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# Gender differences in maxillary and mandibular morphology among the Jordanian population: Implications for orthodontic treatment and ai applications in dentistry

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Abstract: Gender differences in maxillary and mandibular morphology are important for orthodontics, surgery, and forensic identification. Cone-Beam Computed Tomography (CBCT) and Artificial Intelligence (AI) enhance diagnostic precision and efficiency, but AI adoption presents challenges such as data privacy and algorithmic bias. This study investigates gender-based differences in the morphometric features of the maxilla and mandible in Jordanian adults using Cone-Beam Computed Tomography (CBCT) and explores the potential of Artificial Intelligence (AI) in enhancing diagnostics and treatment planning. A retrospective study analyzed 100 CBCT images of Jordanian adults (20-45 years) from medical imaging centers (Sept 2023-Feb 2024). Carestream 3D software was used for image analysis by two researchers. Gender and lateralization differences were examined, along with jaw arch length and intercanine distance. Males exhibited significantly larger maxillary and mandibular dimensions compared to females, particularly in arch lengths and sinus dimensions (p < 0.05), and maxillary and mandibular arch lengths showed the greatest variations. Arch shape analysis revealed that round and U-shaped patterns were more common, with notable gender-specific variations. The findings confirm significant gender-related morphometric differences among Jordanians in jaw anatomy, supporting their relevance in orthodontic planning, forensic identification, and craniofacial analysis. Understanding these anatomical variations enhances personalized dental care. Integrating AI with CBCT imaging can improve landmark detection, treatment customization, and diagnostic precision, contributing to efficient, patient-centered dental interventions.

Keywords: Bone Age, Chronology, Cone beam computed tomography, Maxilla, Mandible.

# 1. Introduction

Facial and cranial bone development provides valuable data about the chronology and the variations that can be identified between males and females at different ages. The mandible and maxilla are key facial bones that develop from the first pharyngeal arch, and play an important role in the development of the face, especially the oral, nasal, and orbital cavities. The Maxilla bone is a paired bone that accommodates the largest paranasal sinus and it has the alveolar arch which carries the upper teeth in children and adults. The mandible is a single facial bone that is movable and forms the temporomandibular joint and it has the alveolar arch which carries the lower teeth in children and adults [1-3]. Jaw bones have several surface anatomical and morphometric features that are key

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landmarks for several medical and dental clinical interventions and applications [4, 5] including forensic, legal, and surgical applications (Table 1) [6-10]. Identifying and understanding the relationship between these features in males and females is an important prerequisite for diagnosing, planning, and designing medical and dental surgical interventions [4, 5]. Successful medical and dental surgical interventions involving the maxilla and mandible including maxillofacial surgeries are commonly performed based on sound knowledge of related anatomical and morphometric features and commonly reported variations.

Different imaging techniques were employed to study both bones such as plain x-ray, panoramic, and recently Cone-beam computed tomography (CBCT). CBCT is a medical imaging system that utilizes X-rays to build valuable volumetric three-dimensional tomography image sections using a conical X-ray beam and reciprocal image detector without bony superposition. Currently, it is widely employed in various applications in the fields of dentistry and medicine such as dental implants, orthodontic treatments, oral and maxillofacial surgery, and radiotherapy as it provides accurate and detailed 3D ultrastructure of three-dimensional over time [11, 12].

A recent paper exploring the shape of dental arches in Jordanian adults revealed that nearly half of the collected samples assume a Catenary arch shape in both jaw bones [13].

Several researchers have described the shape of the jaws as either a V-shape, U-shape, or square shape with different degrees [14].

Maxilla Landmark	Clinical significance		
	1. Connecting nasal and oral cavities		
Incisive foramen	2 .The incisive canal contains important nerves and arteries		
	3 .The prognosis of dental implants could be affected by the morphological changes in		
	incisive foramen and canal		
Maxillary tuberosity	It is mostly used as a graft to augment a deficient alveolar ridge or maxillary sinus before		
	or simultaneously with dental implant insertion.		
Alveolar arch	Fractures to the alveolar arch might lead to tooth loss or malocclusion		
The anterior part of the hard palate (the palatine process of the maxilla)	A partition between nasal and oral passages. Considered as a stable and clinically identifiable landmark for inserting palatal MIs.		
The alveolar process	Loss of this bony part largely affects the health of the periodontal ligament and leads to the progression of periodontal diseases.		
The infraorbital foramen	An infra-orbital nerve block is a procedure required to anesthetize the upper cheeks, lower eyelids, part of the nose, and some maxillary teeth.		
The inferior orbital fissure Considered an important landmark for endoscopic cranial base surgery			
Mandible Landmark	Clinical significance		
Angle of the mandible (Gonial angle)	Can be used as an important tool in forensics to determine age and gender		
Condylar & coronoid processes	Condylar fractures are more common than coronoid process fractures. Displacements and		
	mispositioning are common complications.		
Alveolar process	Subjected to resorption after teeth loss		
Mental foramen	Site for injecting anesthetics to lower incisors		
Mandibular foramen	Inferior alveolar nerve block		
Mandibular canal	Dental Implantology		
Alveolar process	Subjected to resorption after teeth loss		

 Table 1.

 Maxilla and Mandible landmarks and their clinical significance.

The Fourth Industrial Revolution has driven the widespread adoption of AI across various fields, including dentistry, where it aids in diagnostics, treatment planning, and disease prediction. By analyzing complex data, AI enhances patient engagement through chatbots, improves administrative efficiency, and supports accurate diagnoses, particularly in radiographic analysis. However, challenges such as data privacy, algorithm bias, and the risk of over-reliance by dentists in training must be addressed. While AI serves as an augmentative tool rather than a replacement for dentists, its ethical deployment and validation are essential. With proper integration, AI has the potential to make dentistry more precise, efficient, and accessible [15]. The future of AI in dentistry includes developing comprehensive care systems, better decision-making tools, and innovative research. Collaboration between clinicians, researchers, and engineers is crucial for AI's success in this field. Despite concerns over privacy and potential misinterpretations, AI's potential to improve patient care by sharing big data among healthcare providers and researchers is promising [16].

The purpose of this study is to investigate gender differences in the morphometric features of maxillary and mandibular bones in Jordanian subjects using Cone-beam computed tomography (CBCT) 3D images. By integrating artificial intelligence (AI) with CBCT imaging, the study aims to enhance the analysis and automation of identifying anatomical landmarks, improving diagnostic accuracy, and facilitating personalized treatment plans. Additionally, the study seeks to explore AI's potential in detecting bone structure variations, aiding in decision-making during surgical interventions, and addressing challenges related to gender and lateralization differences, ultimately improving precision and efficiency in dental diagnostics and treatment planning.

## 2. Materials and Methods

## 2.1. Study design

A relational retrospective study involving CBCT images of the maxilla and mandible was conducted between September 2023 and February 2024. Images were collected from the data repository of Jordanian medical imaging centers. Obtaining the subject's consent is part of the imaging center's policy for possible future use of any samples for research purposes. Ethical approval by the Hashemite University institutional review board (IRB) to waive the need for written informed consent (Appendix A). One hundred soft copies of anonymized images, coded randomly by numbers with gender and lateralization data were obtained. Initially, CBCT images were screened to meet the inclusion criteria of Adult male and female subjects of Jordanian nationality aged (20-45) years with no mandibular or maxillary deformity or malocclusions. Images of edentulous subjects or subjects with skeletal deformities such as cleft palate, acromegaly, surgical procedures, and V-shaped class II malocclusion were excluded as it might affect the measurements and observations.

Included CBCT mages were used to identify and measure mandibular and maxillary important features of both sides (Table 1 and Figure 1) using the Carestream 3D imaging software Images (New York, USA) by two experienced researchers after the intra and interobserver errors were assessed before data collection. Collected data were categorized based on gender and lateralization (i.e. right and left). In addition, the relationship between jaw arch length and the corresponding intercanine distance was calculated.



Figure 1.

CBCT measurements of Maxillary and Mandibular features. A: Intercanine length, B: Arch Length, C: Arch Length, D: Maxillary Sinus dimensions.

Data analysis: Descriptive statistics including mean, median, percentages, and ratios will be calculated and presented. Inferential statistics will be employed using the proper statistical test based on the normality of the data distribution. Statistical analysis will be performed using the SPSS software package 22, and an  $\alpha = 0.05$  will be used to determine significance (i.e., Type-I error). The Shapiro–Wilk test will be used to evaluate the normality distribution of measured data. The Mann–Whitney U test will be performed for non-normally distributed data while the student T-test for normally distributed data. The rater's reliability will be assessed with the aid of a statistician by performing repeated landmarks on groups at a two-month interval. Landmarks will be then evaluated for the same raters and a coefficient will be measured to determine how reliable are the measured landmarks. The validity of the research will be compared with already published results by other researchers.

# 3. Results

# 3.1. Gender Differences

The age group of participants (n = 100) was (20 - 45) years and the male/female ratio was 48:52. Data collected were analyzed using the SPSS software and descriptive statistics for <u>measurements</u> of maxillary and mandibular features for males and females were presented as tables (Table 2). Comparing maxillary and sinus measurements between males and females reveals that males generally have larger values in most parameters. The Maxillary Arch Length shows the most significant difference, with males measuring 123 mm compared to 70 mm in females. Other measurements, such as Maxillary Intercanine Length, Maxillary Symphysis Midline Length, and Maxillary Sinus Length (Right), are also slightly higher in males. However, Maxillary Sinus Width (Left) is slightly larger in females (Table 2).

These differences likely reflect natural anatomical variations between genders, which are expected in studies of maxillary and sinus structures. Comparing mandibular measurements between males and females shows that males have consistently larger values in all categories. Mandibular Arch Length (132.0 mm vs. 119.9 mm) and Ramus Length (74.3 mm vs. 52.9 mm) exhibit the most significant differences, while Symphysis Menti Length (42.3 mm vs. 29.2 mm) and Mandibular Intercanine Length (36.4 mm vs. 29.1 mm) also show notable variations (Table 2). These differences reflect natural anatomical variations between genders, with males generally having a larger and more developed mandibular structure. Statistical analysis reveals significant gender differences in maxillary and mandibular arch lengths (p = 0.000) and maxillary sinus dimensions, with males generally having larger structures. The Maxillary Sinus Width (Right) (p = 0.020) and Sinus Height (Right and Left) (p =0.018, 0.007) also show significant differences, suggesting gender-related variations in craniofacial development. However, Intercanine width in both the maxilla and mandible (p = 0.670, 0.384) does not significantly differ, indicating that this feature may be less influenced by gender. Similarly, Symphysis Menti Length (p = 0.184) and Ramus Length (p = 0.070) do not show significant variations (Table 2). These findings emphasize sexual dimorphism in maxillary and mandibular structures, which is valuable for forensic identification, orthodontic treatment, and craniofacial research  $\lceil 17, 18 \rceil$ .

#	Feature	Male (Mean ± SD)	Female (Mean± SD)	P value*
1	Maxillary Arch Length (mm)	$121.90 \pm 10.49$	$69.90 \pm 6.52$	0.000
$\mathcal{2}$	Maxillary Intercanine Length (mm)	$32.58 \pm 1.81$	$29.56 \pm 2.60$	0.000
3	Maxillary Symphysis Midline Length (mm)	$17.43 \pm 2.09$	$17.33 \pm 2.16$	0.818
4	Maxillary Sinus Width Right (mm)	$25.31 \pm 3.74$	$23.61 \pm 3.44$	0.020
5	Maxillary Sinus Width Left (mm)	$25.62 \pm 3.65$	$22.61 \pm 3.24$	0.000
6	Maxillary Sinus Height Right (mm)	$34.95 \pm 4.19$	$33.03 \pm 4.02$	0.022
7	Maxillary Sinus Height Left (mm)	$35.14 \pm 3.88$	$32.78 \pm 4.84$	0.008
8	Symphysis Menti Length (mm)	$26.80 \pm 4.05$	$25.06 \pm 3.53$	0.024
9	Mandibular Arch Length (mm)	$131.96 \pm 5.64$	$119.87 \pm 7.74$	0.000
10	Mandibular Intercanine (mm)	$26.40 \pm 2.85$	$24.73 \pm 2.32$	0.002
11	Mandibular Ramus Length (mm)	$62.79 \pm 6.02$	$52.89 \pm 5.91$	0.000
12	Maxillary Arch Length and Intercanine Ratio	$26.94 \pm 2.90$	$42.67 \pm 5.49$	0.000
13	Mandibular Arch Length and Intercanine Ratio	$20.03 \pm 2.26$	$20.69 \pm 2.04$	0.128

Magannomenta	of Mowillow	and Mandibula	Fastures
Measurements	of waxmary	and Manufoular	r eatures.

Table 2.

Note: \*: Significant at p values < 0.05. SD: Standard Deviation.

## 3.2. Gender Differences in Maxillary and Mandibular Arch Shape (Figures 3&4).

The analysis of maxillary arch shapes in females shows that the round shape is the most prevalent (62.0%), followed by the round square shape (20.0%). Less common shapes include the V shape (8.0%), square shape (6.0%), and U shape (4.0%), while the oval shape and oval square shape were not observed. These findings highlight anatomical variations that may be influenced by genetic and environmental factors and have significant implications for orthodontics and prosthetic dentistry, aiding in personalized treatment planning (Table 3).

Meanwhile, the analysis of the distribution of maxillary arch shapes among males shows that the most common arch shape is the round shape (38.0%), followed by the oval square shape (20.0%) and the oval shape (12.0%). Less frequent shapes include the V shape (10.0%), square shape (8.0%), round square shape (8.0%), and U shape (4.0%). These variations highlight differences in dental arch morphology among individuals. The findings can be useful in orthodontics and prosthetic dentistry, aiding in the selection of appropriate arch wires and dental prosthetics tailored to everyone's maxillary arch type (Table 3).

		Arch Shape Count						
Bone	Gender	V Shape	Oval Shape	Oval Square Shape	U Shape	Round Shape	Round Square Shape	Square Shape
Mandible	Female	21	0	0	24	0	0	5
wianuible	Male	8	0	0	35	0	0	7
Maxilla	Female	4	0	0	2	31	10	3
Waxiila	Male	5	6	10	2	19	4	4

 Table 3.

 Distribution of Maxillary and Mandibular Arch Shapes.

The analysis of the mandibular arch shapes among females showed that the U-shape is the most common, representing 48% of the sample, followed by the V-shape at 42%. In contrast, the square shape is the least common, accounting for only 10%. Notably, some shapes, including the oval shape, oval square shape, round shape, and round square shape, are absent from the data, indicating that they were either not observed or not recorded. Overall, the data suggest that the U-shape and V-shape are predominant among females, while other shapes are rare or non-existent in the sample (Table 3).

Table 3 also displays the distribution of lower jaw (mandible) shapes among males, with the U-shape being the most common, representing 70% of the sample. This is followed by the V-shape at 16%, and the square shape at 14%. No data were recorded for other shapes, such as the oval shape, oval square shape, round shape, and round square shape. The findings suggest that the U-shape is the most prevalent among males, significantly outnumbering other shapes. The V- and square shapes are comparatively rare, and the lack of data for certain shapes points to their rarity or complete absence in the sample studied.

# 4. Discussion

This study's findings showed gender differences in selected features of maxillary and mandibular bones. These differences reflect developmental and physiological differences. The study compares maxillary and mandibular measurements between males and females, revealing notable gender differences where males generally exhibit larger values in most parameters. However, some of these measurements showed significant differences while others did not show significant differences, suggesting that these may be less influenced by gender. Overall, the study emphasizes sexual dimorphism in craniofacial structures, which has implications for forensic identification, orthodontic treatment, and craniofacial research.

When comparing our study to previous research, it stands out for its comprehensive analysis of both maxillary and mandibular measurements, as well as sinus dimensions, using CBCT 3D images. This broad approach contrasts with other studies, such as Soundarya, et al. [19] which focus more narrowly on specific dental dimensions like mesiodistal (MD) and cervicoincisal (CI) dimensions of teeth. While Soundarya et al. also emphasize gender differences in dental measurements, our study includes a wider range of maxillary and mandibular parameters, such as arch lengths and ramus length. Arthanari, et al.  $\lceil 20 \rceil$  studied mandibular features mainly related to mandibular ramus dimensions and statistical analysis showed significant gender differences, while concentrating on specific mandibular features our study integrates these measurements with maxillary sinus and arch length dimensions, providing a more holistic perspective on craniofacial sexual dimorphism [21]. In his study Waluyo, et al. [22] reported gender differences regarding the dimensions of the paranasal sinus of the maxilla and inferior alveolar canal of the mandible, which are similar to our study findings, offering an alternative view on sexual dimorphism in craniofacial structures. In terms of significance, our study found that maxillary arch length and ramus length are the most reliable indicators for gender determination, whereas Soundarya, et al. [19] identified the mesiodistal dimension of the maxillary canine and cervicoincisal of the mandibular first molar as more accurate. Arthanari, et al. [20] highlighted mandibular ramus measurements as key gender indicators, achieving an impressive 90% accuracy in gender identification, while our study also found gender differences in the length of the mandibular ramus as well as a broader

range of craniofacial features. Both our study and Waluyo, et al. [22] examined maxillary sinus dimensions, and the findings of both reported larger sinus dimensions in males compared to females with significant differences.

The study reveals notable gender differences in maxillary and mandibular arch shapes in the Jordanian population. In females, the most common maxillary arch shape is the round and the round square shapes. Similarly, males exhibit a similar trend, with round and oval square shapes being the most prevalent shapes. For mandibular arches, the U-shape and V-shape were the most common in both genders. These findings highlight gender-based differences in arch morphology, offering valuable insights for orthodontic and prosthetic treatment planning [23].

The results of the study and those of Aljayousi, et al. [13] reveal both similarities and differences in maxillary and mandibular arch shapes among the Jordanian population. In the study, round arches were the most prevalent in females for the maxillary arch, and the U-shape is dominant in mandibular arches for both genders, especially in males (70%). In contrast, Aljayousi, et al. [13] identified catenary arches as the most common maxillary shape, with half-ellipse/U-shape being more frequent in both maxillary (27.7%) and mandibular (26.7%) arches. While both studies emphasize the prominence of U-shaped arches in mandibular morphology, our study reports a higher frequency of round arches in maxillary shapes, particularly in females, while Aljayousi, et al. [13] found a higher prevalence of catenary forms. Both studies show that square and V-shaped arches are less common, but our study demonstrates more variability in maxillary arch types. These differences may stem from variations in sample characteristics, regional genetics, or environmental factors, with our study offering clearer gender distinctions in arch morphology compared to Aljayousi, et al. [13].

The findings from the study on gender differences in maxillary and mandibular arch shapes in the Jordanian population can be compared to similar studies in other global populations. In this study, maxillary and mandibular arch patterns align with studies that show notable gender differences in arch shapes but with regional variations. For example, Aljanakh and Koralakunte [24] in a Saudi study found that males predominantly had combination tooth forms and ovoid arch forms, while females had square arch forms. Although there were significant gender differences in palatal forms, the tooth form did not show a significant sexual difference. This contrasts with the study, where round arches are more common in females, and the U-shape is prominent in both genders for mandibular arches.

In Egyptian populations, as noted by Bayome, et al. [25] narrower arch dimensions, particularly in the intermolar width, were observed, with an even frequency distribution of the three arch forms. However, in North American white populations, ovoid was the most common arch form, similar to findings in the study, where round arches are also prominent in females. The Egyptian study concluded that narrower archwires are more suitable for Egyptian patients, which suggests a potential consideration for regional differences when planning orthodontic treatments.

Gupta, et al. [26] reported gender differences in arch morphology in the Nepalese population, with females having wider intercanine dimensions and longer maxillary arches, while males had larger mandibular arches. The study also found that Nepali males predominantly had square arch forms, while females exhibited tapering arch forms. This highlights regional and gender-specific variations identical to the study, where U-shaped mandibular arches are more common in males, and round arches are more common in females.

Troedhan, et al. [27] observed that the tapered arch form was most common in their study, predominantly seen in boys, while ovoid and square forms were less common. The presence of a tapered arch form and larger arch width in males differs from the study findings, where round and U-shaped arches predominate. This difference could be attributed to the demographic or sample variations, as this study showed more variability in maxillary arch shapes compared to their findings.

Othman and Harradine [28] studying ethnic Malays and Malaysian Aborigines, found that the most common maxillary arch shape was ovoid, while the square arch was the rarest. They also reported that mandibular arch shapes did not differ significantly between genders. These findings show a notable

difference compared to our study, where round arches are more common in females and U-shaped arches dominate for both genders in the mandibular arch.

Finally, an Italian study by Oliva, et al. [29] found significant differences between males and females, with males having larger arch widths and females having smaller depths, flatter anterior arches, and wider maxillary arches. This suggests that orthodontic treatments should account for these differences, as the study also implies with the clear gender distinctions observed in maxillary and mandibular arch shapes.

In conclusion, while our findings on round maxillary arches in females and U-shaped mandibular arches in both genders are somewhat consistent with global studies, there are notable regional differences, particularly regarding the prominence of arch forms such as catenary, square, and tapered arches. These variations emphasize the importance of considering genetic and environmental factors and regional characteristics when planning orthodontic treatments and dental care across populations. Overall, the studies consistently highlight gender differences in craniofacial structures, each offering unique insights through various parameters, methodologies, and measurement techniques. Together, these studies provide complementary perspectives on how craniofacial and dental features can aid in gender determination, enriching both forensic and clinical research.

#### 4.1. The Impact of the Study in Artificial Intelligence on the Future of Dentistry

Artificial intelligence (AI) has the potential to revolutionize dental care by enabling more accurate diagnoses, personalized treatment plans, and enhanced patient outcomes. By utilizing AI to analyze dental arch shapes, sinus dimensions, and other relevant features, clinicians can develop customized orthodontic and prosthetic treatments. Additionally, AI can help identify patterns in genetic and environmental factors that influence dental health, leading to more precise and tailored interventions. With the advancement of AI technologies, the future of dentistry holds great promise for improving efficiency, accuracy, and patient satisfaction. The results of this study can be applied in the field of artificial intelligence (AI) in dentistry in several practical ways. For example:

- 1. Analysis of Radiographic and Medical Imaging: AI can be used to analyze radiographic images and 3D imaging of the mouth and teeth to extract features such as the shape of the maxillary and mandibular arches and sinus dimensions. Using deep learning techniques, AI models can be trained to identify and analyze various arch shapes more quickly and accurately than traditional methods.
- 2. Personalized Treatment Planning: Based on the diverse shapes discovered in the study, AI can develop specialized programs to tailor orthodontic and prosthetic treatments for each patient. For example, AI algorithms can design dental braces based on the patient's actual maxillary and mandibular arch shapes, using machine learning models trained on population data.
- 3. Gene and Environmental Factor Analysis: AI can help correlate clinical data with genetic or environmental factors, assisting in understanding how these factors influence the shape of the teeth and jaw. This could contribute to the development of more personalized treatments based on a person's genetic traits.
- 4. Early Diagnosis of Oral Diseases: Based on the observations of abnormalities or unusual shapes in the dental arches identified in the study, AI can help clinicians diagnose potential oral conditions early, such as issues with tooth development or the need for orthodontic treatments, leading to early intervention and more effective care.
- 5. Predictive Systems: AI-powered predictive systems can assist clinicians in determining the likelihood of specific conditions based on the anatomical shape of the teeth and jaw, such as predicting the potential for orthodontic issues or surgical needs. This enables clinicians to make more informed decisions about future treatment plans.

Artificial intelligence applications in dentistry can improve diagnostic accuracy and treatment, offering individualized and more tailored solutions based on each patient's anatomical and genetic data.

# 5. Conclusion

In conclusion, this study provides valuable insights into gender differences in the maxillary and mandibular structures of the Jordanian population, highlighting significant anatomical variations between males and females. These findings have important implications for orthodontic treatment, forensic identification, and craniofacial research, emphasizing the importance of considering gender when planning dental interventions. The study's comprehensive approach, combining maxillary, mandibular, and sinus dimensions, offers a broader understanding of craniofacial sexual dimorphism, setting it apart from other studies that focus on narrower aspects.

Furthermore, the potential integration of artificial intelligence (AI) into dentistry, as highlighted by the study, can significantly enhance diagnostic accuracy, treatment planning, and patient outcomes. By leveraging AI technologies to analyze radiographic images, detect genetic and environmental influences, and create personalized treatment plans, the future of dental care is poised for significant advancements. AI can also improve early diagnosis of oral conditions and provide predictive models for future treatments, offering more efficient and precise interventions. Overall, the study not only contributes to the growing body of knowledge on craniofacial morphology but also paves the way for the application of AI in transforming the future of dentistry, making it more tailored, efficient, and patient-centred.

# **Institutional Review Board Statement:**

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of The Hashemite University (protocol code (No.31/1/2023/2024) and date of approval on Sunday 19th November 2023).

## **Transparency:**

The authors confirm that the manuscript is an honest, accurate and transparent account of the study that no vital features of the study have been omitted and that any discrepancies from the study as planned have been explained. This study followed all ethical practices during writing.

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