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Evaluation of morphological and dimensional characteristics of the nasopalatine canal in patients with impacted teeth in the anterior maxilla: a retrospective study

The results of this study were presented as an oral presentation at the 5th International Congress of the Oral Diagnosis and Maxillofacial Radiology Society, April 23–27, 2025, TRNC.

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Background*: The nasopalatine canal (NPC) is a clinically and radiologically significant anatomical structure. This study aimed to comprehensively characterize the morphological, morphometric, and anatomical features of the NPC in individuals with impacted teeth in the anterior maxilla and to classify the spatial relationship between the impacted tooth and the NPC.*

Materials and methods*: A total of 238 cone-beam computed tomography (CBCT) images were evaluated based on the inclusion and exclusion criteria. The NPC was evaluated separately in the axial, coronal, and sagittal planes in all CBCT images. In addition, age, sex, impacted tooth location and position, and its spatial relationship to the NPC (none, apical, middle, or crestal region) were recorded for all images. The independent-samples t-test, Mann–Whitney U test, and Pearson chi-square test were used for statistical analysis.*

Results*: An anatomical relationship between impacted teeth and the NPC was found in 50.4% of cases. Impacted teeth in a mesioangular position were more frequently associated with the NPC than those in other positions. An association was observed between axial NPC shape at all three levels and the relationship of the impacted tooth to the NPC. Differences were found in the external border shape and course of the NPC according to the presence or absence of impacted teeth associated with the NPC. The IF diameter was greater in individuals with impacted teeth associated with the NPC than in those without such an association.*

Conclusions*: The present study demonstrated that the presence of impacted teeth in the anterior maxillary region may lead to alterations in the morphological and dimensional characteristics of the NPC.* (Folia Morphol 2026; 85: e01726155)

Keywords: anatomy; cone-beam computed tomography; impacted teeth; nasopalatine canal

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INTRODUCTION

The nasopalatine canal (NPC), located in the midline of the premaxillary region posterior to the maxillary anterior teeth, is a clinically and radiologically significant anatomical structure, also referred to in the literature as the incisive canal [17]. The oral opening of the NPC is known as the incisive foramen (IF) and is situated in the midline beneath the incisive papilla in the anterior maxilla [15]. The nasal opening of the canal is defined as the Stenson foramen (SF) [25]. Impacted teeth in this region, particularly permanent incisors and supernumerary teeth, may lead to malocclusion, root resorption, eruption disturbances, and esthetic problems [16]. In addition, the close anatomical relationship between impacted teeth and the NPC during surgical removal of these teeth represents a significant factor that increases the risk of complications [21].

The morphology of the NPC exhibits considerable variation among individuals [4]. The length, diameter, and shape of the canal, as well as its relationship with the alveolar crest, may vary according to age, sex, and anatomical differences [9]. Therefore, in the presence of impacted teeth, evaluation of the morphology, dimensions, and spatial relationship of the NPC to the teeth is essential for predicting potential risks during surgical planning. In addition, detailed knowledge of the NPC is crucial in planning oral surgical procedures in the maxillary region, managing nasopalatine cysts, and treating palatal pathologies requiring surgical intervention [3, 7, 23].

Various radiographic modalities are used to determine the localization and morphological characteristics of the NPC [26]. Although two-dimensional radiographs remain important for diagnostic purposes, they are not considered sufficiently reliable for preoperative assessment because of inherent limitations such as superimposition, magnification, and distortion [5]. In addition, impacted teeth may lie outside the area adequately evaluated by these techniques, making it difficult to accurately assess their three-dimensional position, morphology, and relationships with adjacent structures [32]. Therefore, cone-beam computed tomography (CBCT) is recommended for detailed visualization of the NPC, accurate assessment of its relationship with surrounding anatomical structures, and precise localization of impacted teeth [17].

Although numerous studies have investigated the anatomical variations of the NPC [4, 8], research systematically addressing its relationship with impacted teeth remains limited. The aim of this retrospective study was to evaluate the morphology and dimensions of the NPC, as well as its spatial relationship with impacted teeth, in individuals with impacted teeth in the anterior maxillary region. In addition, the study sought to analyze associations between NPC characteristics and patient-related factors, including age, sex, impacted tooth position, and its relationship with the canal, in order to contribute to surgical planning and help prevent potential complications. The null hypothesis was that the presence of impacted teeth in the anterior maxilla does not affect NPC morphology.

MATERIALS AND METHODS

This retrospective study was conducted in accordance with the principles of the Declaration of Helsinki, and ethical approval was obtained from the Clinical Research Ethics Committee of Akdeniz University Faculty of Medicine before the study began (KAEK No. 780). Based on the study by Aydoğan Akgün and Yurttaş [2], the reported prevalence of impacted teeth associated with the NPC (42.8%) was used as a guide, and the sample size of the current study was determined as 208 patients with a 90% confidence level and a 5% margin of error according to the sample size formula for a known population.

Sample collection

In the current study, a total of 930 CBCT image records of patients who presented to the Department of Oral and Maxillofacial Radiology, Faculty of Dentistry, Akdeniz University, for evaluation of impacted teeth between January 2021 and December 2024 were retrospectively reviewed. CBCT images of systemically healthy patients presenting with at least one impacted tooth (incisor or canine) in the anterior maxilla were included in the study.

CBCT images were excluded if the patients had a history of trauma or surgery in the anterior maxilla, missing teeth in the anterior maxillary region, any pathological condition affecting the maxilla (such as cysts or tumors), inadequate image quality, absence of the NPC from the field of view, or craniofacial deformities that could affect the jaw bones. Medical histories were obtained from the digital dental record system.

After applying the above inclusion and exclusion criteria to the CBCT images of 930 patients, a total of 238 CBCT scans (159 females and 79 males) were included in the final analysis.

Imaging procedures

Cone-beam computed tomography images were acquired by the same X-ray technician using a Veraview X800 CBCT device (J. Morita Mfg. Corp., Kyoto, Japan) according to the manufacturer's instructions (320 μm; 4.8 mA; 99 kVp and 17.9 s for a 15 × 15 × 51.2 field of view; and 320 μm; 4.8 mA; 99 kVp and 35.8 s for a 15 × 15 × 13.9 field of view). Scans were analyzed using i-Dixel software (version 2.3.6.1; J. Morita Mfg. Corp., Kyoto, Japan). Data were reconstructed at 0.25-mm intervals parallel to the alveolar bone plane. The reconstructed sections were optimized to allow evaluation of the nasopalatine canal in the coronal and sagittal planes.

All CBCT images were divided equally between two researchers (RSG and SCD), both specializing in dental radiology and having at least 3 years of experience, and were evaluated using the same LED monitor at a viewing distance of approximately 40–50 cm. To maximize image quality, the images were evaluated in a dimly lit room with appropriate tone adjustments. To prevent fatigue, only five CBCT images were evaluated per day by the researchers.

Evaluation of images and the nasopalatine canal

In the axial plane: The shape of the NPC was evaluated separately at the IF, middle, and nasopalatine foramen (NF) levels and divided into three groups: round (separated/unseparated), oval (separated/ /unseparated), and other (heart-shaped, teddy bear-shaped, bean-shaped, balloon-shaped, triangular--shaped, etc.) (Fig. 1) [4, 11].

In the coronal plane: The shape of the NPC was divided into three groups: single-channel, double--channel, and Y-shaped channel. The external border of the NPC was also evaluated as V-shaped, Y-shaped, U-shaped, and reverse V-shaped (Fig. 2) [4].

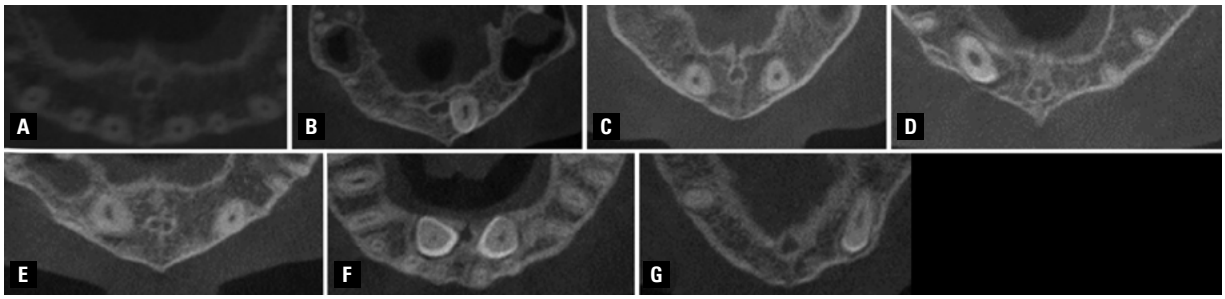


Figure 1. Nasopalatine canal shape in the axial plane: **A.** Round; **B.** Oval; **C.** Heart-shaped; **D.** Teddy bear-shaped; **E.** Bean-shaped; **F.** Balloon-shaped; **G.** Triangular.

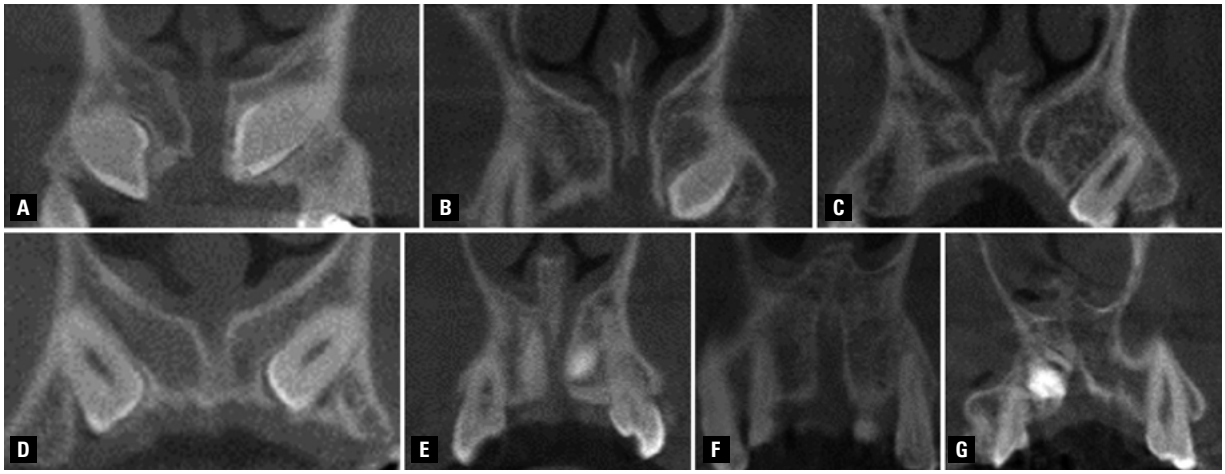


Figure 2. Nasopalatine canal shape in the coronal plane and external border: **A.** Single-channel; **B.** Double-channel; **C.** Y-shaped canal; **D.** V-shaped; **E.** Y-shaped; **F.** U-shaped; **G.** Reverse V-shaped.

In the sagittal plane: The shape of the NPC was divided into seven groups: hourglass-shaped, cone-shaped, funnel-shaped, banana-shaped, cylindrical, tree-branch, and inverted cone-shaped [8]. The course of the NPC was evaluated as vertically straight, vertically curved, slanted straight, and slanted curved (Fig. 3) [11, 28].

In addition, the following measurements were taken in the sagittal plane (Fig. 4):

- nasopalatine foramen (NF) diameter,
- incisive foramen (IF) diameter,
- NPC length,
- NPC angle.

In addition, age, sex, impacted tooth position [vertical, mesioangular, or other (distoangular, buccopalatal, inverted, etc.)], and the level of the impacted tooth along the NPC according to its relationship with the canal (none, apical region, middle region, or crestal region) were recorded for all images (Fig. 5).

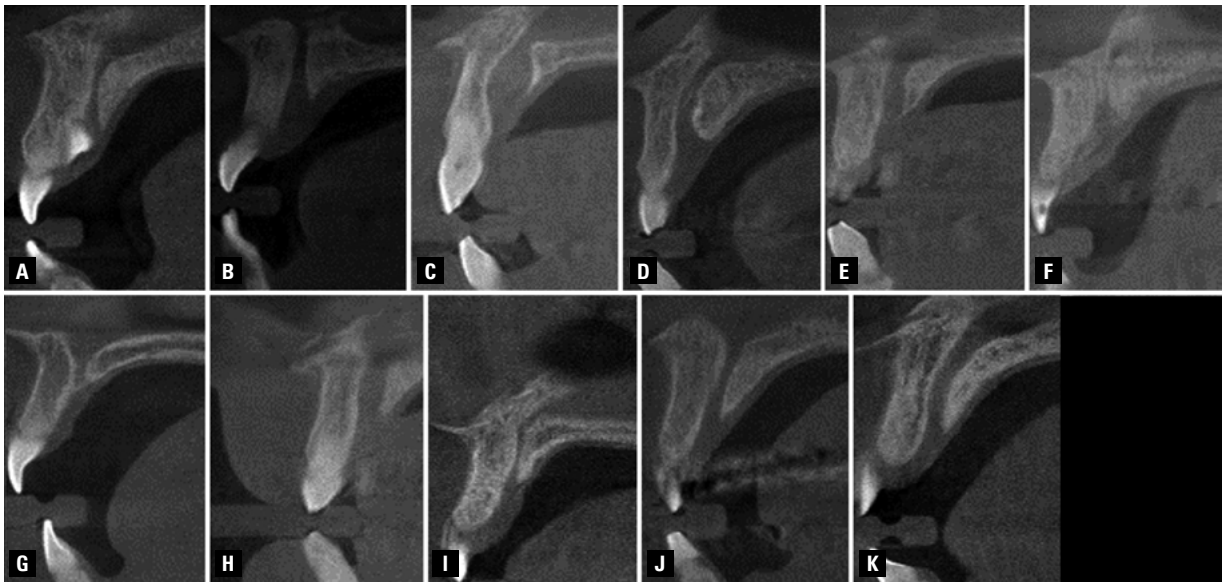


Figure 3. Nasopalatine canal shape and course in the sagittal plane: **A.** Hourglass-shaped; **B.** Cone-shaped; **C.** Funnel-shaped; **D.** Banana-shaped; **E.** Cylindrical; **F.** Tree-branch; **G.** Inverted cone-shaped; **H.** Vertically straight; **I.** Vertically curved; **J.** Slanted straight; **K.** Slanted curved.

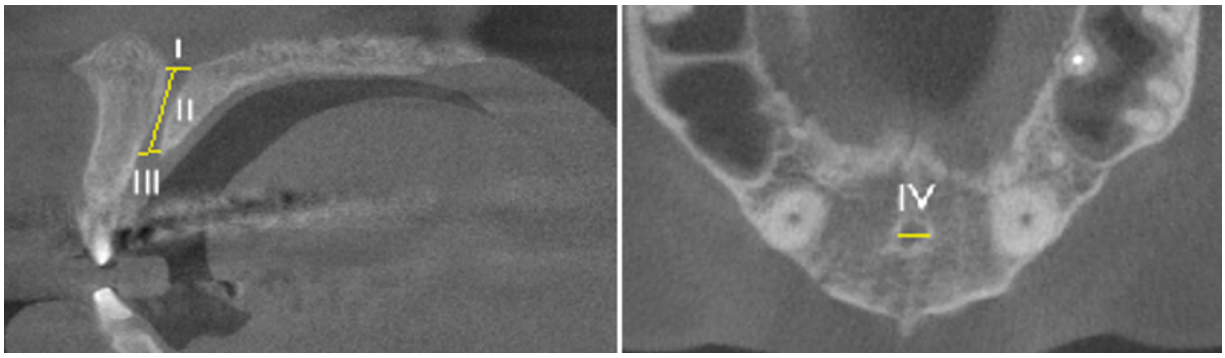


Figure 4. Measurements of the nasopalatine canal (NPC): I — nasopalatine foramen diameter; II — NPC length; III — incisive foramen diameter; IV — NPC diameter.

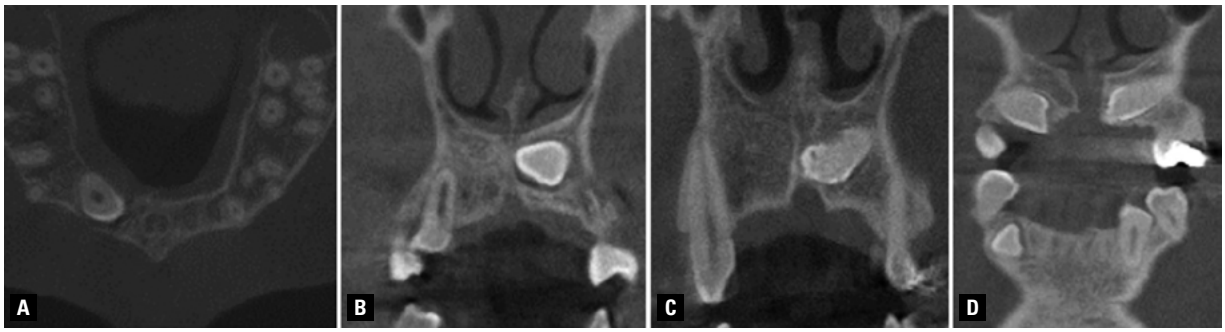


Figure 5. Classification of the spatial relationship between the impacted tooth and the nasopalatine canal: **A.** None; **B.** Apical region; **C.** Middle region; **D.** Crestal region.

Assessment of intra-observer and inter-observer agreement

The observers were calibrated by evaluating 20 CBCT images together, while the remaining images were divided equally and evaluated individually. CBCT images for which the observers were uncertain were evaluated by a third researcher (HT) with 12 years of experience in dental radiology, and a final decision was made. Four weeks later, 50 randomly selected CBCT images were re-evaluated by the third researcher, and interobserver agreement was assessed.

Statistical analysis

Data were statistically analyzed using the SPSS software package (version 23.0; SPSS Inc., Chicago, IL, USA). Normality was assessed using the Shapiro–Wilk test. For analysis of differences between two groups, the independent-samples *t*-test was applied to normally distributed data, and the Mann–Whitney *U* test was used for nonnormally distributed data. The Pearson chi-square test was used to analyze differences between categorical variables. Statistical significance was set at $p < 0.05$. Interobserver agreement was assessed using the kappa coefficient for categorical variables and the intraclass correlation coefficient (ICC) for numerical variables.

RESULTS

The kappa coefficient was above 0.80 for each categorical parameter, while the ICC value was above 0.90 for each numerical parameter.

The current study included CBCT images from 79 male (33.2%) and 159 female (68.8%) patients; the age range was 18–75 years, and the mean age was 33.17 ± 14.58 years. The presence of impacted teeth associated with the NPC did not differ significantly according to sex or age ($p = 0.963$ and $p = 0.783$, respectively). Among the images included in the study, impacted canines were the most frequently observed (n = 223, 93.7%), followed by incisors (n = 10, 4.2%) and both incisors and canines (n = 5, 2.1%). Regarding the position of impacted teeth, the mesioangular position was the most common (n = 218, 79.6%), followed by vertical (n = 32, 11.7%) and other positions (n = 24, 8.8%).

When the relationship between impacted teeth and the NPC was evaluated, no anatomical relationship between the impacted tooth and the canal was observed in 49.6% of cases (n = 118). In contrast, an anatomical relationship between the impacted tooth and the NPC was present in 50.4% of cases (n = 120). The most frequently observed level of this relationship was the crestal level (n = 100, 42.0%), followed by the middle level (n = 12, 5.0%) and the apical level (n = 8, 3.4%). Impacted teeth in a mesioangular position were significantly more frequently associated with the NPC than vertically positioned teeth and teeth in other positions ($p < 0.001$).

The morphological and anatomical characteristics of the NPC observed in the images included in the study are presented in Table 1. The most frequently identified NPC morphology was round on axial sections at the NF, middle, and IF levels (47.4%, 68.9%, and 69.3%, respectively). On coronal sections, a single-channel configuration (59.3%) with a U-shaped external border (50.5%) was most commonly observed, whereas on sagittal sections, a cylindrical canal shape (42.4%) and a vertically straight course (45.0%) were the predominant findings.

Table 1. Morphological features of the nasopalatine canal (NPC) in different planes.

Plane	Feature	Category	n (%)
Axial — NF level	**NPC shape**	Round	113 (47.4%)
		Oval	79 (33.2%)
		Others	46 (19.3%)
Axial — middle level		Round	164 (68.9%)
		Oval	35 (14.7%)
		Others	39 (16.4%)
Axial — IF level		Round	165 (69.3%)
		Oval	21 (8.8%)
		Others	52 (21.8%)
Coronal	**NPC shape**	Single-channel	141 (59.3%)
		Double-channel	61 (25.6%)
		Y-shaped canal	36 (15.1%)
	External border of NPC	U-shaped	120 (50.5%)
		Reverse V-shaped	57 (23.9%)
		Y-shaped	26 (10.9%)
		V-shaped	35 (14.7%)
Sagittal	**NPC shape**	Cylindrical	101 (42.4%)
		Cone-shaped	48 (20.2%)
		Funnel-shaped	23 (9.7%)
		Banana-shaped	30 (12.6%)
		Hourglass-shaped	21 (8.8%)
		Tree-branch	3 (1.3%)
		Inverted cone-shaped	12 (5%)
	NPC course	Vertically straight	107 (45.0%)
		Vertically curved	12 (5.0%)
		Slanted straight	92 (38.7%)
		Slanted curved	27 (11.3%)

IF — incisive foramen; NF — nasopalatine foramen.

Table 2 demonstrates the relationship between NPC morphology and the presence of impacted teeth associated with the NPC. No statistically significant differences were found in NPC shape on coronal and sagittal sections according to the presence of such an association ($p = 0.172$ and $p = 0.654$, respectively). However, a statistically significant association was observed between NPC shape at all three axial levels (IF, middle, and NF) and the relationship of the impacted tooth with the NPC ($p = 0.019$, $p = 0.014$, and $p = 0.006$, respectively). In addition, significant differences were identified in the coronal external border shape and sagittal course of the NPC according to the presence of impacted teeth associated with the NPC ($p = 0.03$ and $p = 0.02$, respectively).

The evaluation of sagittal measurements in relation to the presence of impacted teeth associated with the NPC is shown in Table 3. The IF diameter was greater in individuals with impacted teeth associated with the NPC (3.29 ± 1.05 mm) than in those without such an association (2.92 ± 0.87 mm; $p = 0.004$). No statistically significant differences were found between the two groups for the other measurement parameters ($p > 0.05$).

Table 2. Relationship between nasopalatine canal (NPC) morphology and the presence or absence of an association with impacted teeth.

Impacted tooth–NPC relationship					
Plane	**Feature**	**Category**	**Absence, n (%)**	**Presence, n (%)**	**p value**
Axial — NF level	**NPC shape**	Round	54 (45.8%)	59 (49.2%)	
		Oval	33 (28%)	46 (38.3%)	0.019*
		Others	31 (26.2%)	15 (12.5%)	
Axial — middle level		Round	71 (60.2%)	93 (77.5%)	
		Oval	23 (19.5%)	12 (10%)	0.014*
		Others	24 (20.3%)	15 (12.3%)	
Axial — IF level		Round	72 (61%)	93 (77.5%)	
		Oval	10 (8.5%)	11 (9.2%)	0.006*
		Others	36 (30.5%)	16 (13.3%)	
Coronal	**NPC shape**	Single-channel	67 (56.8%)	74 (61.7%)	
		Double-channel	28 (22.9%)	33 (27.5%)	0.172
		Y-shaped canal	23 (19.5%)	13 (10.8%)	
	External border of NPC	V-shaped	22 (18.6%)	13 (10.8%)	
		U-shaped	49 (41.5%)	71 (59.2%)	0.03*
		Y-shaped	17 (14.4%)	9 (7.5%)	
		Reverse V-shaped	30 (25.4%)	27 (22.5%)	
Sagittal	**NPC shape**	Cylindrical	56 (47.5%)	45 (37.5%)	
		Cone-shaped	21 (17.8%)	27 (22.5%)	
		Funnel-shaped	10 (8.5%)	13 (10.8%)	
		Banana-shaped	16 (13.6%)	14 (11.7%)	0.654
		Hourglass-shaped	10 (8.5%)	11 (9.2%)	
		Tree-branch	1 (0.8%)	2 (1.7%)	
		Inverted cone-shaped	4 (3.3%)	8 (6.6%)	
	NPC course	Vertically straight	42 (35.6%)	65 (54.2%)	
		Vertically curved	5 (4.2%)	7 (5.8%)	0.02*
		Slanted straight	54 (45.8%)	38 (31.7%)	
		Slanted curved	17 (14.4%)	10 (8.3%)	

IF — incisive foramen; NF — nasopalatine foramen.

Table 3. Measurements according to the relationship between impacted teeth and the nasopalatine canal (NPC).

		NF diameter, mm (mean ± SD)	**IF diameter, mm (mean ± SD)**	**NPC length, mm (mean ± SD)**	**NPC diameter, mm (mean ± SD)**
Impacted tooth–NPC relationship	**Absence**	2.62 ± 1.44	2.92 ± 0.87	9.46 ± 2.73	2.68 ± 1.18
	Presence	2.6 ± 1.24	3.29 ± 1.05	9.66 ± 2.57	2.56 ± 1.11
	p value	0.730	0.004*	0.719	0.356

IF — incisive foramen; NF — nasopalatine foramen; SD — standard deviation.

DISCUSSION

According to the findings of this study, changes in NPC morphology were observed in the presence of an impacted tooth in the anterior maxillary region, and the null hypothesis was rejected. Although many studies have examined anatomical variations and morphology of the NPC [8, 28, 29], to the best of our knowledge, no other study has comprehensively evaluated the anatomical variations, morphological features, and dimensions of the NPC in the presence of impacted teeth.

The NPC has been studied using various imaging methods. Güncü et al. [12], Tözüm et al. [31], and Mardinger et al. [20] evaluated the NPC using computed tomography (CT); Song et al. [28] used micro-CT; and Bornstein et al. [6] used CBCT. Although traditional imaging methods used in dentistry have relatively low radiation doses, they are not sufficiently reliable for surgical planning because anatomical structures are evaluated only in two dimensions [14]. In contrast, CBCT is considered one of the most suitable methods for evaluating the dentomaxillofacial region because it offers a lower radiation dose and lower cost than conventional CT [14]. In addition, no significant difference has been reported between linear measurements obtained from CBCT and direct measurements taken from the craniofacial region [24]. In the current study, the NPC was assessed in three planes using CBCT, which has been reported to provide accurate and reliable results in examination of the dentomaxillofacial region [30].

Although various classifications have been proposed for the morphological characteristics of the NPC, there is no commonly accepted standard classification system in the literature, and morphology is classified and named separately in each of the three imaging planes. In the present study, the NPC was classified as round, oval, or other at the IF, middle, and NF levels on axial sections. In the literature, the most frequently observed axial NPC shape is round, followed by heart-shaped and oval forms [1, 11]. In addition, Bahşi et al. [4] examined NPC morphology at the IF, middle, and NF levels, as in the present study, and found the round shape to be most frequent at all three levels, consistent with our study. However, in the present study, the round form was followed by oval and other forms. These differences between studies may have arisen from differences in the axial classification systems used.

In the present study, the shape of the NPC was classified as single-channel, double-channel, or Y-shaped on coronal sections, while the external border of the NPC was classified as V-shaped, Y-shaped, U-shaped, or reverse V-shaped. Bornstein et al. [6], Etoz et al. [8], Gönül et al. [11], and Tercanlı et al. [29] most frequently observed a single-channel structure on coronal sections, while Fernández-Alonso et al. [9], Jornet et al. [19], and Bahşi et al. [4] reported that the most common morphological type was a Y-shaped canal. Furthermore, while Bahşi et al. [4] stated that the most common coronal external border was V-shaped, most external borders were U-shaped in the present study. These differences may be due to differences in sample size or the ethnic composition of the study populations.

In the present study, the NPC was classified as hourglass-shaped, cone-shaped, funnel-shaped, banana-shaped, cylindrical, inverted cone-shaped, or tree-branch on sagittal sections, and its course was classified as vertically straight, vertically curved, slanted straight, or slanted curved. Mardinger et al. [20], Liang et al. [18], Bahşi et al. [4], Fernández-Alonso et al. [9], and Gönül et al. [11] reported a cylindrical form as the most common sagittal NPC morphology, consistent with the present study. In contrast, Etoz et al. [8] reported an hourglass shape as the most common, while Hakbilen and Magat [13] reported a conical shape. According to Gönül et al. [11], the most common course of the NPC was vertically curved, while Tercanlı et al. [29] found it to be slanted straight. In the present study, a vertically straight course was most frequently identified. Differences between our findings and those in the literature may primarily reflect differences in the demographic characteristics of the study populations, including age, sex, and ethnicity. Anatomical variation between populations may affect NPC morphology. In addition, differences in imaging methods, device resolution, slice thickness, and evaluation criteria may also affect the results.

Studies directly examining the relationship between impacted teeth in the anterior maxillary region and NPC morphology are limited. Only one study conducted in Türkiye on this subject was identified [2]. In that study, the relationship of impacted maxillary canines with the maxillary sinus, NPC, and palatal cortical bone was evaluated, and NPC shape was examined on coronal and sagittal sections, while axial shape

was not considered [2]. Overall, 42.8% of impacted canines were associated with the NPC, and a significant relationship was reported only between coronal NPC shape and right impacted canines [2]. In the current study, all impacted teeth in the anterior maxillary region, not only impacted canines, were evaluated, and both NPC morphology and dimensions were examined. The rate of impacted teeth associated with the NPC was 50.4%. This rate indicates a high probability that impacted teeth in the anterior maxillary region have a close anatomical relationship with the NPC. The fact that this relationship was most frequently observed at the crestal level and that mesioangular impacted teeth were more frequently associated with the NPC than teeth in other positions draws attention to the risk of NPC injury, especially during surgical procedures. Furthermore, while no significant difference was observed between coronal and sagittal NPC shapes and the presence of associated impacted teeth, significant differences were found in NPC shape at all three axial levels. Similarly, significant differences were observed in the coronal external border shape and sagittal course of the NPC according to the relationship with impacted teeth. Unlike the limited number of similar studies in the literature [2], the present study evaluated NPC morphology in all three planes and its anatomical relationship with all impacted teeth in the anterior maxillary region. The data suggest that pressure changes in the surrounding bone during the development or positioning of impacted teeth may lead to adaptive morphological changes in NPC shape, diameter, and course.

Mardinger et al. [20] suggested that the NPC is not a static structure and can undergo dimensional changes in response to factors such as age and tooth extraction, and that canal diameter can increase after tooth extraction. The IF diameter of the NPC is generally estimated to be less than 6 mm, and pathological formations should be considered if it exceeds 10 mm [22]. In the literature, the average IF width has been reported to range between 1.75 and 10.90 mm [1, 10, 13, 27]. Different anatomical factors that can affect NPC dimensions have also been reported. Bornstein et al. [6] and Güncü et al. [12] reported that the absence of maxillary anterior teeth is associated with decreased buccal bone plate thickness and NPC length. In the present study, the presence of an anterior impacted tooth associated with the NPC did not affect NPC length, NF diameter, or NPC diameter; however, the IF diameter was significantly greater in individuals with an impacted tooth associated with the NPC than in those without such an association.

The lack of imaging modalities other than CBCT in the present study can be considered a limitation. Evaluating the same patient group with different devices could be useful for observing how device characteristics affect the results. However, the use of a single CBCT device was advantageous in ensuring standardization and preventing unnecessary radiation exposure. In addition, failure to record the laterality of impacted teeth can also be considered a limitation. Considering that several variables affect NPC anatomy, future studies focusing solely on tooth status while keeping other variables constant may provide clearer information about the effect of tooth status on the NPC and surrounding tissues.

Cone-beam computed tomography is an indispensable imaging modality for detailed evaluation of the NPC. By providing three-dimensional visualization of the relationship between impacted teeth and surrounding anatomical structures, CBCT allows more comprehensive preoperative planning and risk assessment. The present study demonstrated that the presence of impacted teeth in the anterior maxillary region may lead to alterations in the morphological and dimensional characteristics of the NPC. These findings provide clinicians with valuable anatomical information during surgical planning. Consequently, the results highlight the importance of considering such anatomical variations in preoperative assessments to enhance surgical safety and optimize treatment outcomes.

ARTICLE INFORMATION AND DECLARATIONS

Data availability statement

The data generated and analyzed in this study are available within the manuscript. Additional information can be obtained from the corresponding author upon reasonable request.

Ethics statement

The study was conducted at the Faculty of Dentistry, Akdeniz University, Antalya, Türkiye, and was approved by the Clinical Research Ethics Committee of Akdeniz University (protocol no. TBAEK-587).

Role of artificial intelligence in creating content
Artificial intelligence was not used in creating content.

Author contributions
RSG and HT designed the study. RSG and SCD performed the research. HT analyzed the data and reviewed and edited the paper. All authors wrote the manuscript, contributed to its revision, and read and approved the final manuscript.

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None.

Conflict of interest
The authors declare no conflict of interest.

Supplementary material
None.

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