

Root Canal Morphology of Premolars in Population of Hyderabad, Pakistan: A Cone Beam Computerised Tomographic Analysis

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ABSTRACT

Objective: To investigate the mean tooth length and root canal configuration of human maxillary and mandibular premolars in the population of Hyderabad, Pakistan, using Cone Beam Computed Tomography (CBCT).

Study Design: Observational study.

Place and Duration of the Study: Department of Operative Dentistry and Endodontics, Liaquat University of Medical and Health Sciences, Jamshoro, Sindh, Pakistan, from December 2022 to March 2023.

Methodology: Using retrospective analysis of CBCT scans, tooth length, the number of roots, and root canal configuration of 536 mandibular and maxillary premolars were assessed in the subpopulation of Pakistan. The data were analysed employing descriptive statistics, Chi-square tests, and One-Way ANOVA to determine the association between various factors and root canal morphology.

Results: Vertucci Type 1 (one canal) was the most common configuration in maxillary premolars, with frequencies ranging from 46.3 to 52.2%. The mean length of all 8 premolars ranged from 20.56 mm to 21.58 mm. C-shaped canal configurations were observed in a small percentage of maxillary and mandibular premolars, with C1 being the most common. No significant association was found between gender and canal configuration or tooth length, and in tooth lengths among different canal configurations.

Conclusion: Vertucci Type 1 was the most common configuration in maxillary premolars, followed by Vertucci Type 4. Single-rooted premolars were more prevalent, while two-root configurations were less common. C-shaped canal configurations were observed in a small percentage of premolars, with higher frequency in mandibular premolars.

Key Words: Cone beam computed tomography, Dental anatomy, Endodontics, Premolars, Root canal morphology.

How to cite this article: Suresh S, Kalhoro FA, Rani P, Memon M. Root Canal Morphology of Premolars in Population of Hyderabad, Pakistan: A Cone Beam Computerised Tomographic Analysis. *J Coll Physicians Surg Pak* 2024; **34(10)**:1238-1244.

INTRODUCTION

Understanding root canal morphology is essential for successful endodontic therapy.¹ Vertucci's classification has been developed to aid clinicians in navigating the complexities of root canal anatomy.²

Cone beam computed tomography (CBCT) has significantly enhanced the comprehensive understanding of root canal anatomy.³ The majority of maxillary first premolars in Pakistani adults displayed two roots (88.7%), while most of the second premolars (78%) presented with a single root. In terms of 1st and 2nd premolars, most of the 1st premolars (55.3%) exhibited a Vertucci Type IV structure, whereas most of the 2nd premolars (66.8%) displayed a Vertucci Type I configuration.⁴

It has been observed that the prevalence of premolars with root canal anomalies varies significantly among demographics, particularly in relation to age.⁵

The investigation of root canal morphologies and configurations remains limited in Asian contexts, particularly in Pakistan.^{6,7} However, by employing CBCT, dentists can efficiently gain insights into the anatomical profiles of a target tooth while simultaneously conserving time and financial resources as well as reducing health risks.⁸

Establishing a correlation between gender, tooth type, and root canal anatomy can aid dentists in anticipating and addressing root canal anatomy. Consequently, the objective of this study was to determine the mean tooth length and root canal configuration of human premolars in the population of Hyderabad, Pakistan, by using CBCT.

By addressing the knowledge gap in root canal morphology, this study aimed to contribute to the improvement of endodontic treatment outcomes by anticipating the canal configuration in routine endodontic cases and the development of more targeted and effective dental care practices in the region.

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Received: August 07, 2023; Revised: April 09, 2023;

Accepted: April 30, 2024

DOI: <https://doi.org/10.29271/jcpsp.2024.10.1238>

METHODOLOGY

This cross-sectional descriptive study was conducted at the Department of Operative Dentistry and Endodontics at the Institute of Dentistry, Liaquat University of Medical and Health Sciences, from December 2022 to March 2023. The study was approved by the Ethical Review Board of the University (Letter No: LUMHS/REC/-143, Dated: 29-09-2022).

A sample size of 73 was calculated using OpenEpi, based on previous literature⁴ on canal configuration of first premolars in the Pakistani subpopulation. Simple random sampling was employed, and both genders were included in the study. Exclusion criteria included root resorption, calcification or periapical lesions, root canal fillings, posts or crown restorations, and blurred or incomplete views of the relevant teeth.

CBCT scans of patients referred to the Advanced Dental Care Center (ADCC) were used for data collection. The CBCT scans had been performed as a part of the patients' treatment planning at ADCC. Scans were conducted with teeth positioned in the volume at intervals of 0.2 mm. The volume was then reconstructed using slices perpendicular to the alveolar process's horizontal axis. CBCT images were analysed with a resolution setting of 1366 x 768 pixels. The analysis was performed in complete darkness on a Dell Inspiron laptop with a 15.6" LCD screen. The brightness and contrast of the CBCT images were adjusted to optimise viewing. The axial, coronal, and sagittal views of each tooth were examined to assess morphology.

The study recorded data on tooth length, the number of roots, and the root canal configuration of mandibular and maxillary premolars. Tooth length was measured using the scale parameter, from the buccal cusp tip to the apex of the tooth in mandibular premolars, and from the palatal cusp tip to the apex of the tooth in maxillary premolars, in millimetres (Figure 1). The number of roots was evaluated in the axial plane and classified as single root, multi root, and three-rooted teeth.⁹ The study also identified teeth with C-shaped root canals as C1, C2, and C3.¹⁰ Root canal configurations were categorised according to Vertucci's classification.²

Statistical analysis was performed using SPSS 21.0 software (SPSS, Inc., Chicago, IL, USA). Descriptive statistics were used to describe the number of roots and root canals, as well as the detection of different root canal morphology. The Chi-square test was used to determine the association between Vertucci classification and gender and means, standard deviations, and coefficients of variation for all variables were calculated for each tooth based on gender.

RESULTS

Sixty-seven out of 100 scans met the inclusion criteria, encompassing 536 premolars. There were 53.7% (n = 36) males and 46.3% (n = 31) females, with an age range of 15-68 years and a mean age of 29.60 ± 11.087 years. Intraexaminer reliability Kappa values ranged from 0.89 to 0.94 for canal configurations and 0.80 to 0.87 for the presence of C-shaped canals.

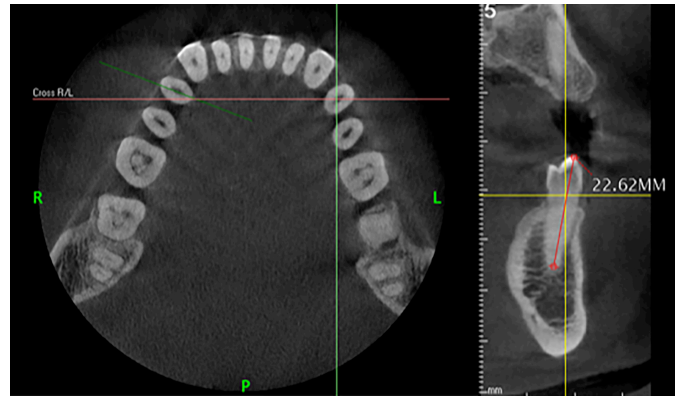


Figure 1: Measuring the length of premolar in CBCT.

Vertucci Type 1 was the most common configuration followed by Vertucci Type 4 (Table I). No significant difference in mean length was observed between the 1st and 2nd premolars in the same quadrant of the jaw (Table II). The number of roots in all premolars showed that a two-root configuration is less common; (Table III) (PI write all tables numbers in brackets to easily understand by busy readers). C-shaped canal configurations were observed in a small percentage of maxillary and mandibular premolars (Table IV).

There was a significant association between gender and tooth length for some premolars, with a weakly positive relationship overall. A weak negative relationship was observed between gender and tooth length due to the non-linear nature of the relationship (Table II).

DISCUSSION

Understanding the prevalence of different canal configurations provides crucial guidance for clinicians when planning endodontic treatments. The prevalence of different Vertucci classifications can be attributed to genetic variations and ethnic factors. Ethnic and genetic factors likely contribute to the observed variations in root canal morphology in the population. These factors can impact treatment planning, complexity, and predictability. While the current study sheds light on these influences, further research is necessary to unravel the genetic underpinnings and ethnic correlations more comprehensively. A deeper understanding of these influences has the potential to revolutionise personalised endodontic care, leading to improved treatment outcomes and enhanced patient management.

The absence of significant differences in mean length between the 1st and 2nd premolars in the same quadrant suggests that tooth length may not vary significantly within a quadrant. However, it is important to note that tooth length can vary among individuals, and other factors such as age, parafunctional habits, and ethnicity can also influence tooth length. The prevalence of C-shaped canals can be influenced by genetic factors and ethnic variations. C-shaped canals pose challenges in endodontic treatment due to their complex anatomy and dental practitioners should be aware of their presence to ensure thorough cleaning and shaping of the root canal system.

Table I: Distribution of Vertucci Class with respect to gender.

Maxilla			Gender		Total	Chi-square value	Asymp. Sig. (2-sided)				
Vertucci			Male	Female							
Right 1 st premolar	1	Count (%Total)	21 (31.3%)	13 (19.4%)	34 (50.7%)	5.211	0.391				
	2	Count (%Total)	3 (4.5%)	4 (6.0%)	7 (10.4%)						
	3	Count (%Total)	1 (1.5%)	3 (4.5%)	4 (6.0%)						
	4	Count (%Total)	10 (14.9%)	7 (10.4%)	17 (25.4%)						
	5	Count (%Total)	1 (1.5%)	3 (4.5%)	4 (6.0%)						
	8	Count (%Total)	0 (0.0%)	1 (1.5%)	1 (1.5%)						
	Total	Count (%Total)	36 (53.7%)	31 (46.3%)	67 (100.0%)						
			Gender						6.216	0.184	
Right 2 nd premolar	1	Count (%Total)	19 (28.4%)	12 (17.9%)	31 (46.3%)	6.025	0.304				
	2	Count (%Total)	2 (3.0%)	4 (6.0%)	6 (9.0%)						
	3	Count (%Total)	7 (10.4%)	10 (14.9%)	17 (25.4%)						
	4	Count (%Total)	7 (10.4%)	2 (3.0%)	9 (13.4%)						
	5	Count (%Total)	1 (1.5%)	3 (4.5%)	4 (6.0%)						
	Total	Count (%Total)	36 (53.7%)	31 (46.3%)	67 (100.0%)						
			Gender						6.108	0.191	
	Left 1 st premolar	1	Count (%Total)	22 (32.8%)	13 (19.4%)			35 (52.2%)	6.108	0.191	
2		Count (%Total)	3 (4.5%)	3 (4.5%)	6 (9.0%)						
3		Count (%Total)	1 (1.5%)	4 (6.0%)	5 (7.5%)						
4		Count (%Total)	9 (13.4%)	7 (10.4%)	16 (23.9%)						
5		Count (%Total)	1 (1.5%)	3 (4.5%)	4 (6.0%)						
8		Count (%Total)	0 (0.0%)	1 (1.5%)	1 (1.5%)						
Total		Count (%Total)	36 (53.7%)	31 (46.3%)	67 (100.0%)						
			Gender				6.108	0.191			
Left 2 nd premolar	1	Count (%Total)	19 (28.4%)	12 (17.9%)	31 (46.3%)	6.108	0.191				
	2	Count (%Total)	2 (3.0%)	3 (4.5%)	5 (7.5%)						
	3	Count (%Total)	7 (10.4%)	11 (16.4%)	18 (26.9%)						
	4	Count (%Total)	7 (10.4%)	2 (3.0%)	9 (13.4%)						
	5	Count (%Total)	1 (1.5%)	3 (4.5%)	4 (6.0%)						
	Total	Count (%Total)	36 (53.7%)	31 (46.3%)	67 (100.0%)						
			Gender						3.208	0.361	
	Mandible										
Left 1 st premolar		1	Count (%Total)	24 (35.8%)	20 (29.9%)	44 (65.7%)	3.208	0.361			
		3	Count (%Total)	0 (0.0%)	2 (3.0%)	2 (3.0%)					
		4	Count (%Total)	1 (1.5%)	0 (0.0%)	1 (1.5%)					
		5	Count (%Total)	11 (16.4%)	9 (13.4%)	20 (29.9%)					
		Total	Count (%Total)	36 (53.7%)	31 (46.3%)	67 (100.0%)					
				Gender						4.940	0.176
		Left 2 nd premolar	1	Count (%Total)	36 (53.7%)	27 (40.3%)			63 (94.0%)	4.940	0.176
	3		Count (%Total)	0 (0.0%)	1 (1.5%)	1 (1.5%)					
5	Count (%Total)		0 (0.0%)	2 (3.0%)	2 (3.0%)						
8	Count (%Total)		0 (0.0%)	1 (1.5%)	1 (1.5%)						
Total	Count (%Total)		36 (53.7%)	31 (46.3%)	67 (100.0%)						
			Gender				7.245	0.64			
Right 1 st premolar	1		Count (%Total)	28 (41.8%)	17 (25.4%)	45 (67.2%)	7.245	0.64			
	3		Count (%Total)	0 (0.0%)	3 (4.5%)	3 (4.5%)					
	4	Count (%Total)	1 (1.5%)	0 (0.0%)	1 (1.5%)						
	5	Count (%Total)	7 (10.4%)	11 (16.4%)	18 (26.9%)						
	Total	Count (%Total)	36 (53.7%)	31 (46.3%)	67 (100.0%)						
			Gender						2.394	0.302	
	Right 2 nd premolar	1	Count (%Total)	36 (53.7%)	29 (43.3%)	65 (97.0%)			2.394	0.302	
		3	Count (%Total)	0 (0.0%)	1 (1.5%)	1 (1.5%)					
8		Count (%Total)	0 (0.0%)	1 (1.5%)	1 (1.5%)						
Total		Count (%Total)	36 (53.7%)	31 (46.3%)	67 (100.0%)						
			Gender								

Table II: Mean length with respect to gender.

Maxilla		Gender	Mean length (mm)	Standard deviation	Minimum (mm)	Maximum (mm)
Premolar						
Right 1 st premolar	Male	21.00	2.10	16.40	26.07	
	Female	20.59	1.29	18.06	22.70	
Right 2 nd premolar	Male	20.85	1.96	17.42	25.02	
	Female	20.23	1.50	16.62	24.45	
Left 1 st premolar	Male	21.26	1.86	16.17	26.18	
	Female	20.40	1.60	17.02	24.45	
Left 2 nd premolar	Male	21.19	1.85	16.32	24.44	
	Female	20.52	1.50	18.44	24.84	
Mandible						
Left 1 st premolar	Male	21.60	1.87	17.27	24.87	
	Female	20.87	1.55	18.15	25.86	
Left 2 nd premolar	Male	21.65	1.95	17.31	25.55	
	Female	21.10	1.83	17.65	24.62	
Right 1 st premolar	Male	21.36	1.70	17.50	26.01	
	Female	20.62	1.93	16.86	24.62	
Right 2 nd Premolar	Male	21.94	1.84	17.50	25.18	
	Female	21.17	1.58	18.75	23.94	

Table III: Distribution of number of roots with respect to gender.

Maxilla			Gender		Total	Chi-square value	Asymp. Sig. (2-sided)
			Male	Female			
Right 1 st premolar	1	Count	18 (26.9%)	16 (23.9%)	34 (50.7%)	0.874	0.646
		(%Total)					
	2	Count	17 (25.4%)	15 (22.4%)	32 (47.8%)		
	3	Count	1 (1.5%)	0 (0.0%)	1 (1.5%)		
		(%Total)					
Total	Count	36 (53.7%)	31 (46.3%)	67 (100.0%)	0.774	0.379	
	(%Total)						
Gender					Total		
Right 2 nd premolar	1	Count	33 (49.3%)	30 (44.8%)	63 (94.0%)	1.910	0.385
		(%Total)					
	2	Count	3 (4.5%)	1 (1.5%)	4 (6.0%)		
	3	Count	0 (0.0%)	0 (0.0%)	0 (0.0%)		
		(%Total)					
Total	Count	36 (53.7%)	31 (46.3%)	67 (100.0%)	1.500	0.221	
	(%Total)						
Gender					Total		
Left 1 st premolar	1	Count	16 (23.9%)	16 (23.9%)	32 (47.8%)	1.500	0.221
		(%Total)					
	2	Count	18 (26.9%)	15 (22.4%)	33 (49.3%)		
	3	Count	2 (3.0%)	0 (0.0%)	2 (3.0%)		
		(%Total)					
Total	Count	36 (53.7%)	31 (46.3%)	67 (100.0%)	1.500	0.221	
	(%Total)						
Gender					Total		
Left 2 nd premolar	1	Count	32 (47.8%)	30 (44.8%)	62 (92.5%)	0.211	0.646
		(%Total)					
	2	Count	4 (6.0%)	1 (1.5%)	5 (7.5%)		
	3	Count	0 (0.0%)	0 (0.0%)	0 (0.0%)		
		(%Total)					
Total	Count	36 (53.7%)	31 (46.3%)	67 (100.0%)	0.211	0.646	
	(%Total)						
Gender					Total		
Mandible							
Left 1 st premolar	1	Count	34 (50.7%)	30 (44.8%)	64 (95.5%)	0.874	0.350
		(%Total)					
	2	Count	2 (3.0%)	1 (1.5%)	3 (4.5%)		
	3	Count	0 (0.0%)	0 (0.0%)	0 (0.0%)		
		(%Total)					
Total	Count	36 (53.7%)	31 (46.3%)	67 (100.0%)	0.874	0.350	
	(%Total)						
Gender					Total		
Left 2 nd premolar	1	Count	36 (53.7%)	31 (46.3%)	67 (100.0%)	Not Applicable	Not Applicable
		(%Total)					
	2	Count	0 (0.0%)	0 (0.0%)	0 (0.0%)		
	3	Count	0 (0.0%)	0 (0.0%)	0 (0.0%)		
		(%Total)					
Total	Count	36 (53.7%)	31 (46.3%)	67 (100.0%)	0.874	0.350	
	(%Total)						
Gender					Total		
Right 1 st premolar	1	Count	35 (52.2%)	31 (46.3%)	66 (98.5%)	Not Applicable	Not Applicable
		(%Total)					
	2	Count	1 (1.5%)	0 (0.0%)	1 (1.5%)		
	3	Count	0 (0.0%)	0 (0.0%)	0 (0.0%)		
		(%Total)					
Total	Count	36 (53.7%)	31 (46.3%)	67 (100.0%)	Not Applicable	Not Applicable	
	(%Total)						
Gender					Total		
Right 2 nd premolar	1	Count	36 (53.7%)	31 (46.3%)	67 (100.0%)	Not Applicable	Not Applicable
		(%Total)					
	2	Count	0 (0.0%)	0 (0.0%)	0 (0.0%)		
	3	Count	0 (0.0%)	0 (0.0%)	0 (0.0%)		
		(%Total)					
Total	Count	36 (53.7%)	31 (46.3%)	67 (100.0%)	Not Applicable	Not Applicable	
	(%Total)						
Gender					Total		

An analysis revealed a notable correlation between gender and the length of certain premolars, indicating an overall trend towards a slightly positive association. This means that, on average, males had slightly longer premolars than females. However, a weak negative relationship was observed due to the non-linear nature of the relationship. It is important to note that the observed associations between gender and tooth length were weak and may not have significant clinical implications.

The morphology of root canals, including the number, size, and location of canals within teeth and across populations, has been the focus of numerous studies. For instance, a study conducted on North Indians¹¹ revealed that Type IV, I, II, and III canal morphologies were more prevalent in maxillary first premolars, with the single root form being the most common. In contrast, permanent maxillary first premolars in Yemeni

population¹² predominantly exhibit single-rooted structures and Vertucci Type II canal morphology, whereas those in Turkiye¹³ are primarily bi-rooted and exhibit Type III canal morphology. In a comparison of the present study with those conducted on Thai,¹⁴ Malaysian,¹⁵ Indian,¹⁶ and Chinese^{17,18} populations, several variations have been observed. The investigation into the Thai population revealed that Vertucci Type 1 stands out as the most prevalent canal configuration, particularly in single-rooted premolars. Similarly, mandibular premolars exhibited a higher incidence of C-shaped canals, while no significant correlation between gender and canal configuration was noted, except for a mild association in mandibular left 1st premolars in the present study. The results align with a study on the Malaysian population, emphasising the predominance of single-rooted premolars and the prevalence of Vertucci Type 1 configuration.

Table IV: Distribution of c-shaped canals with respect to gender.

Maxilla			Gender		Total	Chi-square value	Asymp. Sig. (2-sided)
			Male	Female			
Right 1 st premolar	No C-Shaped Canal	Count (%Total)	36 (53.7%)	29 (43.3%)	65 (97.0%)	2.394	0.302
	C2	Count (%Total)	0 (0.0%)	1 (1.5%)	1 (1.5%)		
	C3	Count (%Total)	0 (0.0%)	1 (1.5%)	1 (1.5%)		
	Total	Count (%Total)	36 (53.7%)	31 (46.3%)	67 (100.0%)		
			Gender		Total	0.874	0.350
Right 2 nd premolar	No C-Shaped Canal	Count (%Total)	35 (52.2%)	31 (46.3%)	66 (98.5%)	1.196	0.550
	C1	Count (%Total)	1 (1.5%)	0 (0.0%)	1 (1.5%)		
	Total	Count (%Total)	36 (53.7%)	31 (46.3%)	67 (100.0%)		
				Gender			
Left 1 st premolar	No C-Shaped Canal	Count (%Total)	35 (52.2%)	29 (43.3%)	64 (95.5%)	1.775	0.183
	C2	Count (%Total)	1 (1.5%)	1 (1.5%)	2 (3.0%)		
	C3	Count (%Total)	0 (0.0%)	1 (1.5%)	1 (1.5%)		
	Total	Count (%Total)	36 (53.7%)	31 (46.3%)	67 (100.0%)		
			Gender		Total	1.418	0.701
Right 1 st premolar	No C-Shaped Canal	Count (%Total)	34 (50.7%)	31 (46.3%)	65 (97.0%)	1.418	0.701
	C1	Count (%Total)	2 (3.0%)	0 (0.0%)	2 (3.0%)		
	Total	Count (%Total)	36 (53.7%)	31 (46.3%)	67 (100.0%)		
				Gender			
Mandible	No C-Shaped Canal	Count (%Total)	26 (38.8%)	23 (34.3%)	49 (73.1%)	0.874	0.350
	C1	Count (%Total)	1 (1.5%)	1 (1.5%)	2 (3.0%)		
	C2	Count (%Total)	0 (0.0%)	1 (1.5%)	1 (1.5%)		
	C3	Count (%Total)	9 (13.4%)	6 (9.0%)	15 (22.4%)		
	Total	Count (%Total)	36 (53.7%)	31 (46.3%)	67 (100.0%)		
				Gender			
Left 2 nd premolar	No C-Shaped Canal	Count (%Total)	35 (52.2%)	31 (46.3%)	66 (98.5%)	2.287	0.515
	C1	Count (%Total)	1 (1.5%)	0 (0.0%)	1 (1.5%)		
	Total	Count (%Total)	36 (53.7%)	31 (46.3%)	67 (100.0%)		
				Gender			
Right 1 st premolar	No C-Shaped Canal	Count (%Total)	31 (47.0%)	22 (33.3%)	53 (80.3%)	0.874	0.350
	C1	Count (%Total)	1 (1.5%)	1 (1.5%)	2 (3.0%)		
	C2	Count (%Total)	2 (3.0%)	2 (3.0%)	4 (6.1%)		
	C3	Count (%Total)	2 (3.0%)	5 (7.6%)	7 (10.6%)		
	Total	Count (%Total)	36 (54.5%)	30 (45.5%)	66 (100.0%)		
				Gender			
Right 2 nd premolar	No C-Shaped Canal	Count (%Total)	35 (52.2%)	31 (46.3%)	66 (98.5%)	0.874	0.350
	C1	Count (%Total)	1 (1.5%)	0 (0.0%)	1 (1.5%)		
	Total	Count (%Total)	36 (53.7%)	31 (46.3%)	67 (100.0%)		
				Gender			

Both studies identified C-shaped canal configurations, with mandibular premolars displaying a higher frequency compared to maxillary premolars. Moreover, gender did not show a significant association with canal configuration in either study. When compared to the Indian population, this study contrasts in terms of the most prevalent canal configurations,

with Type II and Type IV being predominant in India, while Vertucci Type 1 emerged as the most common configuration in this study. The average tooth length in the Indian population was 21.5 mm. In the Chinese population study, maxillary first premolars predominantly exhibited single roots and two root canals, with various Vertucci types, while

mandibular first premolars were mostly single-rooted with Vertucci's Type I configuration.¹⁸

In a divergence from prior findings, the present investigation delineated Vertucci Type 1 configuration to be predominant in maxillary premolars. Subsequently, Vertucci Type IV emerged as the configuration with the second-highest occurrence. The Chinese study reported a higher prevalence of C-shaped canals in mandibular first premolars (3%),¹⁷ compared to this study, which found a small percentage of C-shaped canals in both maxillary and mandibular premolars. These variations among studies may be attributed to factors such as genetic differences, environmental factors, sample size and selection, methodological disparities, observer bias, and intra-examiner variability. Recognising these factors is crucial for researchers to interpret findings accurately and identify potential areas for further investigation. It is imperative to account for these variations when comparing studies and extrapolating their findings to clinical practice.

CONCLUSION

Vertucci Type 1 was the most common configuration in maxillary premolars, followed by Vertucci Type IV. Single-rooted premolars were more prevalent, while two-root configurations were less common. C-shaped canal configurations were observed in a small percentage of premolars, with higher frequency in mandibular premolars. There was no significant association between gender and canal configuration, except for a weak association in mandibular left 1st premolars. Tooth length showed consistent measurements within each tooth type and quadrant, with no significant differences between the 1st and 2nd premolars. Tooth length did not significantly predict canal configuration or complexity.

ETHICAL APPROVAL:

The study was approved by the Ethical Review Board of the LUMHS University, vide Letter No. LUMHS/REC/-143, Dated: 29-09-2022.

PATIENTS' CONSENT:

At the time of their Cone Beam Computed Tomography (CBCT) capture, all patients provided informed consent for the use of their CBCT records for research purposes.

COMPETING INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

SS: Design of work, data analysis, and interpretation of the data.

FAK: Data analysis and critical revision.

PR: Data acquisition and data interpretation.

MM: Critical revision and drafting of the manuscript.

All authors approved the final version of the manuscript to be published.

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