Research Article

Phenotypic Characterization of Skeletal Class III Malocclusion using Principal Component Analysis and Cluster Analysis

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ABSTRACT

Background: Skeletal Class III malocclusion is characterized by several dentofacial deformities linked to environmental and genetic causes. It constitutes a clinical obstacle due to an insufficient understanding of its origins. Thus, proper classification and definition are key to diagnosing and treating this malocclusion correctly.

Objective: This study aimed to identify sub-clusters of skeletal Class III malocclusion in a group of Yemeni adults using multivariate reduction analyses.

Design: This cross-sectional prospective study was conducted at the Orthodontic Graduate Clinics, Faculty of Dentistry, Sana`a University, Sana`a, Yemen.

Material and Methods: This study included lateral cephalometric radiographs of 144 Yemeni adults (67 males and 77 females, mean age 29 years) with true Class III skeletal malocclusion ranging from mild to severe. A total of 62 measurements were used to perform principal component analyses and subsequent cluster analyses.

Results: Eight principal components were identified and represented 79.4% of the variance. The first three main components, which described vertical and sagittal variables as significant descriptors, explained 50.8% of the variance. Cluster analysis identified 5 phenotypic subclusters. Cluster 1 denoted a mild Class III phenotype. Cluster 2 displayed a vertical phenotype with a steep mandibular plane. Cluster 3 displayed a phenotype characterized by a purely severe mandibular prognathism. Cluster 4 showed a severe maxillary retrusion phenotype. Cluster 5 displayed a severe maxillary deficiency with a severe mandibular protrusion.

Conclusion: There was a significant variance demonstrated among sub-phenotypes of a selected group of adult Yemeni Class III populations. Based on these results, further genetic investigations will enable us to uncover the etiological genes associated with each sub-cluster.

KEYWORDS: Class III malocclusion, cluster analysis, multivariate reduction analyses, phenotypes, principal component analysis.

INTRODUCTION

Skeletal Class III malocclusion is a complex multifactorial disorder presented with several phenotypes.[1] A variety of genetic and environmental factors contributed to this malocclusion.[2,3] Previous studies have shown that Class III malocclusion prevalence varies significantly between and within communities, with Southeast Asians having the highest prevalence of 15.8%.[4]

Based on cephalometric radiographic data, researchers conducted multivariate reduction techniques, including principal component analysis (PCA) and cluster analysis (CA), to identify skeletal Class III malocclusion phenotypes. These methods helped improve the clinical understanding of diverse malocclusion phenotypes.[5-11]

PCA is a data reduction method that applies perpendicular linear combinations to reduce large variables into smaller, uncorrelated components. CA incorporates PCA with symmetrical data to identify the underlying characteristics and divides participant collections into clusters based on similarities or dissimilarities.[5–10]

Moreno Uribe et al. reported sub-phenotypes of Class III skeletal malocclusion in 292 Caucasian adults. PCA simplified 63 cephalometric variables into 6 PCs, which explained 81% of the variance. Furthermore, CA divided the participants into five subclusters. 6 Cai et al. used the same method to define sub-clusters in 144 Chinese Class III malocclusion adults. PCA reduced 61 cephalometric variables into 6 PCs, representing 73.7% of the overall variation and CA identified four different clusters.[7]

In a systematic review, De Frutos et al. evaluated the reliability of utilizing sub-clustering to diagnose class III malocclusion across various ethnic backgrounds.[8] They reported that the number of phenotypes ranged from 3 to 14 sub-groups among 7 studies.[6,7,12–14] Furthermore, de Frutos et al. characterize 212 class III adults from southern Europe. PCA diminished 55 skeletal cephalometric variables into 10 axes and accounted for 92.7% of the diversity and CA classified the sample into six different clusters.[9] Yang et al. classified 326 adult Koreans with severe Class III malocclusion before conducting orthognathic surgery. The study used a single ratio and 13 angular cephalometric variables to conduct PCA. SNA, SNB, and Bjork sum were the most characteristic variables employed to perform CA. The participants were divided into 9 diverse clusters.[11]

Class III malocclusion phenotypes vary among different races, which raises doubts about whether findings from previous research can be generalized to other ethnicities or if there are more subtypes to consider. 8 No comprehensive study has defined clinically distinct phenotypes in Yemeni adults. This study aimed to subcluster the different phenotypes of Class III malocclusion using PCA and CA in large, racially homogenous Yemeni adults.

MATERIALS AND METHODS

This cross-sectional study was conducted at the Faculty of Dentistry, Sana`a University, Sana`a, Yemen. Ethical approval was obtained from the Medical Research Ethical Committee (ECA/SU/FD1) at Sana`a University. The research followed the principles of the Helsinki Declaration.

Study sample

The sample size calculation was performed in accordance with previous studies.[7,9] The confidence interval was set at 95%, precision at 30%, power of study at 90%, and a variance of 69% for the measurable variable in the reference group. The calculation revealed the need for 131 participants. It was adjusted for the expected loss proportion at 15%, resulting in a required sample size of 154 participants.

All the included individuals were of Yemeni origin and had skeletal Class III malocclusion. They have a concave profile, an ANB angle ≤ 0º, Wit's appraisal ≤ 0 mm, and anterior crossbites. Exclusion criteria included a history of previous orthodontic treatment and facial injuries; the presence of congenital defects or facial syndromes; and impacted or missing teeth except the third molar.

Patient Recruitment and Clinical Examination:

Participants were recruited from patients seeking orthodontic treatment at the orthodontic clinics at the Faculty of Dentistry, Sana`a University. Each patient was evaluated by extra-oral and intra-oral clinical examinations for verification of the selection criteria. A concave profile was identified with the patient seated at the natural head position with a backward-positioned upper jaw and/or protruded lower jaw with no functional shift. A total of 200 subjects were examined. Forty-four subjects were ruled out based on exclusion criteria. Those matching the criteria signed a written consent after receiving detailed information about the study.

Cephalometric Analysis:

Cephalograms were collected from the medical files of the patients as digital images. They were saved in

JPG format and imported into a cephalometric analysis software (OrisCeph RX CE). All the cephalograms were taken from the same cephalometric machine (PaX-Flex3D P2, Vatech, Korea). The imaging parameters were 85 KVp, 10 mA, and 0.5 to 1 second of radiation time. The exposure was obtained when the patient was positioned in a natural head position with maximum intercuspation.

The study used 31 reference landmarks identified by the orthodontic senior resident (M.A.H.) (Fig. 1). The cephalometric analysis was performed using the OrisCeph RX CE digital software. Table 1 shows the definitions of the anatomical landmarks. Table 2 lists 62 cephalometric variables used in this study (Fig. 2).

Of the 156 cephalograms, 8 were excluded because of inadequate clarity of their anatomical landmarks, whereas 4 were dismissed according to the Eastman correction of the ANB angle values. As a result, the study included 144 subjects (68 men ≥ 18 and 76 women ≥ 16 years). Males had an average age of 28.66 years, and females had an average age of 29.12 years.

Method Error:

A random sample of 20 cephalograms was retraced 3 weeks apart for intra-rater reliability with the same researcher and compared using intraclass correlation (ICC) and Cronbach's alpha tests.[15,16]

Statistical analysis

Statistical analysis was performed using SPSS Windows (IBM SPSS, Version 26.0, Chicago, United States). The first step was to reduce the variables using PCA. The original variables (n = 62) were reduced with PCA to describe the number of principal components. Values with an eigenvalue > 1 and a cumulative difference > 79% were chosen. Varimax rotation was applied which facilitated PCA interpretation. Kaiser normalization procedure was used to prevent the varimax rotation from being influenced by variables with greater explanatory power. Kaiser-Meyer-Olkin (KMO) was applied to test sampling adequacy for PCA and ensure reliable interpreted PCs. Bartlett's test assessed the null hypothesis.[17,18]

K-means CA used standardized PCA scores to identify patients with homogeneous phenotypes. Means and standard deviation values of 62 cephalometric variables were computed for each cluster. A one-way ANOVA analysis and the post-hoc Bonferroni test were used to find significant statistical differences between subclusters. A two-way ANOVA was then performed to compare the mean variances between two subclusters. The OriginPro 2023b statistical and graphing software was used to create two- and three-dimensional graphics in order to visualize the findings of the cluster analysis.

The templates of the resulting skeletal clusters were illustrated graphically by determining the centroid of each cluster. The cluster centroid was identified as the subject nearest to the mean values of that cluster, and the cephalometric radiographs of these subjects were traced, representing the specific features of each cluster.

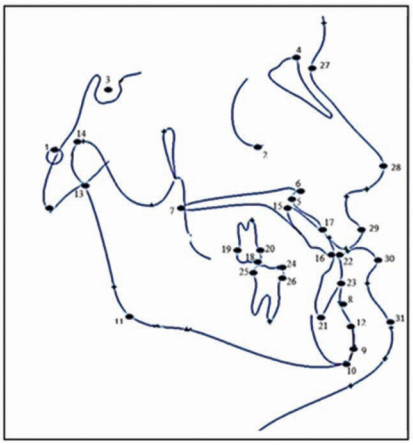

Figure 1: Cephalometric landmarks used in the study.

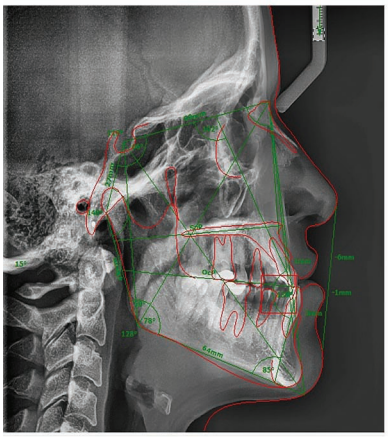

Figure 2: Digital tracing of cephalometric measurements by OrisCeph RX CE.

Table 1: Definitions of the anatomical cephalometric landmarks used in the study

SN	Name	Definition
1	Porion (Po)	Point distal to the most superior surface of the Mandibular condyle at the posterior border of the cephalostat ear rod.
2	Orbital (Or)	The lowest point on the inferior rim of the orbit.
3	Sella (S)	The location of the geometrical center of the bony outline of the Sella turcica.
4	Nasion (N)	The most anterior point on the frontonasal suture is at the midsagittal axis.
5	Point A (A)	The deepest point in the concavity of the premaxilla is between prosthion and ANS.
6	Anterior Nasal Spine (ANS)	It is the anterior crest of the acute maxillary bony process is located at the inferior edge of the anterior nasal aperture.
7	Posterior Nasal Spine (PNS)	It is the posterior spine of the palatine bone that makes up the hard palate.
8	Point B (B)	The deepest, or most posterior, midline point in the mandible's concavity between the infradentale and pogonion .
9	Anatomical Gnathion (Gn)	It is the most anterior midline and the lowest point on the mandibular symphysis.
10	Menton (Me)	It is the lowest point of mandibular symphysis is in the median plane.
11	Gonion (Go)	It is a point located on the curvature of the mandibular angle created by dividing the angle by lines tangent to the lower border of the mandible and the posterior ramus.
12	Pogonion (Pog)	Its most anterior dot in the mandibular symphysis is in the middle line plane.
13	Articulare (Ar)	A point at the connection of the lower border of the posterior cranial base and the posterior border of the ramus.
14	Condylion (Co)	It is the most superior posterior landmark of the condyle.
15	U1 Tip (U1)	It is the incisal edge of the most protruding maxillary central incisor.
16	U1 Apex (U1 Root)	It is the root apex of the most protruding maxillary central incisor.
17	U1 Labial Gingival Border (U1GB)	Labial cemento-enamel junction (CEJ) of the most protruding maxillary central incisor.
18	U6 Occlusal Point (U6Occ)	The tip of the mesial buccal cusp of the left upper (most superior, distal) molar.
19	U6 Distal point (U6Dist)	Distal surface of the maxillary first molar, perpendicular to the occlusal plane.

20	U6 Mesial point (U6Mes)	Mesial surface of the maxillary first molar, perpendicular to the occlusal plane
21	LI Tip (L1 Tip)	It is the incisal edge of the most protruding mandibular central incisor.
22	Lower Incisor Apex (L1 Root)	It is the root apex of the most protruding mandibular central incisor.
23	L1 Labial Gingival Border (L1GB)	Labial cemento-enamel junction (CEJ) of the most projected mandibular central incisor.
24	L6 Occlusal Point (L6 Occ)	The tip of the mesial buccal cusp of the left mandibular (most superior, distal) molar.
25	L6 Distal point (L6 Dist)	Distal surface of the mandibular first molar, perpendicular to the occlusal plane.
26	L6 Mesial point (L6 Mes)	Mesial surface of the mandibular first molar, perpendicular to the occlusal plane.
27	ST Nasion (N')	The point of the most concavity in the midline between the forehead and the nose.
28	Tip of Nose (Pn)	The most prominent or anterior point of the anterior curve of the nose.
29	Upper Lip anterior point (UL)	It is the point at the most anterior part of the upper lip curve.
30	Lower Lip anterior point (LL)	It is the point at the most anterior part of the lower lip curve.
31	ST Pogonion (Pog')	Located in the midsagittal plane, it is the most anterior point on the ST chin.

Table 2: Cephalometric variables used in this study

A. Skeletal variables		
Cranial Base	**Intermaxillary**	**B. Dental variables**
Saddle/Sella Angle (SN-Ar) (°)	ANB (°)	U1 - SN (°)
Ant Cranial Base (SN) (mm)	Facial Plane to AB (AB-NPg) (°)	U1 - NA (°)
Post Cranial Base (S-Ar) (mm)	Facial Plane to SN (SN-NPg) (°)	U1 - NA (mm)
Midface Length (Co-A) (mm)	U1 - FH (°)	U1 - FH (°)
Maxilla	P-A Face Ht (S-Go/N-Me) (%)	IMPA (L1-MP) (°)
SNA (°)	Y-Axis (N-S-Gn) (°)	L1 - NB (°)
Convexity (NA-APg) (°)	Mx/Md Diff (Co-Gn - Co-ANS) (mm)	L1 - NB (mm)
N-A || HP (mm)	Wits Appraisal (AO-BO) (mm)	L1 Protrusion (L1-APg) (°)

Mx Unit Length (Co-ANS) (mm)	Ant Face Ht (N-Me) (mm)	L1 Protrusion (L1-APg) (mm)
	Upper Face Ht (N-ANS) (mm)	FMIA (L1-FH) (°)
Mandible	Nasal Ht (N-ANS/N-Me) (%)	UADH (U1-PP) (mm)
SNB (°)	PFH:AFH (Co-Go/N-Me) (%)	LADH (L1-MP) (mm)
Facial Angle (FH-NPg) (°)	FMA (FH-MP) (°)	UPDH (U6-PP) (mm)
Gonial/Jaw Angle (Ar-Go-Me) (°)	SN - GoGn (°)	LPDH (L6 - MP) (mm)
Chin Angle (Id-Pg-MP) (°)	Occ Plane to SN (°)	Overjet (mm)
Ramus Height (Ar-Go) (mm)	Occ Plane to FH (°)	Overbite (mm)
Length of Mn Base (Go-Pg) (mm)	FH - SN (°)	
Facial Taper (N-Gn-Go) (°)		**C. Soft Tissue variables**
Articular Angle (S-Ar-Go) (°)		Upper Lip to E-Plane (mm)
N-B || HP (mm) Lower Lip to E-Plane (mm)		Lower Lip to E-Plane (mm)
N-Pg || HP (mm)		U Lip to ST N Perp (FH) (mm)
B to N Perp (FH) (mm)		L Lip to ST N Perp (FH) (mm)
Pg to N Perp (FH) (mm)		ST Pg to ST N Perp (FH) (mm)
Mn Unit Length (Co-Gn) (mm)		
Pg - NB (mm)		
Post Facial Ht (mm) (Co-Go)		

RESULTS

The sample was collected between January and August 2023. Intraclass coefficient (ICC) values and Cronbach's alpha test for 62 cephalometric measurements presented values > 0.90.

The PCA revealed that 8 PCs explained 79.40% of the total variation, and they showed the greatest diversity in the collected data. The 8 vectors were orthogonal and unrelated, reflecting perpendicular directions in space (Figure 3). The first 3 PCs accounted for around half of the variance (50.80%).

The first PC represented the sagittal position of the mandible and maxilla. It described most of the variance, representing 23.40% of the total variation. PC2 showed the anteroposterior and vertical linear variables, which explained 15.50% of the variance. PC3 explained 12.20% of the variance, representing the vertical length measurements. PC4 denoted the mandibular incisor variables, which explained 8.80% of the variation. PC5 described 6.20% of the variance and showed the maxillary and mandibular linear lengths. PC6 denoted the horizontal intermaxillary discrepancy, which represented 5.40% of the variance. PC7 explained that 4.10% of the variance represented measurements of the sagittal position of the maxilla and mandible. Finally, PC8 showed the upper incisor variables explained 4.10% of the variation (Table 3).

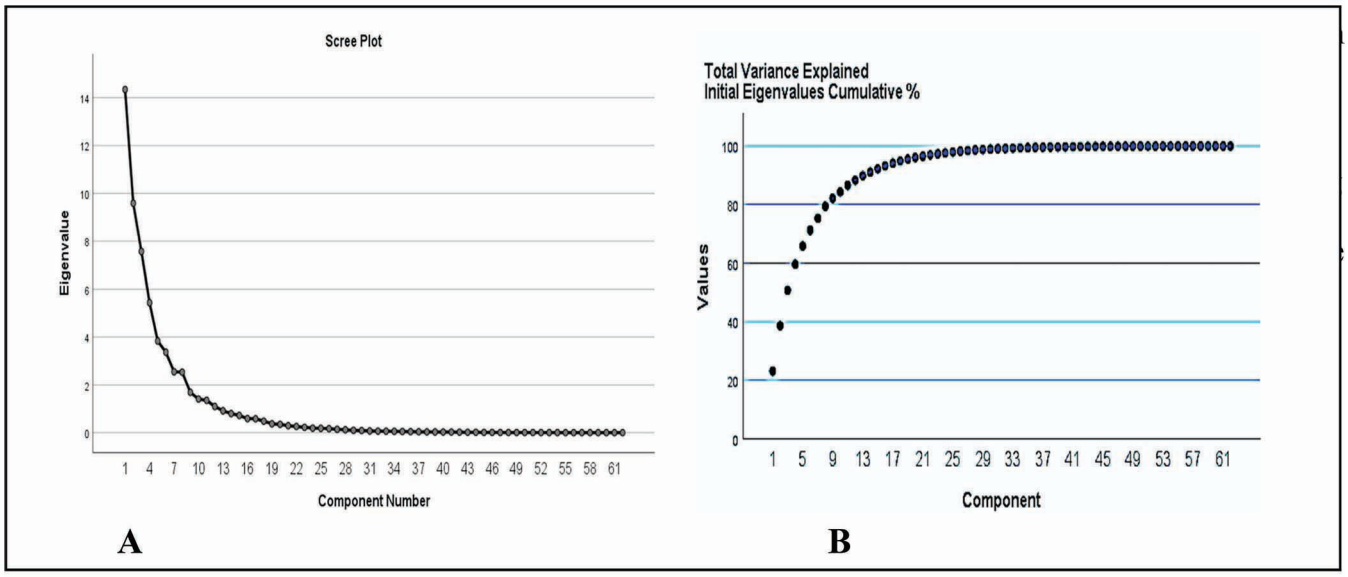

Figure 3: (A) Screen plot of PCs describing the eigenvalue of every principal axis. (B) the proportion of variation explained by each axis and the cumulative proportion of total variation described.

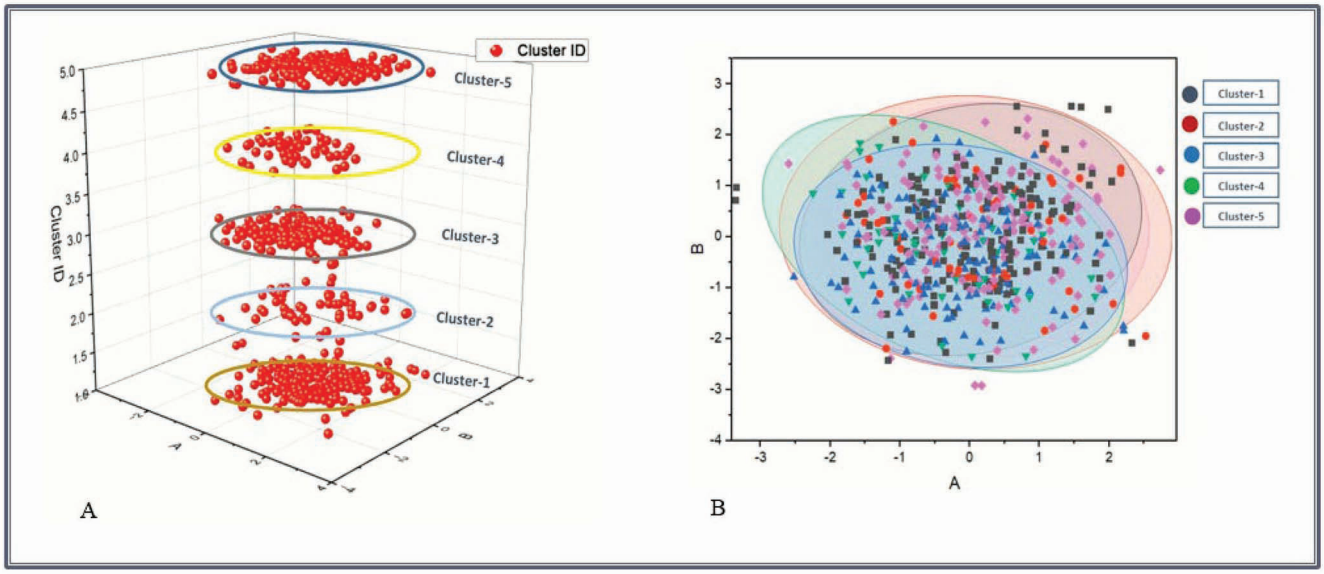

Figure 4: (A) and (B) show 3-D and 2-D plots, respectively, of 5 different clusters of CIII malocclusion subjects.

Cluster 1 had the highest number of observations, with 45 subjects, 37.77% male and 62.22% female, presenting a borderline Class III phenotype with mild maxillary retrusion and mandibular protrusion. Cluster 2, the vertical phenotype, had the second-fewest observations, with 14 subjects, 78.57% male and 21.43% female. It was characterized by an increase in mandibular size with a steep MP and an increase in lower anterior facial height (LAFH).

Cluster 3 consisted of 32 subjects, with 21.87% male and 78.13% female. They had a concave profile, a small and normally positioned maxilla, and a slightly large and severely protruding mandible with a normal MP. Cluster 4 had the fewest observations, with 13 subjects, 23.10% male and 76.90% female. This group had a severely retrusive and small maxilla, a slightly large and normal mandibular position, a normal MP, and a normal LAFH. Cluster 5 had the second-highest number of cases, with 40 subjects, 72.50% men and 27.50% women. Subjects exhibited a concave profile, a severely retrusive and small maxilla, a significantly large and protrusive mandible, a flat MP, and a normal LAFH. Figure 5 shows the templates for the final result for each cluster.

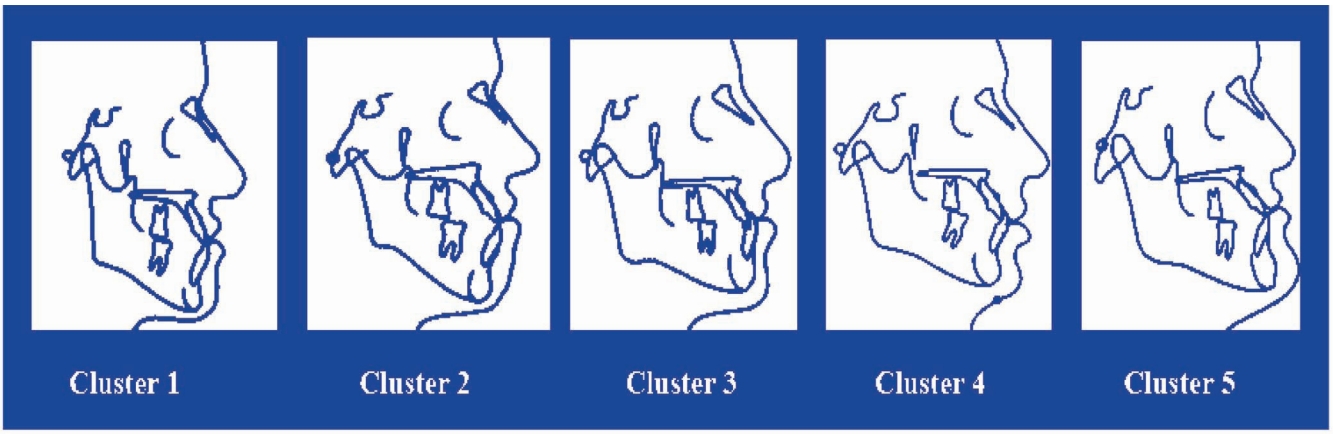

Figure 5: Cluster templates. A description of the cephalometric traces of the templates that were created for each cluster.

Table 5 shows the descriptive statistical analysis of all variables in each subcluster. There were statistically significant differences in all measurements between the 5 clusters, except for 2 variables: chin angle (Id-Pg-MP) and articular angle (S-Ar-Go). Table 6 shows the two-way ANOVA test for multiple comparisons of the variables between each of the two subclusters.

This study identified three clusters with higher female-to-male ratios (C1, C3, and C4). In contrast, two phenotypes had higher male-to-female ratios (C2 and C5), representing the vertical and severe prognathic mandibular phenotypes, respectively. Males exhibited larger facial heights, a lesser retruding maxillary position, a longer maxillary length, and a more protruding and larger mandible compared with female subjects.

DISCUSSION

Multivariate statistical methods, including PCA and CA, are frequently used to identify specific sub-phenotypes of skeletal class III malocclusion by analyzing a large number of cephalometric variables. The identification of 8 PCs from 62 cephalometric variables in the current study was consistent with the previous findings reported by De Frutos-Valle[9] and Alshoaibi LH.[10] The first 3 PCs explained the vertical and sagittal relationships of the mandible and maxilla, with the cranial base representing 50.80% of the variation, consistently with several studies.[5-7,9,10,19]

Table 3: Summary of Principal Component Analysis

principal components	PC1	PC 2	PC 3	PC 4	PC 5	PC 6	PC 7	PC 8
Variance Explained [a] %	23.14	15.46	12.20	8.77	5.43	4.11	4.11	4.11
Cumulative Percentage [b] %		38.60	50.80	59.57	65.75	71.18	75.30	79.38
Variables [c]	SNA (°)	Facial taper (°) (NPg – Gn -Go)	LFH (ANS-Me) (mm)	L1-APg (°)	Midface length (Co-A) (mm)	Convexity angle (NA-Pg) (°)	A to N-Perp (FH) (mm)	U1 - NA (°)
	N-A|| HP (mm)	P.A Facial height (S-Go: N-Me) %	MX to MD diff. (CoGn – CoANS) (mm)	L1-APg (mm)	MX unit length (Co-ANS) (mm)	Over Jet (mm)	Pg to N-Perp (FH) (mm)	U1-NA (mm)
	SNB (°)	P.A Face height (Co-Go :N-Me) %	UADH (U1 – PP) (mm)	L1-NB (mm)	MD unit length (Co-Gn) (mm)	Wit`s appraisal	Facial angle (FH-N-Pg) (°)	U1- SN (°)

	N-B|| HP (mm)	Ramus height (Co-Go) (mm)	UPDH (U6 – PP) (mm)	L1-NB (°)	MD base length Go-Pg (mm)	AO-BO (mm)	FH-SN (°)	U1- FH (°)
	N-Pg || HP (mm)		LADH (L1 – PP) (mm)	L1-MP (°)	ACB length (NS) (mm)	Lower lip s.t.- N Perp (mm)		
	SN- N-Pg (°)		LPDH (L6 – PP) (mm)		PCB length (S-Ar) (mm)			

a: represents the variance described by every principal component in PCA
b: illustrates the cumulative variation as a consequence of each PC added successively.
c: exhibits the variables contributing the most in each PC. MX: Maxilla; MD: Mandible; ACB: Anterior cranial base; PCB: Posterior cranial base; UADH: upper anterior dental height; UPDH: upper posterior dental height; LADH: lower anterior dental height; LPDH: lower posterior dental height; U1: upper incisor; L1: lower incisor; U6: upper first molar; L6: lower first molar.

Table 4: Summary of Cluster Analysis

Attribute	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5
Frequency (male, female)	45 (17 , 28)	14 (11, 3)	32 (7, 25)	13 (3,10)	40 (29, 11)
Proportion % (male, female)	31.25 % (38, 62)	9.70 % (79, 21)	22.20% (22,78)	9 % (23. 77)	27.80 % (72,28)
Profile	Slightly Concave	Slightly Straight	Concave	Slightly Concave	Concave
Cranial Base angulation (Saddle angle)	Normal	Normal	Normal	Obtuse	Normal
Length of anterior cranial base	Short	Normal	Short	Normal	Normal
Length of posterior cranial base	Short	Normal	Short	Normal	Normal
Maxillary position	Slightly Retrusive	Retrusive	Normal	Severely Retrusive	Severely Retrusive
Maxillary size	Small	Normal	Small	Small	Slightly small
Mandibular position	Slightly protruding	Slightly Retrusive	Severely Protrusive	Normal position	Severely Protrusive
Mandibular size	slightly increased	significantly larger	slightly increased	slightly increased	Significantly larger
Mandibular Angulation (MP)	Normal	Steep	Normal	Normal	Flat
Lower Anterior Facial Height	Normal	Increased	Short	Normal	Normal
Upper Incisor Position	Normal	Protrusive	Normal	Normal	Protrusive
Lower Incisor Position	Retrusive	Retrusive	Retrusive	Normal	Retrusive

Table 5: Mean and standard deviation (SD) of variables for each cluster and statistical significance between the clusters

Cephalometric Measurements	Cluster 1 N= 45		Cluster 2 N= 14		Cluster 3 N= 32		Cluster 4 N= 13		Cluster 5 N= 40		P-value	Significance
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Skeletal Variables												
(SN-Ar) Angle (º)	126.90	4.80	121.50	5.49	123	4.86	130.80	5.95	122.20	3.92	0.000	***
(S-N) (mm)	62.67	2.30	67.29	2.46	61.41	2.07	65.86	2.28	67.13	2.92	0.000	***
(S-Ar) (mm)	27.98	2.80	31.71	3.20	28.12	2.46	29.23	3.08	32.30	3.09	0.000	***
SNA Angle (º)	78.17	3.30	79.52	4.56	80.96	3.24	75.80	2.31	79.20	3.78	0.000	***
N-A || HP (mm)	-4.80	3.24	-3.13	3.65	-2.44	2.91	-5.49	3.53	-3.19	3.45	0.006	**
A to N-Perp (FH) (mm)	-1.87	3.70	-5.64	2.87	-2.88	2.65	-4.62	2.57	-3.57	3.58	0.002	**
(Co-ANS) (mm)	75.70	4.26	81.46	3.16	74.48	5.40	79.40	4.71	80.20	4.74	0.000	***
SNB Angle (º)	80.96	2.70	82.24	3.82	84.92	3.23	78.15	2.58	85	3.08	0.000	***
Facial Angle (FH-NPg) (º)	90.82	3.70	86.36	2.31	90.88	3.17	88.08	2.43	92.78	3.40	0.000	***
(Id-Pg-MP) (º)	60.29	5.60	59.36	5.20	60.62	7.92	61.69	8.67	59.7	8.41	0.904	NS
Facial taper (N-Gn-Go) (º)	62.08	4.60	58.65	2.72	61.09	4.39	68.37	3.60	66.13	4.59	0.000	***
Length of MD Base (Go-Pg) (mm)	72.24	4	73.34	4.36	71.08	4.14	73.36	4.86	77.83	5.80	0.000	***
N-B || HP (mm)	-3.67	4.40	-1.46	6.79	2.89	4.70	-7.86	4.23	3.37	5	0.000	***
N-Pg || HP (mm)	-3.40	4.90	-1.60	7.10	3.41	5.09	-7.67	4.20	5.36	5.67	0.000	***
Pg to N-Perp (FH) (mm)	1.64	6.80	-7	4.69	1.50	5.44	-3.30	4.09	4.95	6	0.000	***
Length of MD unit (Co-Gn) (mm)	111.70	6.30	117	5.06	107.90	6.69	108.10	5.07	117.4	7.34	0.000	***
Pg to NB (mm)	0.42	1.50	-0.14	0.86	0.25	1.37	1	1.29	1.63	2.10	0.000	***
Gonial angle (Ar-Go-Me) (º)	126.60	7.10	136	7.98	130.20	7.81	123	5.68	123.10	7.63	0.000	***
Articular angle (S-Ar-Go) (º)	143.20	7.30	142	7.87	140.70	7	140	5.20	143.10	6.77	0.351	NS
Ramus Height (Ar Go) (mm)	46	4.30	46.13	3.29	42.56	3.10	44.76	4.38	50.32	3.66	0.000	***
PFH (Co-Go) (mm)	54.99	4.60	54.55	4.58	51	3.70	52.54	4.85	58.76	4	0.000	***
ANB (º)	-1.88	1.60	-1.70	1.15	-3.62	1.80	-1.66	1.34	-4.86	1.60	0.000	***

Convexity (NA-APg) (º)	-5.84	4.10	-5.29	3.20	-8.27	4.36	-6.21	3.35	-12.64	3.75	0.000	***
Facial plane to AB (AB-NPg) (º)	3.27	2.06	2.71	1.94	5.13	2.90	2.69	1.37	6.80	3	0.000	***
Facial plane to SN (SN-NPg) (º)	81.18	2.50	82.07	3.71	85.16	3.10	78.69	2.36	86.00	3.10	0.000	***
Midface length (Co-A) (mm)	75.31	4.60	80.29	2.92	74.31	4.20	78.23	3.94	79.54	4.52	0.000	***
MD\Mx Diff (CoGn -CoANS) mm	36.29	4.66	35.68	5.62	32.39	5.13	28.60	2.52	37.23	5.15	0.000	***
Witts Appraisal (AO-BO) (mm)	-7.84	2.96	-9.43	3.35	-9.28	2.70	-6.77	2.68	-9.70	3.54	0.007	**
FMA (FH-MP) (º)	26.98	5.50	34.86	3.80	28.04	5.19	24.69	3.28	21.25	5.02	0.000	***
SN-Go-Gn (º)	34.23	5.14	35.95	4.77	31.28	5.89	31.69	3.37	25.69	5.32	0.000	***
Occlusal plane to SN (º)	16.48	3.54	16.13	3.53	13.59	4.12	18.70	3.68	10.96	4.25	0.000	***
(Occlusal plane -FH) angle (º)	6.73	3.86	11.71	2.67	7.87	3.50	8.69	3.86	4.28	3.77	0.000	***
FH-SN (º)	12	15.60	4.96	2.37	5.74	2.30	10.03	3.39	6.69	2.80	0.010	*
Y-Axis (NS-Gn) (º)	68.71	2.75	67.50	3.44	64.08	3.60	68.20	2.42	63.03	2.94	0.000	***
AFH (N-Me) (mm)	113.14	7.15	120	6.83	104.50	6.70	109.60	3.50	113.65	6.99	0.000	***
UFH (N-ANS) (mm)	47.44	3	51.20	2.63	45.32	3.13	51.13	2.35	49.49	3.10	0.000	***
LFH (ANS-Me) (mm)	65.82	5.90	69.06	6.36	59.24	5.16	58.59	2.98	64.54	6.10	0.000	***
P. AFH (S-Go-N-Me) %	62.49	4.96	61.14	4.29	63.56	4.80	63.54	3.41	69.35	4.07	0.000	***
Nasal Ht (N-ANS : N-Me) %	41.99	2.43	42.68	2.53	43.40	2.40	46.60	1.76	43.39	2.40	0.000	***
P : AFH (Co-Go : N-Me) %	49.33	4.76	45.34	3.55	49.56	3.87	48.60	4.10	52.53	3.90	0.000	***
Dental Variables												
U1-SN (º)	106.50	5.70	111.62	6.15	106.68	6	99.25	4.38	111.49	5.80	0.000	***
U1-NA (º)	28.13	5.79	31.60	5.56	25.78	6.24	23.40	4.22	32.27	5.20	0.000	***
U1-FH (º)	118.18	6.97	118.57	5.67	114.95	7.04	109.58	4.57	119.10	6.60	0.000	***

U1-NA (mm)	7.91	2	8.93	2.05	6.44	1.10	5.23	1.42	8.35	2.25	0.000	***
UADH (U1-PP) (mm)	26.89	3.23	27.20	3.76	24.21	3.40	22.77	1.64	26.15	3.88	0.000	***
UPDH (U6-PP) (mm)	22.07	2.49	22.28	2.56	19.60	2.30	21.04	4.93	21.74	2.30	0.001	**
IMPA (L1-MP) (º)	83.67	7.99	84.07	5.73	79.66	5.96	88.15	6.50	82.57	7.75	0.008	**
L1-NB (º)	21.38	6.90	25.50	4.28	18.38	4.68	20.41	5.95	15.77	5.60	0.000	***
Protrusion of L1 angle (L1-APg) (º)	24.57	5.76	27.60	4.34	22.74	4.38	24.44	4.34	23.40	5.17	0.042	*
FMIA (L1-FH) (º)	69.31	7.58	61.07	5.21	72.38	5.94	67.15	5.93	76.30	6.02	0.000	***
L1-NB mm	4.76	1.78	6.43	1.45	4.09	1.40	3.54	1.05	3.10	1.90	0.000	***
L1 Protrusion (L1-APg) (mm)	6.05	2.42	8.09	1.78	5.77	1.94	4.77	1.88	5.10	2.59	0.001	**
LADH (L1-MP) (mm)	38.38	3.20	40.47	2.53	36.07	2.34	36.08	5.39	38.73	3.35	0.000	***
LPDH (L6-MP) (mm)	29.45	2.73	30.90	3	26.45	2.05	28.57	2.95	30.41	2.56	0.000	***
Inter Incisal angle (U1-L1) (º)	133.40	11.40	125.10	8.95	139.86	8.99	138.49	7.96	137.75	9.10	0.000	***
Overjet (mm)	-0.16	2.87	-0.61	2.57	-2.34	2.25	-1.93	1.79	-1.27	2.23	0.003	**
Overbite (mm)	-0.45	1.80	-1.95	2.31	1.43	2.59	1.57	1.26	0.70	2.67	0.000	***
Soft Tissue Variables												
Upper lip to Esthetic-Plane (mm)	-6.16	1.55	-5.79	2.26	-7.19	2.36	-7.62	1.39	-8.12	2.36	0.000	***
Upper lip to S.T N-P FH (mm)	-2.29	1.89	-1.36	1.90	-1.59	2.03	-0.15	1.46	-3.13	1.90	0.000	***
Lower lip to Esthetic-Plane (mm)	-1.20	2.16	0.79	2.29	-1.17	2.60	-1.38	1.26	-2.07	2.40	0.004	**
Lower lip to S.T N-P FH (mm)	-3.42	3.15	-2.14	2.74	-4.06	2.50	-1.62	1.50	-6.12	2.57	0.000	***
ST Pg to S.T NP FH (mm)	1.18	4.66	6.79	4.54	0.69	3.20	4.23	2.56	-3.40	4.20	0.000	***

*** The mean difference is significant (P ≤ 0.001); ** significant (P ≤ 0.01); * significant (P ≤ 0.05);
NS not significant

Table 6: Significance (p-values) for two-way cluster comparison

Cephalometric variables	1-2	1-3	1-4	1-5	2-3	2-4	2-5	3-4	3-5	4-5
(SN-Ar) Angle (º)	.000*	.001*	.011*	.000*	.318	.000*	.649	.000*	.451	.000*
(S-N) (mm)	.000*	.028*	.000*	.000*	.000*	.137	.839	.000*	.000	.110
(S-Ar) (mm)	.000*	.825	.169	.000*	.000*	.027*	.513	.245	.000	.001*
SNA Angle (º)	.208	.001 *	.035 *	.169	.203	.007 *	.780	.000 *	.038 *	.003 *
N-A || HP (mm)	.099	.002*	.508	.025*	.510	.065	.958	.005*	.338	.030*
A to N-Perp (FH) (mm)	.000*	.188	.009*	.018*	.010*	.420	.045*	.111	.372	.325
Maxillary unit length (Co-ANS) mm	.000*	.253	.012*	.000*	.000*	.258	.389	.001*	.000*	.596
SNB Angle (º)	.173	.000 *	.004 *	.000 *	.007 *	.001 *	.004 *	.000 *	.910	.000 *
Facial Angle (FH-NPg) (º)	.000*	.945	.009*	.007*	.000*	.178	.000*	.011*	.016*	.000 *
Chin angle (Id-Pg-MP) (º)	.676	.842	.541	.710	.587	.406	.880	.656	.593	.392
Facial taper (N-Gn-Go) (º)	.010*	.322	.000 *	.000 *	.082	000 *	.000 *	.000 *	.000 *	.105
Length of MD Base (Go-Pg) (mm)	.445	.289	.447	.000 *	.136	.988	.003*	.142	.000 *	.004*
N-B || HP (mm)	.142	.000 *	.008*	.000 *	.006*	.001*	.002*	.000 *	.676	.000 *
N-Pg || HP (mm)	.280	.000 *	.013*	.000 *	.004*	.004*	.000 *	.000 *	.129	.000 *
Pg to N-Perp (FH) (mm)	.000*	.916	.009*	.011*	.000 *	.107	.000 *	.015*	.015*	.000 *
Length of MD unit (Co-Gn) (mm)	.007*	.012*	.080	.000 *	.000 *	.000 *	.909	.925	.000 *	.000 *
Pg to NB (mm)	.252	.643	.255	.001*	.446	.067	.001	.158	.000*	.225
Gonial angle (Ar-Go-Me) (º)	.000*	.042*	.124	.029*	.013*	.000 *	.000 *	.004*	.000 *	.982
Articular angle (S-Ar-Go) (º)	.615	.120	.146	.962	.518	.428	.644	.766	.140	.161
Ramus Height (Ar Go) (mm)	.918	.000 *	.300	.000 *	.004*	.353	.001*	.081	.000 *	.000 *
PFH (Co-Go) (mm)	.733	.000 *	.071	.000 *	.011*	.226	.002*	.596	.000 *	.008*
ANB (º)	.744	.000 *	.673	.000 *	.000 *	.932	.000 *	.000 *	.001 *	.000 *
Convexity (NA-APg) (º)	.643	.009*	.770	.000 *	.019*	.544	.000 *	.114	.000 *	.000 *
Facial p to AB angle (AB-NPg) (º)	1.000	.017*	1.000	.000 *	0.032*	1.000	.000 *	.037*	.055	.000 *
Facial p to SN angle (SN-NPg) (º)	.323	.000 *	.008*	.000 *	.001*	.003*	.000 *	.000 *	.229	.000 *
Midface length (Co-A) (mm)	.002*	1.000	.330	.000 *	.000 *	1.000	1.000	.064	.000 *	1.000
MD\Mx Diff (CoGn -CoANS) mm	.681	.001*	.000 *	.382	.037*	.000 *	.310	.021*	.000 *	.000 *
Witts Appraisal (AO-BO) (mm)	.096	.046*	.271	.007*	.882	.027*	.778	.015*	.569	.004*
FMA (FH-MP) (º)	.000*	.358	.148	.000 *	.000 *	.000 *	.000 *	.043*	.000 *	.032*

SN-Go-Gn (º)	1.000	.155	1.000	.000 *	.058	.354	.000 *	1.000	.000 *	.004*
Occlusal plane to SN (º)	1.000	.016*	.697	.000 *	.435	.858	.000 *	.001 *	.052 *	.000 *
(Occlusal plane -FH) angle (º)	.000 *	1.000	.915	.025 *	.013 *	.339	.000 *	1.000	.001 *	.001 *
FH-SN (º)	.119	.032 *	1.000	.076	1.000	1.000	1.000	1.000	1.000	1.000
Y-Axis (NS-Gn) (º)	.197	.000 *	.618	.000 *	.001	.535	.000 *	.000 *	.147	.000 *
AFH (N-Me) (mm)	.001 *	.000 *	1.000	1.000	.000 *	.000 *	.002*	.022	.000 *	.063
UFH (N-ANS) (mm)	.001 *	.025*	.001*	.019*	.000 *	1.000	.633	.000 *	.000 *	.867
LFH (ANS-Me) (mm)	.625	.000 *	.001 *	1.000	.000 *	.000 *	.110	1.000	.001 *	.012 *
P. AFH (S-Go-N-Me) %	1.000	1.000	1.000	.000 *	1.000	1.000	.000 *	1.000	.000 *	.002 *
Nasal Ht (N-ANS : N-Me) %	1.000	.119	.000 *	.075	1.000	.000 *	1.000	.001 *	1.000	.000 *
P : AFH (Co-Go : N-Me) %	.022*	1.000	1.000	.006*	.020 *	.416	.000 *	1.000	.032 *	.042*
U1-SN (º)	.005*	.909	.000 *	.000 *	.008 *	.000 *	.940	.000 *	.001 *	.000 *
U1-NA (º)	.426	.721	.084	.009 *	.014*	.002*	1.000	1.000	.000 *	.000 *
U1-FH (º)	1.000	.364	.001 *	1.000	.893*	.005	1.000	.144	.090	.000 *
U1-NA (mm)	.787	.001 *	.000 *	1.000	.001 *	.000 *	1.000	.527	.000 *	.000 *
UADH (U1-PP) (mm)	1.000	.009*	.002*	1.000	.068	.009*	1.000	1.000	.147	.023*
UPDH (U6-PP) (mm)	1.000	.001 *	1.000	1.000	.022 *	1.000	1.000	1.000	.010*	1.000
IMPA (L1-MP) (º)	.854	.017*	.049 *	.486	.057	.143	.504	.000 *	.089	.016 *
L1-NB (º)	.212	.259	1.000	.000 *	.002 *	.234	.000 *	1.000	.596	.132
Protrusion of L1 angle (L1-APg) (º)	.523	1.000	1.000	1.000	.032*	1.000	.085	1.000	1.000	1.000
FMIA (L1-FH) (º)	.001 *	.424	1.000	.000 *	.000 *	.159	.000 *	.153	.121	.000 *
L1-NB mm	.012*	.857	.208	.000 *	.000 *	.000 *	.000 *	1.000	.149	1.000
L1 Protrusion (L1-APg) (mm)	040*	1.000	.748	.541	.018*	.002 *	.000 *	1.000	1.000	1.000
Inter Incisal angle (U1-L1) (º)	.076	.032*	.821	.306	.000 *	.005*	.000 *	1.000	1.000	1.000
Overjet (mm)	.551	.000 *	.023 *	.039 *	.029 *	.164	.386	.610	.067	.400
Overbite (mm)	.332	.005*	.055	.215	.000 *	.001 *	.003 *	1.000	1.000	1.000
Upper lip to Esthetic-Plane (mm)	1.000	.312	.253	.000 *	.347	.220	.003 *	1.000	.560	1.000
Upper lip to S.T N-P FH (mm)	1.000	1.000	.000 *	.445	1.000	1.000	.032*	.225	.009*	.000 *
Lower lip to Esthetic-Plane (mm)	.055	1.000	1.000	.821	.088	.155	.001*	1.000	.999	1.000
Lower lip to S.T N-P FH (mm)	1.000	1.000	.356	.000 *	.231	1.000	.000 *	.067	.016 *	.000 *
ST Pg to S.T NP FH (mm)	.000 *	1.000	.190	.000 *	.000 *	1.000	.000 *	.093	.000 *	.000 *

*P-values < 0.05

Several studies reported substantial variations in the size of captured PCs.[5–7,9,10,19] In particular, Bui et al.[5] and De Frutos et al.[9] identified 5 and 10 PCs which covered 67% and 92.70% of their overall sample variance respectively. Moreno et al.[6] and Li et al.[7] identified 6 PCs, which represented 81.20% and 73% of their overall variation, respectively.

Class III malocclusion participants were classified using 8 PCs as factors for CA. This study used a clustering algorithm to determine the number of Class III subclusters, carried out separately in 3–7 subclusters. The models that included 6 or 7 clusters were rejected because of their great similarity and because one of the clusters contained fewer than 5 cases. The 3-cluster model was also rejected due to data loss and the absence of clearly detailed phenotypes. Furthermore, the 4-cluster model did not include a separate cluster of individuals exhibiting an important vertical Class III phenotype compared with the 5-cluster model. A further cluster confirmation was carried out by locating individuals nearest to the cluster means and checking their cephalometric data to confirm that all of the clusters expressed distinct, significant clinical Class III phenotypes. Moreover, this study used the cluster validation graph as one of the scientific methods for selecting the optimal number of clusters. As a result, the graph confirmed that the five clusters had the most statistical significance. Consequently, the 5-cluster model was selected because it represents the most clinically significant and statistically reliable phenotypes.

Several studies used CA to classify patients with Class III malocclusion. Bui et al.[5] and Moreno et al.[6] reported 5 clusters in Caucasians; this is the same as the number of phenotypic subclusters identified in this study. De Frutos et al.[9,20] detected 6 and 4 clusters, respectively. Asians presented 4 clusters, as reported by Li et al.[7] and Alshoaibi et al.[10]. In another Asian study, Li et al.[21] identified 14 sub-phenotypes, but this may not accurately represent the most common skeletal class III malocclusion sub phenotypes. Conversely, studies on Caucasians by Auconi et al.[22,23] and Abu Alhaija et al.[14] found 3 sub-phenotypes that may be considered simplistic and not practical for clinical use. A systematic review 8 suggested a classification system with 4–7 clusters may be effective for clinical application when combined with comprehensive sub-grouping.

The current study found that the first cluster, with a slight maxillary retrusion and mandibular protrusion, was the most representative group, accounting for 31.25% of the sample. This cluster was similar to C3 in Caucasians.[6,9,20] In previous studies by Bui et al.[5] and Li et al.[7], the retrusive jaw phenotype was the most representative group, while in this study, the retrusive jaw phenotype (C4) was the least representative, accounting for only 9% of the sample.

This research found that Cluster 5 was the most severe skeletal sub-phenotype of Class III malocclusion, which had the second-largest group of participants, with 27.77%. It had a combination of severe mandibular prognathism and severe maxillary deficiency. Conversely, this phenotype had the fewest cases reported in previous studies[6,7,9,10,14], possibly due to selection processes or because this phenotype was the least commonly found in adults of those ethnic groups.

This study found gender differences in clusters, with 3 clusters having significantly higher female-to-male ratios (C1: 62.20%, C3: 78.10%, and C4: 76.90%). Li et al.[7] found that 2 clusters (C3 and C4) had higher female distributions than men (67.40% and 75%, respectively), while De Frutos et al.[9] found 3 clusters with female-to-male ratio differences greater than 40%. It is therefore necessary to take into account the gender variations in Class III craniofacial characteristics and the related variations in sub phenotypes.

The aforementioned studies proved the existence of racial disparities between Caucasian and Asian populations, suggesting the need to conduct further studies on other ethnicities. As a result, this study provides the first scientifically valuable data on the skeletal sub-phenotyping of Class III malocclusion in Yemeni subjects.

Study Limitations

There are limitations to this study, including the use of two-dimensional cephalograms, which may not accurately represent facial morphological structure. The exclusion of various ethnic groups could potentially impact generalizability. A significant limitation was the lack of data about familial history, which prevented an accurate evaluation of malocclusion development and its association with specific subclusters.

Clinical Application

Identifying sub-clusters of Class III malocclusions provides an accurate diagnosis and personalized treatment plans, enabling orthodontists to make better

choices for interventions like orthopedic appliances or orthognathic surgery. Therefore, early detection of craniofacial growth can greatly improve compliance in those cases where early intervention is most effective.

Future Projects

Classification of the skeletal sub-clusters of Class III malocclusion can help us better understand the correlations between genotype and phenotype. This knowledge can help researchers generate new preventative strategies, improved treatment planning, and precise, personalized treatments for patients with a particular sub-phenotype of Class III malocclusion.

CONCLUSION

Eight principal components, which interpreted 79.40% of the overall variance observed in the 62 variables, were documented and five distinct clusters within Class III malocclusion were identified. These phenotypic clusters were: mild Class III phenotype; vertical phenotype; Class III with mandibular protrusion; Class III with maxillary retrusion; and severe Class III with maxillary retrusion and mandibular protrusion.

List of Abbreviations

PC: principal component; PCA: principal component analysis; CA: cluster analysis; C: cluster; ICC: intra-class correlation coefficient.

DECLARATIONS

Participant consent and ethics approval

This prospective cross-sectional study was ethically approved by the Ethical Committee on Medical Research (ECA/SU/FD1) of Sana`a university. All methods were performed in compliance with the Helsinki Declaration's principles. Furthermore, all participants signed a form of written consent and approved to use the information for research purposes.

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Interests of Competing

The authors did not declare any competing interest.

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