y.; Ren, M.; Wang, M.; Zhao, W.; Zeng, T.; Liu, F.; Zhu, S. Orofacial Myofunctional Changes in Skeletal Class III Patients after Bimaxillary Orthognathic Surgery. *J. Plast. Reconstr. Aesthet. Surg.* **2022**, *75*, 3526–3533. [CrossRef]
22. Meneses-Santos, D.; Costa, M.D.M.A.; Inocêncio, G.S.G.; Almeida, A.C.; Vieira, W.A.; Lima, I.F.P.; Paranhos, L.R. Effects of Low-Level Laser Therapy on Reducing Pain, Edema, and Trismus after Orthognathic Surgery: A Systematic Review. *Lasers Med. Sci.* **2022**, *37*, 1471–1485. [CrossRef]
23. Joachim, M.V.; Richter, D.E.; Mohana, A.; Labeeb, M.; Abdelraziq, M.; Abu El-Naaj, I. Quality of Life After Class III Repair Orthognathic Surgery: Five-Year Retrospective Study. *J. Craniofac. Surg.* **2021**, *32*, 2588–2591. [CrossRef]

24. Alyahya, A.; Aldubayan, A.; Swennen, G.R.J.; Al-Moraissi, E. Effectiveness of Different Protocols to Reduce Postoperative Pain Following Orthognathic Surgery: A Systematic Review and Meta-Analysis. *Br. J. Oral Maxillofac. Surg.* **2022**, *60*, e1–e10. [CrossRef] [PubMed]
25. Bousquet, B.; Green, M.A.; Caillouette, C.N.; Simon, J.; Padwa, B.L.; Resnick, C.M. How Much Opioid Medication Do Patients Need After Orthognathic Surgery? *J. Oral Maxillofac. Surg.* **2022**, *80*, 1174–1182. [CrossRef] [PubMed]
26. Khamashta-Ledezma, L.; Naini, F.B.; Manisalı, M. Review of Nasal Changes with Maxillary Orthognathic Surgery. *J. Istanb. Univ. Fac. Dent.* **2017**, *51*, S52–S61. [CrossRef]
27. Van Loon, B.; van Heerbeek, N.; Bierenbroodspot, F.; Verhamme, L.; Xi, T.; de Koning, M.J.J.; Ingels, K.J.A.O.; Bergé, S.J.; Maal, T.J.J. Three-Dimensional Changes in Nose and Upper Lip Volume after Orthognathic Surgery. *Int. J. Oral Maxillofac. Surg.* **2015**, *44*, 83–89. [CrossRef] [PubMed]
28. Dadmehr, S.; Shooshtari, Z.; Alipour, M.; Eshghpour, M.; Shaban, B.; Vaezi, T.; Samieirad, S. Is Preemptive Oral Tizanidine Effective on Postoperative Pain Intensity after Bimaxillary Orthognathic Surgery? A Triple-Blind Randomized Clinical Trial. *World J. Plast. Surg.* **2022**, *11*, 37–45. [CrossRef]
29. Takashima, K.; Oono, Y.; Takagi, S.; Wang, K.; Arendt-Nielsen, L.; Kohase, H. Acute Postoperative Pain after Orthognathic Surgery Can Be Predicted by the Preoperative Evaluation of Conditioned Pain Modulation and Pain Catastrophizing. *Pain Rep.* **2022**, *7*, e989. [CrossRef]
30. Degala, S.; Shetty, S.K.; Bhanumathi, M. Evaluation of Neurosensory Disturbance Following Orthognathic Surgery: A Prospective Study. *J. Maxillofac. Oral Surg.* **2015**, *14*, 24–31. [CrossRef]
31. Kim, Y.-K.; Kim, S.-G.; Kim, J.-H. Altered Sensation After Orthognathic Surgery. *J. Oral Maxillofac. Surg.* **2011**, *69*, 893–898. [CrossRef]
32. Yamamoto, T.; Fujii-Abe, K.; Fukayama, H.; Kawahara, H. Hypoesthesia Associated with Mandibular Movement after Sagittal Split Ramus Osteotomy. *Oral Maxillofac. Surg.* **2017**, *21*, 313–319. [CrossRef]
33. Schlund, M.; Grall, P.; Ferri, J.; Nicot, R. Effect of Modified Bilateral Sagittal Split Osteotomy on Inferior Alveolar Nerve Neurosensory Disturbance. *Br. J. Oral Maxillofac. Surg.* **2022**, *60*, 1086–1091. [CrossRef]
34. Hanfesh, A.; Salma, R.G.; Al Mutairi, K.; AlShiha, S.K.; Al Otaibi, S. The Neurosensory Deficit of Inferior Alveolar Nerve Following Bilateral Sagittal Split Osteotomy: A Prospective Study. *Oral Maxillofac. Surg.* **2021**, *26*, 401–415. [CrossRef] [PubMed]
35. Thiem, D.G.E.; Schneider, D.; Hammel, M.; Saka, B.; Frerich, B.; Al-Nawas, B.; Kämmerer, P.W. Complications or Rather Side Effects? Quantification of Patient Satisfaction and Complications after Orthognathic Surgery—A Retrospective, Cross-Sectional Long-Term Analysis. *Clin. Oral Investig.* **2021**, *25*, 3315–3327. [CrossRef] [PubMed]
36. Ahmad, Z.; Breeze, J.; Williams, R. Numbness of the Lower Lip Does Not Adversely Affect Quality of Life or Patients' Satisfaction after Mandibular Orthognathic Surgery. *Br. J. Oral Maxillofac. Surg.* **2018**, *56*, 421–424. [CrossRef] [PubMed]

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Review

Point-of-Care Virtual Surgical Planning and 3D Printing in Oral and Cranio-Maxillofacial Surgery: A Narrative Review

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Abstract: This paper provides an overview on the use of virtual surgical planning (VSP) and point-of-care 3D printing (POC 3DP) in oral and cranio-maxillofacial (CMF) surgery based on a literature review. The authors searched PubMed, Web of Science, and Embase to find papers published between January 2015 and February 2022 in English, which describe human applications of POC 3DP in CMF surgery, resulting in 63 articles being included. The main review findings were as follows: most used clinical applications were anatomical models and cutting guides; production took place in-house or as "in-house—outsourced" workflows; the surgeon alone was involved in POC 3DP in 36 papers; the use of free versus paid planning software was balanced (50.72% vs. 49.27%); average planning time was 4.44 h; overall operating time decreased and outcomes were favorable, though evidence-based studies were limited; and finally, the heterogenous cost reports made a comprehensive financial analysis difficult. Overall, the development of in-house 3D printed devices supports CMF surgery, and encouraging results indicate that the technology has matured considerably.

Keywords: 3D printing; point-of-care; virtual surgical planning; additive manufacturing; maxillofacial surgery; cranial surgery; in-house 3D printing; hospital-based printing

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1. Introduction

The complex anatomy and functionality of the craniofacial structures, together with the pursuit of the best clinical outcome, demand state-of-the-art, patient-specific treatments. Though three-dimensional printing (3DP) has been around since 1986, the technology became highly visible once medical researchers began exploring 3DP and its role in personalized medicine [1]. Companies, research facilities, hospital-based 3DP laboratories, or the associations of the previously mentioned entities produce patient-specific surgical devices for oral and cranio-maxillofacial (CMF) surgery [2–4]. Externalized virtual surgical planning (VSP) and 3DP can be considered expensive, with a significant financial impact on the healthcare system [5]. They are also time-consuming, causing problematic delays for urgent cases [6]. A universally accepted definition of point-of-care 3DP (POC 3DP) is difficult to provide; however, literature defines it as the just-in-time creation of 3D printed anatomic models, surgical instruments, or other medical devices based on the patient's imaging data, either at the place of patient care or in a facility owned by the health care provider [7]. Special efforts have been made so that surgeons can directly manufacture patient-specific devices at the POC in order to cope with urgent medical demands and reduce the economic impact that these technologies have on the healthcare system [8,9].

In medicine, analytic investigations on 3DP are conducted on a wide spectrum of surgical specialties—orthopedics, spinal surgery, maxillofacial surgery, neurosurgery, and cardiac surgery—which are, generally, analyzed together [10]. Despite CMF surgery's influential role in the development and use of additive technologies, few studies have focused strictly on the analysis of in-house VSP and 3D printing of this specialty [2,10–16].

This paper aims at providing an overview on the usage of virtual surgical planning and 3D printing at the point-of-care in CMF surgery based on a review of articles from three major literature databases. We focused our investigation on the following parameters: clinical applications, infrastructure, the time necessary for planning/printing, operating time, cost, and outcomes.

2. Materials and Methods

2.1. Information Sources

We structured a search in the electronic databases of PubMed, Web of Science, and Embase on articles published between January 2015 and February 2022, and performed the final electronic search on all databases in March 2022.

2.2. Search Strategy

The following terms were searched: "3D printing", "three-dimensional printing", "additive manufacturing", "maxillofacial surgery", "cranial surgery", "in-house", and "hospital printed", in combination with the Boolean operator "AND". To find all possible combinations of papers, we performed twelve separate searches. For the complete search strategy for PubMed database, see Supplementary Table S1. A manual search of the identified articles was also conducted.

2.3. Eligibility Criteria

The selection criteria included publications that described the human application of virtual surgical planning and 3D printing, were released between January 2015 and February 2022, were available in full text, and were written in the English language. We excluded papers that had no hospital-based potential, studies on dental applications and bioprinting, reviews, and duplicates. Manual title and abstract screening were done immediately after electronic filters were applied, thereby eliminating duplicates. Any further missed duplicates were removed when papers were introduced in Mendeley (Mendeley Software, London, UK), a bibliographic software used to acquire and arrange all references. Furthermore, we retained titles containing "low-cost", "entry-level", "in-office", "office-based", "surgeon driven", "self-made", and "open source" so as to not overlook potential uses in the hospital environment. The selected eligible papers went through a full-text overview, and we analyzed the ones selected in detail using an Excel evidence table to report relevant study characteristics.

2.4. Data Collection Process

Data were extracted using a standardized form, which included the following information: (1) authors' names and publication year, (2) clinical application, (3) accommodation of infrastructure, (4) human resources involved, (5) software, (6) hardware and materials, (7) planning time, (8) production (3DP time), (9) operating room time, (10) cost, and (11) outcome (Supplementary Table S2).

3. Results

3.1. Selection of Sources of Evidence

The database search, using the keywords previously mentioned without any filters, resulted in 4361 papers. After applying electronic database filters (inclusion criteria), we retained 2651 papers. The manual screening of titles and abstracts resulted in the exclusion of 2577 articles, leading to 74 eligible articles. Eleven papers were excluded from the analysis due to reduced or no relevant data referring to POC 3DP. The included studies were case reports, case series, and technical notes with a retrospective review of relevant data. No authors clearly described a prospective study design in the selected papers. Finally, the review included a total of 63 articles. The search strategy is evidenced in Figure 1.

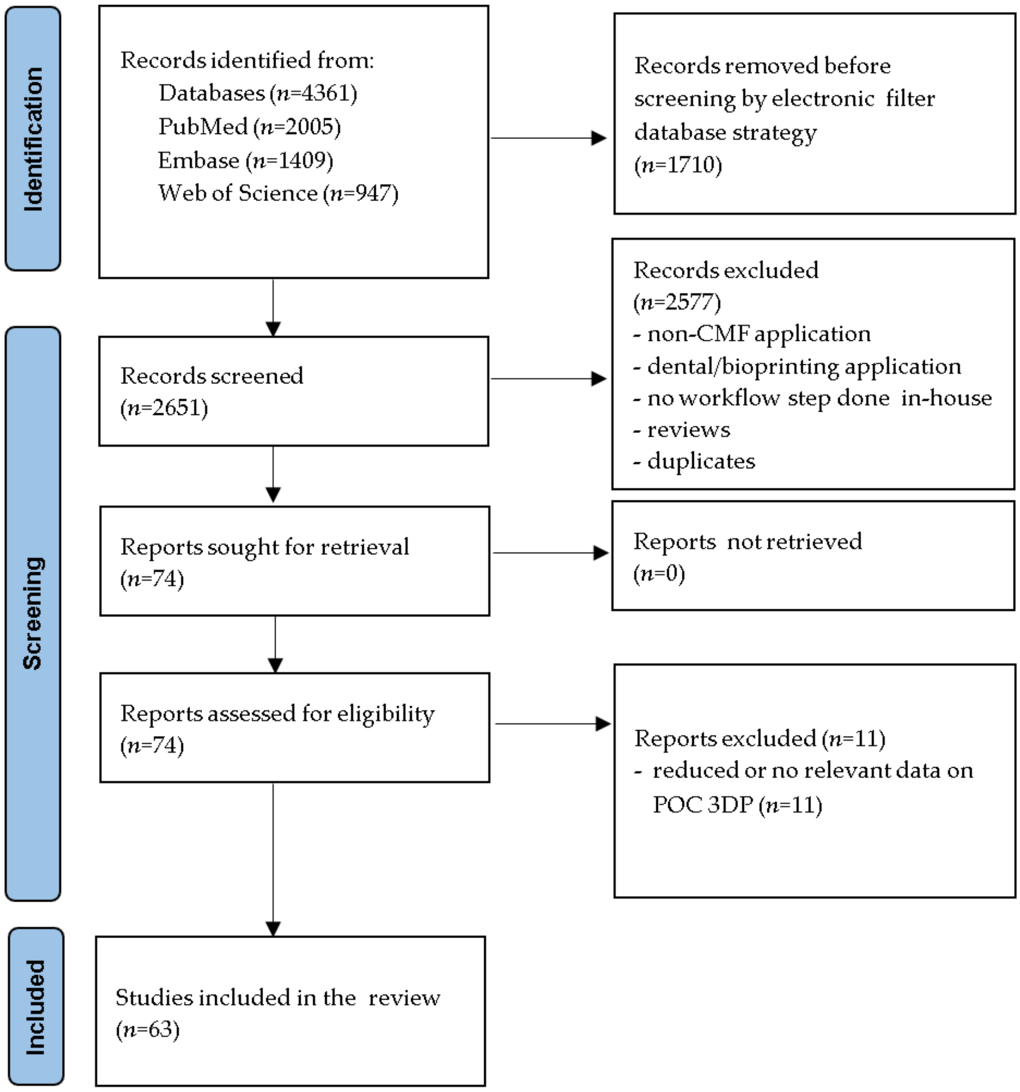

Figure 1. Schematic representation of the strategy for the selection of final articles.

3.2. Clinical Applications

Anatomical models were the most common patient-specific devices planned and produced at the point-of-care. These were used for preoperative planning in cases of complex anatomy, such as arterio-venous malformations, pre-bending osteosynthesis gear (metal plates, meshes), or pre-forming grafts [6,9,17–36]. The utility of 3D models extended to patient information and consent, the education of medical staff, quality control, or forensics [37,38].

Models were followed by cutting/positioning guides that address mandibular and maxillary reconstructions with the help of vascularized fibula, iliac crest, or scapular grafts [3,4,19,39–56].

Cranioplasty plates used for cranial reconstructions were commonly produced in the hospital of treatment either by directly printing molds or by printing the cranial plate template based on which a silicon mold is obtained. Polymethylmethacrylate (PMMA) was the material of choice used for the fabrication of cranial implants through this procedure [57–62]. Molds were also used for stenting meshes used for orbital reconstructions [53,63–65].

One way to address the in-house production of patient-specific medical devices was reported by Yang et al. (2020), who designed a prototype of the patient-specific osteosynthesis plate that was sent to engineers who optimized the final product [4]. Implantable devices with a full in-house workflow are not common but efforts are being made towards their development. Philipp Honigmann et al. (2018) reported the experimental production of implantable devices (osteosynthesis plate, cranioplasty plate, midface-zygomatic bone) with the help of fused filament fabrication technology (FFF)—all with potential in-house production [66]. A percentual distribution of the in-house clinical applications mentioned across all articles can be consulted in Figure 2.

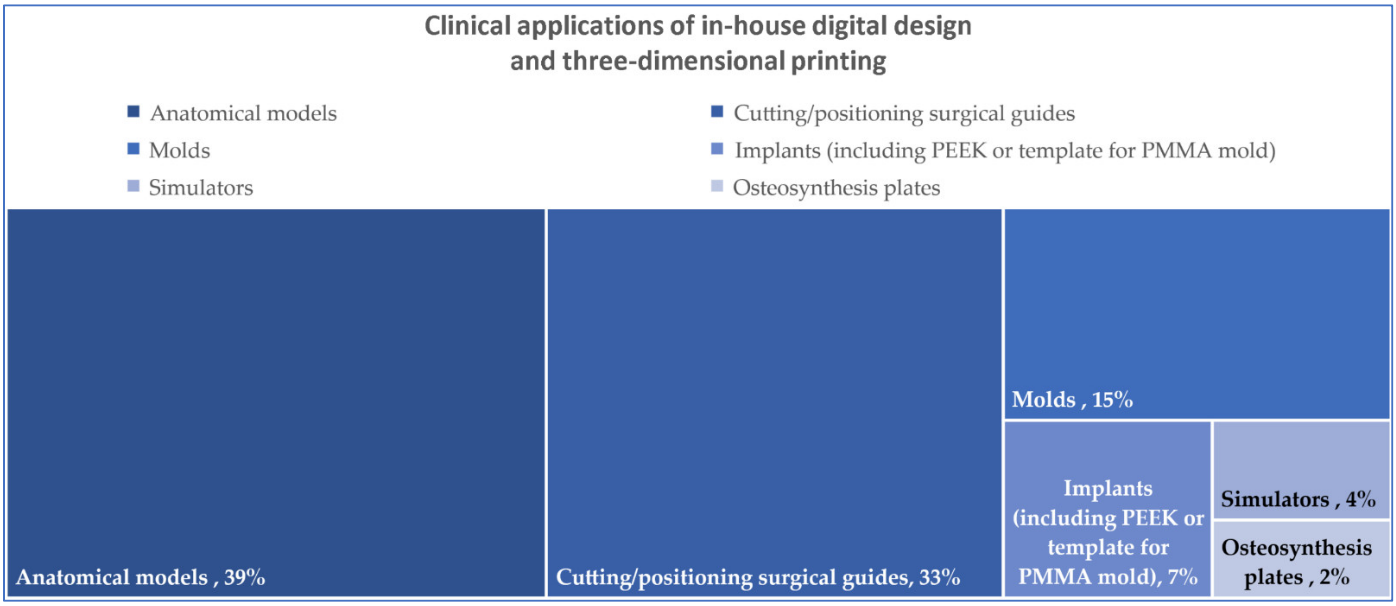

Figure 2. In-house 3DP of clinical applications across the studies and their percentual distribution.

3.3. *Infrastructure*

3.3.1. Housing of Virtual Planning and 3D Printing Infrastructure

The analysis of the data showed inhomogeneous reporting regarding the housing of planning and 3D printing infrastructure. Some authors mentioned that the process of production took place in the treatment facility (hospital 3DP laboratories, radiology-based 3D printing facilities, information technology departments) or straightforward as "in-house" [4,6,9,17,18,20,23,25,27,29–38,40,43–56,59–62,64,65,67–71]. Some authors did not clearly state the accommodation of infrastructure but rather evoked the in-house concept [19,21,22,39,41,57,72–74]. Others reported planning carried out in the institution of treatment, while printing was outsourced [4,26,28,42,63]. In one case, virtual surgical planning was undertaken with a commercial provider via videoconferencing, as is usual for other elective CMF cases. However, instead of being printed by the VSP provider, the resulting stereolithography file (STL) was downloaded and printed in-house [36]. Finally, papers also report work carried out in the laboratory/for research purposes, validating the experimental work for potential in-house use [24,58,66,75].

3.3.2. Software

The scope of the present section is to give an overview on the software solutions used for the POC development of medical devices in CMF surgery. We use brand names that are/can be protected but are not marked with ®. Software solutions, according to the purpose of use, can be classified as segmentation software: e.g., MIMICS Innovation Suite (Materialise Inc., Leuven, Belgium), 3D Slicer [76], and In Vesalius (CTI Renato Archer, Campinas, Brazil); planning software: e.g., 3-matic (Materialise Inc., Leuven, Belgium), Blender (Blender Foundation; Amsterdam, Netherlands), and MeshMixer (Autodesk Inc, California, USA); or software solutions that can do both, such as the powerful CMF ProPlan (Materialise Inc., Leuven, Belgium).

Some software solutions are easily accessible because they are free (free license or open-source), which makes them useful for point-of-care facilities with a small budget, while others are available only with a paid license. In this review, we will not address the issues surrounding the use of software with or without medical certification, as it is a regulatory issue. Figure 3 depicts an overview of the software solutions utilized, including the type of software (open source/free, paid license), the number of quotes for each software, and the percentual distribution of free and paid software use.

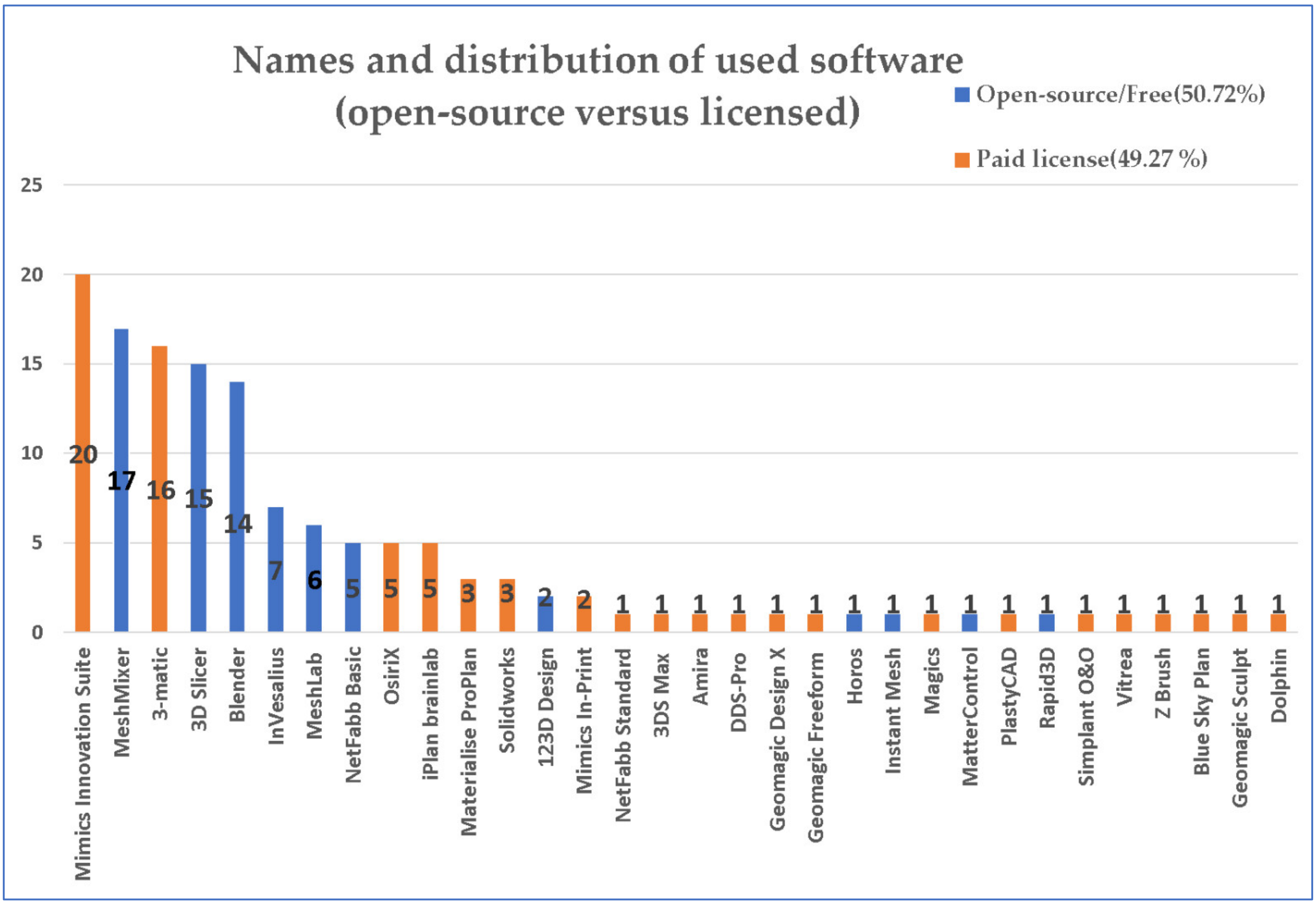

Figure 3. Graphical representation of the used software, number of mentions across the reviewed articles, and percentual usage distribution of free versus paid software.

While 21 paid license software and only 11 free software were used, a closer look at the number of times each software was mentioned indicates a balanced ratio between free and paid versions (50.72% free vs. 49.27% paid). For three software (Ayra, Ikeria SARL, Sevilla, Spain; Volume Extractor 3.0, i-Plants systems, Iwate, Japan; and

POLYGONALmeister Ver. 4; UEL Corp., Tokyo, Japan) data on license type were undisclosed/unavailable online [31,40].

3.3.3. The 3D Printers and Materials Used at Point-of-Care

Printers that use Fused Deposition Modeling (FDM)/Fused Filament Fabrication (FFF) technology are most used at the point-of-care, likely due to their low price tag. For models, FDM/FFF techniques use PLA or ABS, while PEEK becomes a valuable option for implantable devices [3,9,17,20–24,26,28–32,35–38,40,44–51,53,57–59,63,64,66,71–75]. Stereolithography, Polyjet/MultiJet/MaterialJet, and Digital light processing use resins/photopolymers [3,6,18,19,24,33–35,37,39–41,51,52,54–56,59–62,65,67–70]. ColorJet(CJP)/Binder jetting (BJ) printing involves two major components—a core (powder) and a liquid binder [25,55]. These technologies are recognized for their high accuracy, biocompatibility, and sterilization tolerance. Selective laser sintering/melting (SLS/SLM) use powders (polyamide 12 or titanium) to create the final products [4,28,42].

Figure 4 provides information on 3D printing techniques and frequency of use. Some printing techniques are only mentioned as being part of an in-house process (design carried out in-house with outsourced printing), as they are not yet widely accessible for hospital use (marked with ″**″) [4,28].

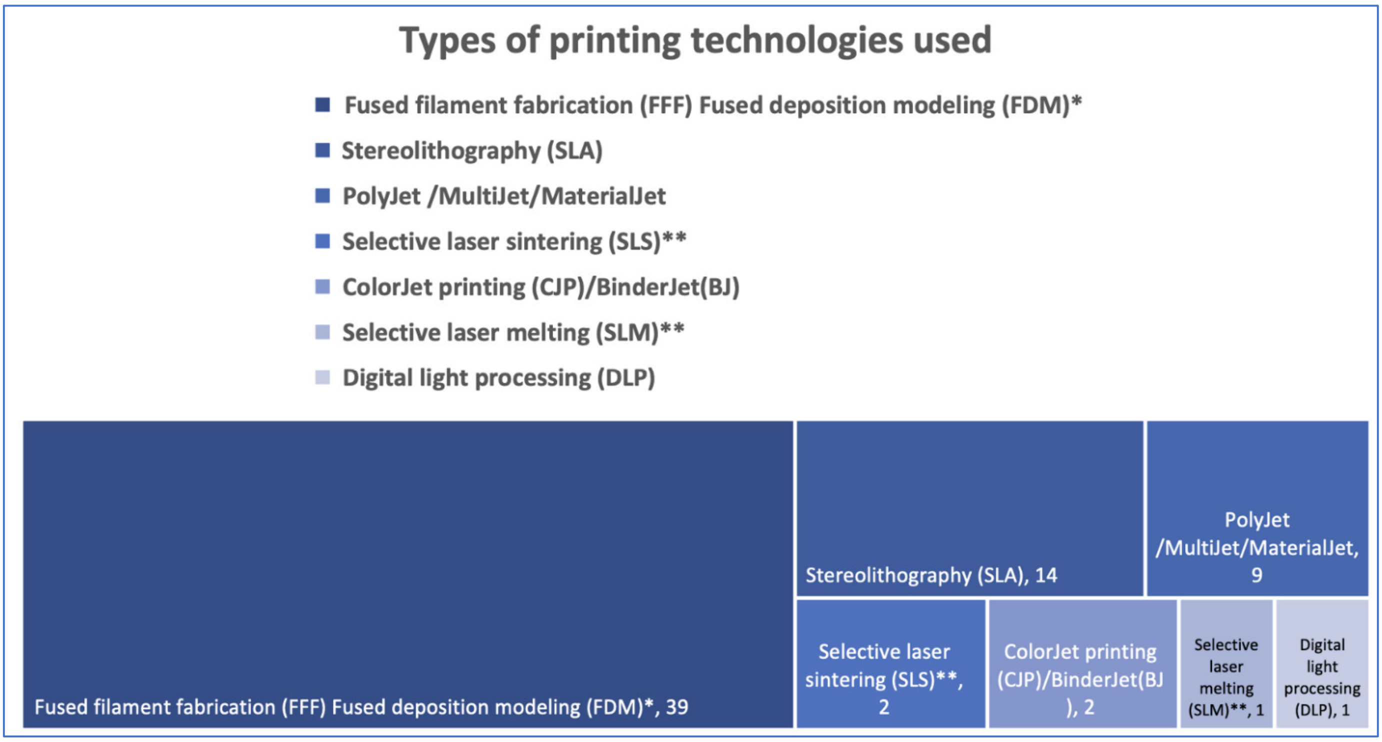

Figure 4. Printing technologies used across the studies (″*″—the same technology; ″**″—described as being part of an in-house process but not yet widely accessible for hospital use).

3.4. Human Resources Involvement

The human resources involved in the process of 3D printing at the point-of-care in a CMF surgery department refer to: the surgeon alone (thirty-six papers), surgeon and radiologist (five papers), surgeon and information technology specialist/bioengineer (six papers), radiologist and technician (two papers), radiologist alone (one paper), and technician alone (one paper). The rest of the papers had no reference to the human resources involved. No reference was encountered concerning who performs administrative tasks, such as the acquisitions of computers, software, consumable materials, or maintenance. Clear details regarding who carries out the printing and post-processing work are also overlooked in the reviewed articles.

3.5. Time Management for in-House 3DP Products

3.5.1. Planning Time

Planning time was mentioned in 31 of the 63 evaluated papers. Reports were made in minutes, hours, or days, either as intervals or as an average. Where time intervals were given, the average was calculated. All reports were transformed into hours. The average planning time reported in the 31 papers was 4.44 h, covering segmentation and actual virtual planning. One of the shortest reported planning times was 0.25 h, Evins et al. (2018) needed an average of 14.6 min of virtual planning (from CT data import to printing initiation) for FDM-produced craniofacial prosthesis and molds [58]. The longest average planning time reported was 30 h, due to the production of customized surgical mandibular/fibula osteotomy guides [40]. The hours of planning can span over a few days, as oftentimes surgeons perform this work in their spare time. The rest of the papers did not mention the time spent on planning or were limited to mentioning that the fabrication process took only a few hours, without clear numbers to support their report [28,44]. Other authors focused on reporting the entire production time without making separate time reports on virtual planning, 3D printing, and post-processing [31,35,49,55,60].

Planning time depended on the complexity of the intervention or the necessary learning curve to become accustomed to the software capabilities. Zavattero et al. (2020) needed 6 months to become accustomed to the software [39,48]. Planning time was influenced by the type of software used. Professional software requires less time, while nonprofessional software planning took almost double the time, due to the learning curve and user-friendliness of professional software [24].

3.5.2. Three-Dimensional Printing Time

Actual printing times can range from a few hours to multiple days, as it depends on the printing technique, size, complexity, and number of printed parts [37]. Otherwise, the printing process is automated and does not necessarily require human supervision [26].

Because of multiple printing techniques and applications, as well as the inhomogeneous way authors reported printing time, the data were summarized based on the most common techniques and applications used at the point-of-care. Reports were made in minutes and hours, as time intervals or as averages; where time intervals were given, the average was calculated in hours.

Using FDM/FFF technique, mandibular/maxillary models and cutting guides taken altogether needed an average printing time of 7.8 h [3,9,20,21,23,29,45–49,51,53,75]. Molds/cranial plates took an average printing time of 3–4 h [57,58,72], while an orbital model claimed 24 h (considering printer booting, setting the machine, printing, removing support, and cleaning the piece) [24]. Other applications, such as in-house-made complex head models for preoperative patient education and consultation, surgical planning, and resident training took longer printing times, around 48 h [38]. To obtain a general view of the FDM printing time, Bergeron et al., reported a mean printing time of 7.9 h for clinical applications, such as anatomical models of the cranium, mandible, and orbit, with the printing phase time per model ranging from 2 h 36 min to 26 h 54 min [36].

With the help of SLA technology, authors reported printing cranial plate molds in an average printing time of 6.8 h, with times ranging from 3–5 h for the template ring, 5–8 h for the template mold in the case of the "springform" technique cranioplasty, and up to 10 h for the classical type of cranial plate mold [59,62]. A temporal bone model used as a simulator was printed in 7 h [67], orbital models and molds for orbital implant pre-bending were printed in 11.5 h [65], while mandibular and fibula cutting/positioning guides were printed in an average of 2.52 h [3,51,56].

Few of the remaining printing techniques had reports on printing time but to disclose some of them, we will mention three examples: models of arteriovenous malformations were printed in an average of 9 h (6–12 h) by PolyJet technique, an orbital floor model was printed with the help of MultiJet Printing in 18 h, and a mandibular model was printed with ColorJet Printing in 4.5 h (270 min) and used for reconstruction plate pre-bending [18,24,25].

The shortest reported printing time referred to a mandibular model that was printed using DLP technology in 1 h, with 30 min of post-processing. However, the authors mentioned that this was a prototype printer unavailable to most clinicians and with a substantial price. They suggested that printing the same part with SLA technology would take around 5 to 7 h [6]

Post-processing can be manual or semi-automatic, as it involves—depending on technique—the removal of the support material, sandblasting, light curing, washing, and sterilization. Post-processing is an important part of the production chain but few authors mentioned the necessary amount of time for this process with reports varying from 30 min to 2 h [6,20,46,51,52,67].

3.5.3. Operating Time

In the evaluated papers, the assessment of surgical time regarding procedures that involved point-of-care 3D planning/printing is heterogenic but most state time reduction. We can split the papers into three major categories.

The first and most relevant category refers to papers that reported reduced OR time, backed up by numbers and statistics based on comparisons made between the intervention group (on which the point-of-care 3D printing application was used) and the conventional group [6,18,30,31,35,42]. To exemplify, Weinstock et al. (2015) reported that the surgical time (from initial incision to closure) was 12% faster in the two cases of arterio-venous malformations that used 3D models (on average, approximately 30 min faster with 3D models; non-model cases 285 and 288 min, 3D model cases 254 and 257 min, respectively) [18]. Ganry et al. (2017), using fibula cutting guides planned in-house and printed outsourced, reported that the surgical procedure time was reduced by 1.5 h on average [42]. Marschall et al. (2019) printed reduced mandible models of trauma patients for plate pre-bending and claimed that OR treatment time was 1.5 h versus an approximate time of 2.25 h for traditional open reduction and internal fixation (ORIF) [6]. Using 3D printed anatomical models of the mirrored orbit for the pre-bending of orbital meshes, Sigron et al. (2021) calculated that the mean duration of the surgery was significantly reduced by 35.9 min in the intervention group (58.9 (SD: 20.1) min) compared to the conventional group (94.8 (SD: 33.0) min, p-value = 0.003).

A second category of papers reported actual operating room time but without any other calculations to prove operating room time economy (though in some of the papers' literature data on operating time were taken as reference for comparison) [17,21,25,34,40,41,46,47,56,57,59–62,69].

The third category of papers discussed reduced operating room time. However, the statement was not backed up by numbers and statistics from the authors' experience but rather by the literature references, personal suppositions, or expectations [19,20,22,23,26,27,29,32,39,44,48,49]. The rest of the authors did not mention/address the subject of operating room time, or the operating time did not apply to their study.

3.6. Costs

The visible published costs for the in-house approach might seem low when authors report just the price of the material used to print a medical device or when some of the costs are omitted, but most of the time the actual costs are higher when all expenses are taken into account [47]. The main costs one should address are rent for housing the infrastructure, human resource expenses (training and surgeon's time), computer, software license (acquisition and renewal), 3D printer's price, and running costs (printing material, accessories, and maintenance).

To aid readers in search of pure informative costs, we will provide the reported costs of key elements in the point-of-care production of surgical devices, neglecting the cost to house the infrastructure and price of computers as they were not reported.

Concerning human resources, costs are region specific: Goetze et al. (2017) reported personnel costs of 367 EUR for printing one cutting guide, Legocki et al. (2017) mentioned a 45 USD/hour rate for an information technology employee, while Spaas and Lenssen (2019) based their calculations on the labor cost of a junior surgeon in Belgium at around 15.24 EUR/hour [9,20,39]. Training of personnel can cost 225 USD for a 3 h session in 3D printer operation and can reach 3000 EUR for a 2-day professional training session on how to use a segmentation/3D planning software [17,51].

If one does not use a free software solution, a license price was reported to vary from 300 USD for a lifelong software license (DDS-Pro) [72] to yearly renewable licenses that vary from 699 USD (Osirix)[20] to 12,000 EUR/year (MIMICS) [24]. In another paper, the most commonly used software pack, MIMICS, had a detailed quotation that reached 21,000 USD/year for the three-module configuration (base module, performing segmentation, and 3D reconstruction, costing 5833 USD; a design module, which provides design tools to create devices, 8726 USD, an analysis module costing 6388 USD) [60].

Printer acquisition prices depend on technology, with FDM printers ranging from 600 USD to 5000 USD and above [20,21,23,28,29,36,40,45,47–49,51,57,59,73]; only two of the papers that reported prices for FDM printers also reported cost for maintenance (200 USD/year)/printer protection plan (350 USD/year) [17,24]. Stereolithography printers can be purchased at prices that range from 3500 USD to approximately 5000 USD, with all accessories included (UV light, washing machine) [3,51,59,67]. Printers over the prices of 50,000 USD, such as the 3D System ProJet 3510 or the 300,000 USD EOSINT P385 are beyond the budget of most hospitals and can be found either in research laboratories (housed within a hospital) or in outsourced facilities [24,28].

Printing materials are represented by: (1) filaments (Polylactic acid (PLA) with a cost varying from 11.90 to 60 USD/kg [20,21,24,29,51,72,73], while Acrylonitrile butadiene styrene (ABS) is reported to cost around 43 USD/kg [23]; (2) photopolymers (have multiple prices reported: 175 USD/kg, 200 USD/cartridge, 280 EUR/1L, and even 570 USD/2 kg, depending on the indication/properties [6,24,51,67]); and (3) powders (polyamide 12 or titanium), which had no reported costs [4,28,42]. We consider these prices to only be informative, as companies adapt their prices to consumers in accordance to buying power or based on individual deals.

Unfortunately, the heterogeneity of the reported data prevented an in-depth analysis with a true comprehensive cost analysis. By far, the article that most efficiently reported their cost data analysis was published by Abo Sharkh and Makhoul (2019). We consider their example a model of good practice [3].

3.7. Outcome of Point-of-Care Virtual Planning and 3D Printing

Parameters related to outcome differed from author to author, and throughout the literature, we did not find a standardized procedure for reporting outcomes. A clear, outcome-based classification of the papers was difficult to create due to the heterogenous way outcomes were reported. However, guided by the evidence-based principles, two categories could be individualized: outcomes backed up by numbers and statistics and outcomes that were not. On the side of outcomes backed up by numbers, the following parameters were highlighted among reported data: accuracy, reduction of operating room time, cost-effectiveness, and blood loss.

The accuracy of the clinical result is of utmost interest, but only 20 out of 63 papers sustained their findings with objective numbers and statistics. In-house-produced fibula and mandibular/maxillary cutting guides were reported as accurate by assessing the reproduction of the planned results in eight papers. All reconstruction procedures were considered successful, with a good match between the digitally planned and the final result of the surgery [4,9,40,42,44,45,51,56].

Concerning the orbit, accuracy evaluation focused on assessing pre- and post-surgical orbital volume, implant fit at the fracture site, and ophthalmic examinations made before surgery and post-operatively [30,32,34,35,53,64].

Chamo et al. (2020) studied in-house cranioplasty implant templates used to create molds, with results suggesting that deviations for the test groups did not exceed 1 mm, which is an acceptable accuracy for clinical routine in craniofacial reconstruction [74]. Tel et al. (2020) showed in numbers the accuracy of cranial reconstructions using cranioplasty plates obtained with the help of 3D printed molds [60]. Sharma et al. (2021) went to the next level and proved that point-of-care FFF 3D-printed PEEK cranial PSIs had high dimensional accuracy and repeatability [71].

Hatz et al. (2019) conducted a study comparing mandibular models printed with entry-level printers accessible in hospital facilities with models printed by industrial printers and found that the accuracy of in-house printed models can serve the surgical management of maxillofacial pathology [28]. Legocki et al. (2017) found similar accuracy results but on a smaller group of neonatal, pediatric, and adult-sized mandibular models [20]. Naros et al. (2018) went further, demonstrating that mandibular models used to pre-bend titanium reconstruction plates accurately reconstruct the symmetry and continuity of resected mandibles [25].

Though operating room time economy was already discussed, we would like to stress again that although multiple studies evoked a reduced surgical time, only six supported their statements with findings and numbers based on comparisons between the group on which the point-of-care 3D printing application was used and the conventional group [6,18,30,31,35,42].

Although cost-efficiency was suggested as a positive outcome by a great number of articles included in the standard analysis, only 10 papers stated cost-efficiency being backed up by numbers [3,9,17,20,28,30,39,47,60,62]. Even so, every cited group of authors has its own standard of analysis (we focused here on papers in which a form of comparison was carried out between investment/expenses and the costs cited in the literature or provided by industry). Therefore, making an in-depth evaluation of cost-efficiency as an outcome at the international level has not been feasible.

Narita et al. (2020) assessed blood loss when using 3D models in orthognathic surgery, reporting a mean amount of bleeding (grams) of 252.2 ± 97.7 g (with 3D models) vs. 331.2 ± 85.9 (without 3D models) [31].

While the rest of the papers reported a good outcome; unfortunately, they were not backed up by numbers or statistics. Besides the parameters priorly mentioned, a good outcome also concerned parameters such as safety of use, efficiency, precision, facial symmetry, or low rate of perioperative complications.

4. Discussion

In CMF surgery, many organizations (businesses, research centers, hospital 3DP laboratories) work together to accomplish virtual surgical planning and the manufacturing of patient-specific surgical equipment, typically following a process such as the one shown in Figure 5.

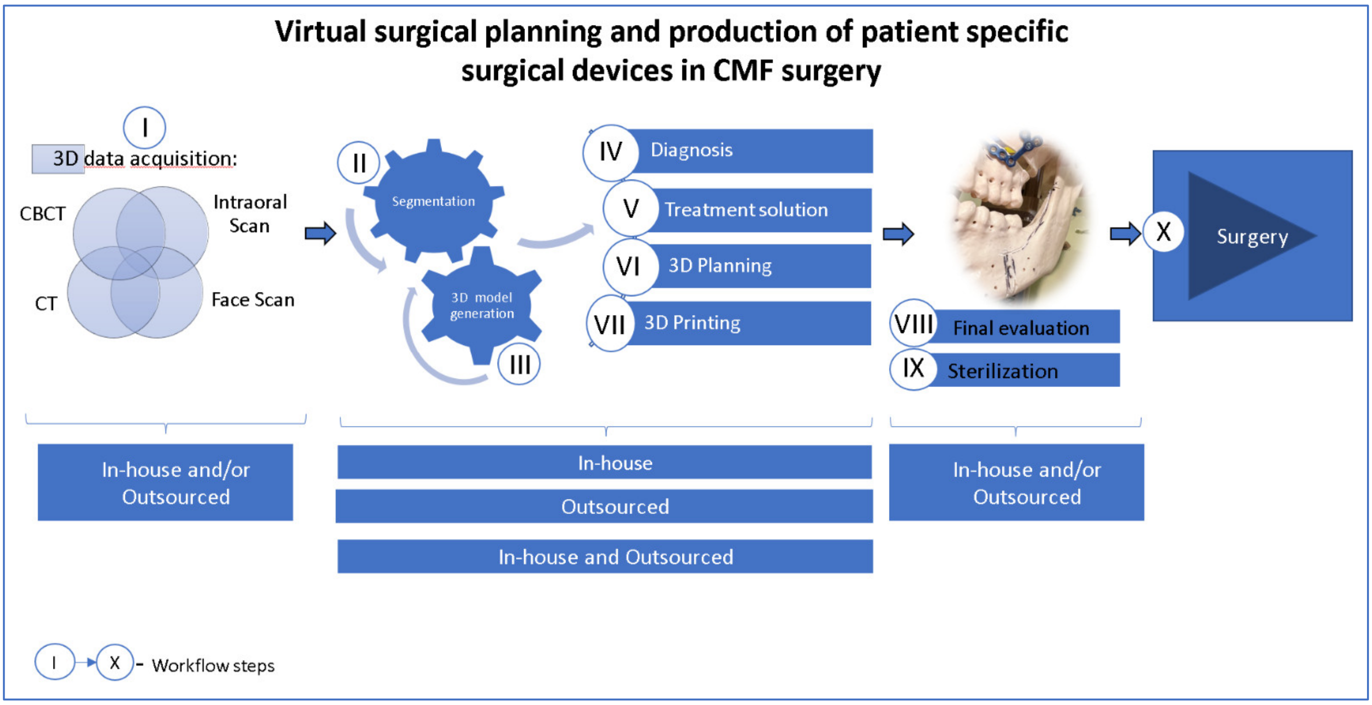

Figure 5. Manufacturing workflow for patient-specific surgical devices in CMF surgery.

Most analytic studies/reviews address virtual surgical planning and additive manufacturing focused on the application of 3D printing in a variety of medical fields. Concerning CMF surgery, in most of the papers, in-house manufacturing was investigated alongside outsourced 3D printing without a clear distinction. Our research also includes publications on the potential in-house use of 3D printing in maxillofacial surgery. To the best of our knowledge, this is one of the few studies that focuses only on point-of-care VSP and 3D printing in CMF surgery, addressing such a wide range of parameters over a long period of time (7 years). Additionally, this data collection is of great assistance when deciding to deploy a virtual surgical planning and 3D printing facility at the point-of-care.

Anatomical models are the most often produced in-house patient specific devices (39% of in-house CMF clinical applications) followed closely by cutting guides (32% of in-house CMF clinical applications), while molded cranial plates are the most often used in-house produced implanted devices. The direct printing of implantable devices requires costly equipment and particular circumstances that are difficult to obtain in a hospital environment; however, efforts have been made to develop techniques and printers that can solve this problem [66,71].

Planning surgery involves the use of dedicated software. Most software solutions come with paid licenses alongside the benefit of a user-friendly interface, easy learning curve, customer support, and medical certification. Due to their availability and cost-efficiency, many researchers/clinicians have turned toward free/open-source software solutions. In the European Union, virtual surgical planning software is defined as a medical device, and the use of a medically unauthorized software makes the surgeon accountable for a potential software-induced medical error. Nonetheless, the surgeon is equally accountable even if he/she uses a medically approved surgical planning software [43]. In the end, the Hippocratic principle of "primum non nocere" ("above all, do no harm") is more prevalent than ever.

Printers that use FDM/FFF technology are by far the most used at the point-of-care, most likely due to their low-price tag and because of printing affordable anatomical models comparable with professional-grade models [28]. The main drawback of these printers is that they cannot print implantable devices yet, but efforts have been made to introduce desktop printers that can utilize Polyether Ether Ketone (PEEK) capable of printing patient-specific implants directly at the point-of-care, under the supervision of the treating surgeon [66,71]. SLA printers follow FDM printers in frequency of use, being widely exploited to print a broad spectrum of patient-specific devices like molds, cutting guides, or orbital models [3,34,51,56,59–62,65]. Finally, data found in the reviewed papers showed that hospital based 3DP laboratories access professional services when they need parts to be printed by selective laser sintering/melting (SLS/SLM) due to special conditions for printing and regulations.

According to our results, the primary human resource participating in the process of point-of-care 3D planning and printing include surgeons, radiologists, and information technology/bioengineering experts. Surgeons are increasingly enthusiastic about autonomy in virtual surgical planning and 3D printing to save costs, eliminate recurring online meetings, and prevent long delivery timeframes. Data regarding who is responsible for computer purchases, software, consumable materials, or maintenance were not addressed in the research reviewed. The imaging department and the 3D printing laboratory need to work together because the image datasets used in the digital workflow determine the end product's quality and accuracy. The authors noticed a tendency for synergistic collaboration between the two entities. Establishing 3D printing laboratories inside or in strong collaboration with the radiology department is an example of good practice [6,18,26,34].

Concerning the timeline, this paper referred to three important parameters: the planning period, the printing and post-processing period, and the operation room's time efficiency. The average planning time reported in the review-selected studies was 4.4 h. Because healthcare employees are paid by the hour and operating room cost-efficiency is assessed as money per unit of time, all these parameters also have an economic influence. The cost of planning time was not quantified, except for three studies [9,20,39], which is an evident flaw that must be addressed, as it highlights the issue of balancing time invested in planning and real economic/clinical benefits.

One of the key benefits of point-of-care 3D printing is that production takes less time than typical commercial delivery time frames [3,20,40,42,60]. Time management primarily impacts the outcome of patients suffering from acute afflictions, such as trauma or malignancy. Moreover, operation room time affects the patient's clinical outcome in terms of the amount of time spent under general anesthesia, and it is also helpful in assessing indirect hospital cost savings due to the lessened use of the operation room [30]. While operative time can be shortened [6,18,25,30,35,42], this hypothesis requires prospective studies.

The cost of in-house 3D printing in CMF surgery can be perceived as high when summing up the initial investment in infrastructure but can also be considered low, when considering that a cutting guide is reported to cost 2 USD [44]. The reported costs of self-printed parts lack consistency. Most authors did not mention or only partially addressed direct costs (accommodation of infrastructure, software, training, computer, printer, and material costs) or time costs for 3D planning, printer set-up, post-processing, and maintenance.

Researchers must find ways to prove indirect savings obtained through operating room time economy. Studies must evaluate whether the externalization of VSP and 3DP means supplementary expense while the internalization of these services means savings for the hospital. POC 3DP promoters should also face central governmental authorities with research data pleading for an accelerated patient recovery leading to the immediate socio-economical reintegration of the patients that would otherwise be a burden for the social care system. Therefore, we encourage future research to present data in a much more structured, transparent, and objective manner, respecting health economics evaluation/reporting standards [77].

A consensus on reporting the surgical outcome of POC 3DP in CMF surgery could not be identified. Most of the studies reported positive outcomes but few provided quantitative evidence to support their clinical outcome. Consequently, neither of the selected studies measured surgical outcomes comprehensively. As point-of-care 3D printing becomes more mature, hospitals and clinics have started moving from simple applications to more complex applications, such as self-printed implantable devices. This process demands the demonstration of clinical efficacy and device safety. Consequently, to avoid researcher bias, the next important step is to involve as many independent groups of researchers as possible in validating POC-printed patient specific devices (PSI) through prospective clinical studies [78].

4.1. Limitations and Strengths

Despite its narrative nature, the current study provides a systematic and comprehensive overview on the concept of hospital-based virtual surgical planning and 3D printing. However, we are aware that some papers might have been missed. A lack of consistent data and heterogenous reports that are not always backed up by numbers and statistics suggest the need for more transparent and objective studies based on standardized reporting. Nevertheless, this is one of the first studies to address the use of in-house 3D printing in CMF surgery from such a broad time perspective—a span of seven years.

The results presented in this paper give an elaborate overview of the reported data on infrastructure, human resource, software, and printers used at the point-of-care. This set of data is highly valuable for anyone considering implementation/usage of virtual surgical planning and 3D printing at the point-of-care, not only in CMF surgery but also in other surgical specialties.

4.2. Further Research

Our review identified gaps that further research can fill: (1) a standardized guide to reporting data on the use of point-of-care 3D printing, applied not only to oral and cranio-maxillofacial surgery but also to the entire medical field; (2) a guide on the process of the integration of 3D printing and digital workflows in the hospital environment; and (3) the study of regulations and standards in order to establish verification and validation protocols, focused on monitoring point-of-care production processes with checkpoints to ensure device safety.

5. Conclusions

Oral and cranio-maxillofacial surgery supports the development of in-house 3D printed devices with promising results that suggest that the technology has reached maturity. The field of clinical applications is broad and continuously expanding, as it is currently being used from basic clinical applications up to complex surgical challenges. This data collection can help inform decisions when implementing virtual surgical planning and 3D printing in hospital departments or to serve as motivation for future research that can further develop point-of-care 3D printing in CMF surgery. In order to consolidate the role of point-of-care 3D printed devices in standard clinical practice and be seen as a viable alternative to outsourced professional solutions, further prospective, rigorous, and long-term assessments of clinical efficacy, cost-effectiveness, and device safety need to be conducted.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm11226625/s1, Supplementary Table S1. Search strategies for PubMed database; Supplementary Table S2. Data collection process.

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References

1. Hull, C.W. Apparatus for Production of Three-Dimensional Objects by Stereolithography. U.S. Patent 4575330A, 19 December 1986.
2. Louvrier, A.; Marty, P.; Barrabé, A.; Euvrard, E.; Chatelain, B.; Weber, E.; Meyer, C. How useful is 3D printing in maxillofacial surgery? *J. Stomatol. Oral Maxillofac. Surg.* **2017**, *118*, 206–212. https://doi.org/10.1016/j.jormas.2017.07.002.
3. Sharkh, H.A.; Makhoul, N. In-House Surgeon-Led Virtual Surgical Planning for Maxillofacial Reconstruction. *J. Oral Maxillofac. Surg.* **2020**, *78*, 651–660. https://doi.org/10.1016/j.joms.2019.11.013.
4. Yang, W.; Zhang, C.-Y.; Choi, W.; Zhu, W.-Y.; Li, D.; Chen, X.-S.; Du, R.; Su, Y.-X. A novel 'surgeon-dominated' approach to the design of 3D-printed patient-specific surgical plates in mandibular reconstruction: A proof-of-concept study. *Int. J. Oral Maxillofac. Surg.* **2019**, *49*, 13–21. https://doi.org/10.1016/j.ijom.2019.05.005.
5. Rustemeyer, J.; Melenberg, A.; Sari-Rieger, A. Costs incurred by applying computer-aided design/computer-aided manufacturing techniques for the reconstruction of maxillofacial defects. *J. Cranio-Maxillofac. Surg.* **2014**, *42*, 2049–2055. https://doi.org/10.1016/j.jcms.2014.09.014.
6. Marschall, J.S.; Dutra, V.; Flint, R.L.; Kushner, G.M.; Alpert, B.; Scarfe, W.; Azevedo, B. In-House Digital Workflow for the Management of Acute Mandible Fractures. *J. Oral Maxillofac. Surg.* **2019**, *77*, 2084.e1–2084.e9. https://doi.org/10.1016/j.joms.2019.05.027.
7. Arce, K.; Morris, J.M.; Alexander, A.E.; Ettinger, K.S. Developing a Point-of-Care Manufacturing Program for Craniomaxillofacial Surgery. *Atlas Oral Maxillofac. Surg. Clin.* **2020**, *28*, 165–179. https://doi.org/10.1016/j.cxom.2020.06.002.
8. State of the Healthcare Market 2020: Point-of-Care 3D Printing Trends. Available online: https://www.materialise.com/en/blog/healthcare-market-trends-point-of-care (accessed on 20 April 2022).
9. Spaas, C.; Lenssen, O. Economic analysis of a low-cost virtual surgical planning protocol for mandibular reconstruction: A case series. *Br. J. Oral Maxillofac. Surg.* **2019**, *57*, 743–748. https://doi.org/10.1016/j.bjoms.2019.06.017.
10. Tack, P.; Victor, J.; Gemmel, P.; Annemans, L. 3D-printing techniques in a medical setting: A systematic literature review. *Biomed. Eng. Online* **2016**, *15*, 115. https://doi.org/10.1186/s12938-016-0236-4.
11. Jacobs, C.A.; Lin, A.Y. A New Classification of Three-Dimensional Printing Technologies: Systematic review of three-dimensional printing for patient-specific craniomaxillofacial surgery. *Plast. Reconstr. Surg.* **2017**, *139*, 1211–1220. https://doi.org/10.1097/prs.0000000000003232.
12. Hoang, D.; Perrault, D.; Stevanovic, M.; Ghiassi, A. Surgical applications of three-dimensional printing: A review of the current literature & how to get started. *Ann. Transl. Med.* **2016**, *4*, 456–456. https://doi.org/10.21037/atm.2016.12.18.
13. Malik, H.H.; Darwood, A.R.; Shaunak, S.; Kulatilake, P.; El-Hilly, A.A.; Mulki, O.; Baskaradas, A. Three-dimensional printing in surgery: A review of current surgical applications. *J. Surg. Res.* **2015**, *199*, 512–522. https://doi.org/10.1016/j.jss.2015.06.051.
14. Martelli, N.; Serrano, C.; van den Brink, H.; Pineau, J.; Prognon, P.; Borget, I.; El Batti, S. Advantages and disadvantages of 3-dimensional printing in surgery: A systematic review. *Surgery* **2016**, *159*, 1485–1500. https://doi.org/10.1016/j.surg.2015.12.017.
15. Lin, H.-H.; Lonic, D.; Lo, L.-J. 3D printing in orthognathic surgery—A literature review. *J. Formos. Med. Assoc.* **2018**, *117*, 547–558. https://doi.org/10.1016/j.jfma.2018.01.008.
16. Murtezani, I.; Sharma, N.; Thieringer, F.M. Medical 3D printing with a focus on Point-of-Care in Cranio- and Maxillofacial Surgery. A systematic review of literature. *Ann. 3D Print. Med.* **2022**, *6*, 100059. https://doi.org/10.1016/j.stlm.2022.100059.
17. Mendez, B.M.; Chiodo, M.V.; Patel, P.A. Customized "In-Office" Three-Dimensional Printing for Virtual Surgical Planning in Craniofacial Surgery. *J. Craniofacial Surg.* **2015**, *26*, 1584–1586. https://doi.org/10.1097/scs.0000000000001768.
18. Weinstock, P.; Prabhu, S.P.; Flynn, K.; Orbach, D.B.; Smith, E. Optimizing cerebrovascular surgical and endovascular procedures in children via personalized 3D printing. *J. Neurosurg. Pediatr.* **2015**, *16*, 584–589.
19. Mottini, M.; Seyed Jafari, S.M.; Shafighi, M.; Schaller, B. New approach for virtual surgical planning and mandibular reconstruction using a fibula free flap. *Oral Oncol.* **2016**, *59*, e6–e9.

20. Legocki, A.T.; Duffy-Peter, A.; Scott, A.R. Benefits and Limitations of Entry-Level 3-Dimensional Printing of Maxillofacial Skeletal Models. *JAMA Otolaryngol.-Head Neck Surg.* **2017**, *143*, 389–394. https://doi.org/10.1001/jamaoto.2016.3673.
21. Velasco, I.; Vahdani, S.; Ramos, H. Low-cost Method for Obtaining Medical Rapid Prototyping Using Desktop 3D printing: A Novel Technique for Mandibular Reconstruction Planning. *J. Clin. Exp. Dent.* **2017**, *9*, e1103–e1108. https://doi.org/10.4317/jced.54055.
22. Ahmed, S.; VanKoevering, K.K.; Kline, S.; Green, G.E.; Arts, H.A. Middle cranial fossa approach to repair tegmen defects assisted by three-dimensionally printed temporal bone models. *Laryngoscope* **2017**, *127*, 2347–2351.
23. Elegbede, A.; Diaconu, S.C.; McNichols, C.H.; Seu, M.; Rasko, Y.M.; Grant, M.P.; Nam, A.J. Office-Based Three-Dimensional Printing Workflow for Craniomaxillofacial Fracture Repair. *J. Craniofacial Surg.* **2018**, *29*, e440–e444. https://doi.org/10.1097/scs.0000000000004460.
24. Valding, B.; Zrounba, H.; Martinerie, S.; May, L.; Broome, M. Should You Buy a Three-Dimensional Printer? A Study of an Orbital Fracture. *J. Craniofacial Surg.* **2018**, *29*, 1925–1927. https://doi.org/10.1097/scs.0000000000005048.
25. Naros, A.; Weise, H.; Tilsen, F.; Hoefert, S.; Naros, G.; Krimmel, M.; Reinert, S.; Polligkeit, J. Three-dimensional accuracy of mandibular reconstruction by patient-specific pre-bent reconstruction plates using an "in-house" 3D-printer. *J. Cranio-Maxillofacial Surg.* **2018**, *46*, 1645–1651. https://doi.org/10.1016/j.jcms.2018.05.047.
26. Guest, W.; Forbes, D.; Schlosser, C.; Yip, S.; Coope, R.; Chew, J. Imaging-Based 3-Dimensional Printing for Improved Maxillofacial Presurgical Planning: A Single Center Case Series. *Can. Assoc. Radiol. J.* **2019**, *70*, 74–82. https://doi.org/10.1016/j.carj.2018.10.002.
27. King, C.; Shafi, A.; Burke, E. Optimising the management of concurrent symphyseal/parasymphyseal and bilateral extracapsular condylar fractures using three-dimensional printing. *Oral Maxillofac. Surg.* **2019**, *24*, 217–219. https://doi.org/10.1007/s10006-019-00820-y.
28. Hatz, C.R.; Msallem, B.; Aghlmandi, S.; Brantner, P.; Thieringer, F.M. Can an entry-level 3D printer create high-quality anatomical models? Accuracy assessment of mandibular models printed by a desktop 3D printer and a professional device. *Int. J. Oral Maxillofac. Surg.* **2020**, *49*, 143–148. https://doi.org/10.1016/j.ijom.2019.03.962.
29. Hassan, S.; Jelon, A.; Rahim, N.I.H.A.; Yahya, M.A.; Omar, N. Fast and economical protocol for in-house virtual planning and 3D-printed surgical templates in mandibular reconstruction. *J. 3D Print. Med.* **2020**, *4*, 83–90. https://doi.org/10.2217/3dp-2019-0026.
30. Sigron, G.R.; Rüedi, N.; Chammartin, F.; Meyer, S.; Msallem, B.; Kunz, C.; Thieringer, F.M. Three-Dimensional Analysis of Isolated Orbital Floor Fractures Pre- and Post-Reconstruction with Standard Titanium Meshes and "Hybrid" Patient-Specific Implants. *J. Clin. Med.* **2020**, *9*, 1579. https://doi.org/10.3390/jcm9051579.
31. Narita, M.; Takaki, T.; Shibahara, T.; Iwamoto, M.; Yakushiji, T.; Kamio, T. Utilization of desktop 3D printer-fabricated "Cost-Effective" 3D models in orthognathic surgery. *Maxillofac. Plast. Reconstr. Surg.* **2020**, *42*, 24. https://doi.org/10.1186/s40902-020-00269-0.
32. Lassausaie, A.; Sesqué, A.; Barthélémy, I.; Depeyre, A. Virtual Surgery Planning and Three-Dimensional Printing Template for Osteotomy of the Zygoma to Correct Untreated Zygomaticomaxillary Complex Fracture. *J. Craniofacial Surg.* **2020**, *31*, 1142–1145. https://doi.org/10.1097/scs.0000000000006551.
33. Akiki, R.K.; Jehle, C.C.; Crozier, J.; Woo, A.S. Using 3D Printing and Mirror Image Modeling in Orbital Floor Reconstruction. *J. Craniofacial Surg.* **2021**, *32*, 2465–2467. https://doi.org/10.1097/scs.0000000000007672.
34. Dvoracek, L.A.; Lee, J.Y.; Unadkat, J.V.; Lee, Y.H.; Thakrar, D.; Losee, J.E.; Goldstein, J.A. Low-Cost, Three-Dimensionally–Printed, Anatomical Models for Optimization of Orbital Wall Reconstruction. *Plast. Reconstr. Surg.* **2020**, *147*, 162–166. https://doi.org/10.1097/prs.0000000000007495.
35. Sigron, G.; Barba, M.; Chammartin, F.; Msallem, B.; Berg, B.-I.; Thieringer, F. Functional and Cosmetic Outcome after Reconstruction of Isolated, Unilateral Orbital Floor Fractures (Blow-Out Fractures) with and without the Support of 3D-Printed Orbital Anatomical Models. *J. Clin. Med.* **2021**, *10*, 3509. https://doi.org/10.3390/jcm10163509.
36. Bergeron, L.; Bonapace-Potvin, M.; Bergeron, F. In-house 3D Model Printing for Acute Cranio-maxillo-facial Trauma Sur-gery: Process, Time, and Costs. *Plast. Reconstr. Surg. Glob. Open* **2021**, *9*, e3804.
37. Matsumoto, J.S.; Morris, J.M.; Foley, T.A.; Williamson, E.E.; Leng, S.; McGee, K.P.; Kuhlmann, J.L.; Nesberg, L.E.; Vrtiska, T.J. Three-dimensional Physical Modeling: Applications and Experience at Mayo Clinic. *RadioGraphics* **2015**, *35*, 1989–2006. https://doi.org/10.1148/rg.2015140260.
38. Gomez-Feria, J.; Narros, J.L.; Ciriza, G.G.; Roldan-Lora, F.; Schrader, I.M.; Martin-Rodríguez, J.F.; Mir, P. 3D Printing of Diffuse Low-Grade Gliomas Involving Eloquent Cortical Areas and Subcortical Functional Pathways: Technical Note. *World Neurosurg.* **2021**, *147*, 164–171.e4. https://doi.org/10.1016/j.wneu.2020.12.082.
39. Goetze, E.; Gielisch, M.; Moergel, M.; Al-Nawas, B. Accelerated workflow for primary jaw reconstruction with microvascular fibula graft. *3D Print. Med.* **2017**, *3*, 1–9. https://doi.org/10.1186/s41205-017-0010-7.
40. Bosc, R.; Hersant, B.; Carloni, R.; Niddam, J.; Bouhassira, J.; De Kermadec, H.; Bequignon, E.; Wojcik, T.; Julieron, M.; Meningaud, J.-P. Mandibular reconstruction after cancer: An in-house approach to manufacturing cutting guides. *Int. J. Oral Maxillofac. Surg.* **2017**, *46*, 24–31.
41. Hatamleh, M.M.; Yeung, E.; Osher, J.; Huppa, C. Novel Treatment Planning of Hemimandibular Hyperplasia by the Use of Three-Dimensional Computer-Aided-Design and Computer-Aided-Manufacturing Technologies. *J. Craniofacial Surg.* **2017**, *28*, 764–767. https://doi.org/10.1097/scs.0000000000003438.
42. Ganry, L.; Quilichini, J.; Bandini, C.M.; Leyder, P.; Hersant, B.; Meningaud, J.P. Three-dimensional surgical modelling with an open-source software protocol: Study of precision and reproducibility in mandibular reconstruction with the fibula free flap. *Int. J. Oral Maxillofac. Surg.* **2017**, *46*, 946–957.

43. Ganry, L.; Hersant, B.; Quilichini, J.; Leyder, P.; Meningaud, J. Use of the 3D surgical modelling technique with open-source software for mandibular fibula free flap reconstruction and its surgical guides. *J. Stomatol. Oral Maxillofac. Surg.* **2017**, *118*, 197–202. https://doi.org/10.1016/j.jormas.2017.03.002.
44. Numajiri, T.; Morita, D.; Nakamura, H.; Yamochi, R.; Tsujiko, S.; Sowa, Y. Designing CAD/CAM Surgical Guides for Maxillary Reconstruction Using an In-house Approach. *J. Vis. Exp.* **2018**, *138*, e58015. https://doi.org/10.3791/58015.
45. Orabona, G.D.; Abbate, V.; Maglitto, F.; Bonavolontà, P.; Salzano, G.; Romano, A.; Reccia, A.; Committeri, U.; Iaconetta, G.; Califano, L. Low-cost, self-made CAD/CAM-guiding system for mandibular reconstruction. *Surg. Oncol.* **2018**, *27*, 200–207. https://doi.org/10.1016/j.suronc.2018.03.007.
46. Smithers, F.A.E.; Cheng, K.; Jayaram, R.; Mukherjee, P.; Clark, J.R. Maxillofacial reconstruction using in-house virtual surgical planning. *ANZ J. Surg.* **2018**, *88*, 907–912. https://doi.org/10.1111/ans.14353.
47. Numajiri, T.; Morita, D.; Nakamura, H.; Tsujiko, S.; Yamochi, R.; Sowa, Y.; Toyoda, K.; Tsujikawa, T.; Arai, A.; Yasuda, M.; et al. Using an In-House Approach to Computer-Assisted Design and Computer-Aided Manufacturing Reconstruction of the Maxilla. *J. Oral Maxillofac. Surg.* **2017**, *76*, 1361–1369. https://doi.org/10.1016/j.joms.2017.11.042.
48. Zavattero, E.; Fasolis, M.; Novaresio, A.; Gerbino, G.; Borbon, C.; Ramieri, G. The Shape of Things to Come: In-Hospital Three-Dimensional Printing for Mandibular Reconstruction Using Fibula Free Flap. Laryngoscope 2020, *130*, E811–E816.
49. McAllister, P.; Watson, M.; Burke, E. A Cost-Effective, In-House, Positioning and Cutting Guide System for Orthognathic Surgery. *J. Maxillofac. Oral Surg.* **2017**, *17*, 112–114. https://doi.org/10.1007/s12663-017-1067-y.
50. Beckers, O.; Coppey, E.; Mommaerts, M. Computer-aided design and manufacturing construction of a pilot guide for a bone-anchored epithesis to replace an absent pinna. *Int. J. Oral Maxillofac. Surg.* **2020**, *50*, 815–819. https://doi.org/10.1016/j.ijom.2020.10.006.
51. Ostas, D.; Hedesiu, M.; Roman, C.R.; Cosma, C.; Ciurea, M.; Rotaru, H. Design Workflow for Mandibular Reconstruction. Opportunities and Limitations of In-house Virtual Surgical Planning. *J. Med Biol. Eng.* **2021**, *41*, 482–493. https://doi.org/10.1007/s40846-021-00633-z.
52. Mascarenhas, W.; Makhoul, N. Efficient in-house 3D printing of an orthognathic splint for single-jaw cases. *Int. J. Oral Maxillofac. Surg.* **2021**, *50*, 1075–1077. https://doi.org/10.1016/j.ijom.2020.12.016.
53. Maglitto, F.; Orabona, G.D.; Committeri, U.; Salzano, G.; De Fazio, G.R.; Vaira, L.A.; Abbate, V.; Bonavolontà, P.; Piombino, P.; Califano, L. Virtual Surgical Planning and the "In-House" Rapid Prototyping Technique in Maxillofacial Surgery: The Current Situation and Future Perspectives. *Appl. Sci.* **2021**, *11*, 1009. https://doi.org/10.3390/app11031009.
54. Šimić, L.; Kopačin, V.; Mumlek, I.; Butković, J.; Zubčić, V. Improved technique of personalised surgical guides generation for mandibular free flap reconstruction using an open-source tool. *Eur. Radiol. Exp.* **2021**, *5*, 30. https://doi.org/10.1186/s41747-021-00229-x.
55. Postl, L.; Mücke, T.; Hunger, S.; Bissinger, O.; Malek, M.; Holberg, S.; Burgkart, R.; Krennmair, S. In-house 3D-printed surgical guides for osseous lesions of the lower jaw: An experimental study. *Eur. J. Med Res.* **2021**, *26*, 25. https://doi.org/10.1186/s40001-021-00495-w.
56. Ritschl, L.M.; Kilbertus, P.; Grill, F.D.; Schwarz, M.; Weitz, J.; Nieberler, M.; Wolff, K.-D.; Fichter, A.M. In-House, Open-Source 3D-Software-Based, CAD/CAM-Planned Mandibular Reconstructions in 20 Consecutive Free Fibula Flap Cases: An Explorative Cross-Sectional Study with Three-Dimensional Performance Analysis. *Front. Oncol.* **2021**, *11*, 3751. https://doi.org/10.3389/fonc.2021.731336.
57. Hay, J.A.; Smayra, T.; Moussa, R. Customized Polymethylmethacrylate Cranioplasty Implants Using 3-Dimensional Printed Polylactic Acid Molds: Technical Note with 2 Illustrative Cases. *World Neurosurg.* **2017**, *105*, 971–979.e1. https://doi.org/10.1016/j.wneu.2017.05.007.
58. Evins, A.I.; Dutton, J.; Imam, S.S.; Dadi, A.O.; Xu, T.; Cheng, D.; Stieg, P.E.; Bernardo, A. On-Demand Intraoperative 3-Dimensional Printing of Custom Cranioplastic Prostheses. *Oper. Neurosurg.* **2018**, *15*, 341–349. https://doi.org/10.1093/ons/opx280.
59. Morales-Gómez, J.A.; Garcia-Estrada, E.; Leos-Bortoni, J.E.; Delgado-Brito, M.; Flores-Huerta, L.E.; De La Cruz-Arriaga, A.A.; Torres-Díaz, L.J.; de León, R.M.-P. Cranioplasty with a low-cost customized polymethylmethacrylate implant using a desktop 3D printer. *J. Neurosurg.* **2019**, *130*, 1721–1727. https://doi.org/10.3171/2017.12.jns172574.
60. Tel, A.; Tuniz, F.; Fabbro, S.; Sembronio, S.; Costa, F.; Robiony, M. Computer-Guided In-House Cranioplasty: Establishing a Novel Standard for Cranial Reconstruction and Proposal of an Updated Protocol. *J. Oral Maxillofac. Surg.* **2020**, *78*, 2297.e1–2297.e16. https://doi.org/10.1016/j.joms.2020.08.007.
61. Tel, A.; Tuniz, F.; Sembronio, S.; Costa, F.; Bresadola, V.; Robiony, M. Cubik system: Maximizing possibilities of in-house computer-guided surgery for complex craniofacial reconstruction. *Int. J. Oral Maxillofac. Surg.* **2021**, *50*, 1554–1562. https://doi.org/10.1016/j.ijom.2021.07.008.
62. Pöppe, J.P.; Spendel, M.; Schwartz, C.; Winkler, P.A.; Wittig, J. The "springform" technique in cranioplasty: Custom made 3D-printed templates for intraoperative modelling of polymethylmethacrylate cranial implants. *Acta Neurochir.* **2021**, *164*, 679–688. https://doi.org/10.1007/s00701-021-05077-7.
63. Callahan, A.B.; Campbell, A.A.; Petris, C.; Kazim, M. Low-Cost 3D Printing Orbital Implant Templates in Secondary Orbital Reconstructions. *Ophthalmic Plast. Reconstr. Surg.* **2017**, *33*, 376–380. https://doi.org/10.1097/iop.0000000000000884.
64. Abbate, V.; Iaconetta, G.; Califano, L.; Pansini, A.; Bonavolonta, P.; Romano, A.; Salzano, G.; Somma, T.; D'Andrea, L.; Orabona, G.D. Self-Made Rapid Prototyping Technique for Orbital Floor Reconstruction: Showcases for Technical Descriptio. *J. Craniofacial Surg.* **2019**, *30*, 2106–2110. https://doi.org/10.1097/scs.0000000000006004.

65. Menzel, C.L.; Hammacher, A.; Lommen, J.; Schorn, L.K.F.; Handschel, J.; Holtmann, H. Orbit in a Box: A Simplified Technique for Patient-Specific Virtually Planned Orbital Floor Reconstruction. *J. Craniofacial Surg.* **2020**, *31*, 1117–1119. https://doi.org/10.1097/scs.0000000000006158.
66. Honigmann, P.; Sharma, N.; Okolo, B.; Popp, U.; Msallem, B.; Thieringer, F.M. Patient-Specific Surgical Implants Made of 3D Printed PEEK: Material, Technology, and Scope of Surgical Application. *BioMed Res. Int.* **2018**, *2018*, 4520636. https://doi.org/10.1155/2018/4520636.
67. Freiser, M.E.; Ghodadra, A.; Hirsch, B.E.; McCall, A.A. Evaluation of 3D Printed Temporal Bone Models in Preparation for Middle Cranial Fossa Surgery. *Otol. Neurotol.* **2019**, *40*, 246–253. https://doi.org/10.1097/mao.0000000000002073.
68. Williams, F.C.; Hammer, D.A.; Wentland, T.R.; Kim, R.Y. Immediate Teeth in Fibulas: Planning and Digital Workflow With Point-of-Care 3D Printing. *J. Oral Maxillofac. Surg.* **2020**, *78*, 1320–1327. https://doi.org/10.1016/j.joms.2020.04.006.
69. Schön, S.N.; Skalicky, N.; Sharma, N.; Zumofen, D.W.; Thieringer, F.M. 3D-Printer-Assisted Patient-Specific Polymethyl Methacrylate Cranioplasty: A Case Series of 16 Consecutive Patients. *World Neurosurg.* **2021**, *148*, e356–e362. https://doi.org/10.1016/j.wneu.2020.12.138.
70. Cole, T.S.; Graham, D.T.; Wakim, A.A.; Bohl, M.A.; Morgan, C.D.; Catapano, J.S.; Smith, K.A.; Sanai, N.; Lawton, M.T. Local 3-Dimensional Printing of a Calvarium-Anchored Ventricular Catheter Occlusion Device. *Neurosurg. Open* **2021**, *2*, okab024. https://doi.org/10.1093/neuopn/okab024.
71. Sharma, N.; Aghlmandi, S.; Dalcanale, F.; Seiler, D.; Zeilhofer, H.-F.; Honigmann, P.; Thieringer, F. Quantitative Assessment of Point-of-Care 3D-Printed Patient-Specific Polyetheretherketone (PEEK) Cranial Implants. *Int. J. Mol. Sci.* **2021**, *22*, 8521. https://doi.org/10.3390/ijms22168521.
72. Msallem, B.; Beiglboeck, F.; Honigmann, P.; Jaquiéry, C.; Thieringer, F. Craniofacial Reconstruction by a Cost-Efficient Template-Based Process Using 3D Printing. *Plast. Reconstr. Surg. Glob. Open* **2017**, *5*, e1582. https://doi.org/10.1097/gox.0000000000001582.
73. Liu, Y.; Gao, Q.; Du, S.; Chen, Z.; Fu, J.; Chen, B.; Liu, Z.; He, Y. Fabrication of cerebral aneurysm simulator with a desktop 3D printer. *Sci. Rep.* **2017**, *7*, srep44301. https://doi.org/10.1038/srep44301.
74. Chamo, D.; Msallem, B.; Sharma, N.; Aghlmandi, S.; Kunz, C.; Thieringer, F.M. Accuracy Assessment of Molded, Patient-Specific Polymethylmethacrylate Craniofacial Implants Compared to Their 3D Printed Originals. *J. Clin. Med.* **2020**, *9*, 832. https://doi.org/10.3390/jcm9030832.
75. Werz, S.M.; Zeichner, S.J.; Berg, B.-I.; Zeilhofer, H.-F.; Thieringer, F. 3D Printed Surgical Simulation Models as educational tool by maxillofacial surgeons. *Eur. J. Dent. Educ.* **2018**, *22*, e500–e505. https://doi.org/10.1111/eje.12332.
76. Fedorov, A.; Beichel, R.; Kalpathy-Cramer, J.; Finet, J.; Fillion-Robin, J.-C.; Pujol, S.; Bauer, C.; Jennings, D.; Fennessy, F.; Sonka, M.; et al. 3D Slicer as an image computing platform for the Quantitative Imaging Network. *Magn. Reson. Imaging* **2012**, *30*, 1323–1341. https://doi.org/10.1016/j.mri.2012.05.001.
77. Husereau, D.; Drummond, M.; Petrou, S.; Carswell, C.; Moher, D.; Greenberg, D.; Augustovski, F.; Brigs, A.H.; Mauskopf, J.; Loder, E. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *Int. J. Technol. Assess. Health Care* **2013**, *29*, 117–122.
78. Diment, L.E.; Thompson, M.S.; Bergmann, J.H.M. Clinical efficacy and effectiveness of 3D printing: A systematic review. *BMJ Open* **2017**, *7*, e016891. https://doi.org/10.1136/bmjopen-2017-016891.