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RESEARCH ARTICLE

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Anatomical phenotype of obstructive sleep apnea patients based on cluster analysis

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Abstract

Objectives: To generate a novel subtype of obstructive sleep apnea (OSA) based on anatomical features and verify the differences in the response of different subtypes to orthodontic treatment, thus providing a theoretical reference for clinical decision-making.

Materials and Methods: A K-means cluster analysis was performed for this retrospective serial study, which includes 722 OSA patients, aged 44.0 (36.0, 54.0) years, 80.2% male, with apnea-hypopnea index (AHI) of 23.2 (13.4, 39.6) events·h^{-1}, and body mass index (BMI) of 25.47 ± 3.00 kg·m^{-2}. All samples were divided into three subtypes based on AHI, BMI, and five variables of craniofacial measurements. Sixty-seven cases with mandibular advancement devices (MAD) therapeutic results were further applied to validate the efficacy and side effects of this treatment in different subtypes.

Results: Two hundred and thirty patients (31.9%) were characterized as cluster 1: AHI of 17.65 (11.80, 30.42) events·h^{-1}, BMI of 23.65 ± 2.62 kg·m^{-2}, with skeletal Class II high-angle shape. Cluster 2 included 278 patients (38.5%): AHI of 17.00 (11.00, 26.48) events·h^{-1}, BMI of 25.36 ± 2.53 kg·m^{-2}, soft palate length (SPL) of 39.25 mm (36.12, 42.20), with basically normal skeleton and normal airway size. Cluster 3, consisting of 214 patients (29.6%), exhibited a combination of anatomical deformity and obesity, with the highest AHI and BMI of 45.35 (30.42, 62.53) events·h^{-1} and 27.57 ± 2.59 kg·m^{-2} respectively, but less deformity degree than cluster 1. Cluster 2 had the highest response rate and relatively mild side effects with MAD.

Conclusions: Orthodontic treatment based on anatomical morphology could exert a better effect on mild-moderate OSA patients with mild skeletal deformity.

KEYWORDS
cluster analysis, craniofacial features, mandibular advancement devices, obstructive sleep apnea, subtype

Xu Gong and Xuemei Gao contributed equally to this work.

1 | INTRODUCTION

Obstructive sleep apnea (OSA) is recognized as a complex and heterogeneous syndrome, with different aetiology,[1,2] predisposing factors,[3] clinical presentations,[4,5] and comorbidities.[6] Currently, overnight polysomnography (PSG) remains the gold standard for the diagnosis of OSA.[7] The assessment of its severity and its management have intimately been linked to a single metric, the apnea-hypopnea index (AHI).[8,9] However, it is increasingly recognized that the heterogeneity of OSA is not captured only by the AHI.[10] Therefore, it is necessary to add multiple factors to the comprehensive evaluation of OSA.

One way to approach the heterogeneity of OSA is to classify the disorder into smaller and more homogeneous subtypes, sometimes referred to as "phenotypes".[11] Unsupervised cluster analysis has recently been used to identify subtypes of patients who are diagnosed with OSA. Previous studies mainly focused on subjective symptoms, polysomnographic variables, and comorbidities.[5,12–14] Pien et al[15] discovered that OSA treatment response patterns differed by initial clinical phenotype and positive airway pressure (PAP) adherence. These studies have deepened the understanding of OSA heterogeneity and may assist the clinician in the selection of treatment options.

Craniofacial features are known to be an important anatomical factor of OSA, and OSA-related features mainly include a decreased SNB angle (indicating mandible retrusion), reduced mandible length, maxilla deficiency, steep mandibular plane, inferiorly positioned hyoid bone, decreased cranial base length, decreased posterior airway space (PAS), etc.[16–20] However, no uniform results have been obtained due to the high heterogeneity of previous studies.[16] OSA treatment is traditionally targeted to anatomical traits, which includes continuous positive airway pressure (CPAP), the placement of mandibular advancement devices (MAD), upper airway surgery, weight loss, and positional therapy.[1] However, craniofacial features are seldom considered in the comprehensive analysis of subtypes. Thus, it is of great value to investigate a novel phenotype of OSA based on craniofacial features, which would help orthodontists better evaluate OSA patients seeking MAD treatment. The aim of this study is to generate a new subtype based on anatomical features and verify the differences in the response of different subtypes to MAD treatment, thus providing a theoretical reference for clinical decision-making.

2 | MATERIALS AND METHODS

This retrospective cross-sectional study was registered in the Chinese Clinical Trial Registry (Identifier: ChiCTR2000038751). It was approved by the ethics committee of Peking University School and Hospital of Stomatology (PKUSSIRB-202054026). This study is in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

2.1 | Participants

The 722 samples came from 827 consecutive snoring patients who referred for mandibular advancement device (MAD) treatment in the Sleep Center of Peking University School and Hospital of Stomatology.

The inclusion criteria were as follows:

1. aged 18 years or over;
2. had both baseline polysomnography (PSG) and standardized lateral cephalogram;
3. baseline PSG showing AHI equal to or over five events·h^{-1}.

The exclusion criteria were as follows:

1. diagnosed with other sleep disorders;
2. incomplete or poor imaging data;
3. with cleft lip and palate, congenital syndrome, or other craniofacial dysplasia;
4. history of craniofacial surgery which might affect the initial morphology;
5. referred to orthognathic surgery or combined with uvulopalatopharyngoplasty (UPPP).

Finally, a total of 722 patients with OSA (579 males and 143 females) were recruited for this study. One hundred and two patients were excluded because AHI <5 events·h^{-1}, and 3 patients were excluded due to a history of craniofacial surgery. Among the 722 patients, 67 had PSG feedback and 33 had post-treatment questionnaires, and they were included in follow-up cases in clinical application response analysis.

On the basis of body mass index (BMI) value according to Chinese standard, the patients could be categorized into: Normal: BMI < 24 kg·m^{-2}; Overweight: 24 ≤ BMI < 28 kg·m^{-2}; Obesity: BMI ≥ 28 kg·m^{-2}.

2.2 | Polysomnography

Each patient in our study underwent overnight polysomnography in a qualified sleep center at other general hospitals. The polysomnography included full electroencephalogram (EEG), bilateral electro-oculogram (EOG), chin electromyogram (EMG), leg EMG, electrocardiogram (ECG), nasal/oral airflow thermistor, pulse oximetry, and body position sensors. PSGs were acquired and scored following the guidelines of the American Academy of Sleep Medicine.[21] AHI (event·h^{-1}), apnea index (AI, event·h^{-1}), hypopnea index (HI, event·h^{-1}) and the lowest O_2 saturation ($LSaO_2$, %) were measured. OSA severity was defined based on AHI and patients were classified as mild (5 ≤ ODI < 15 events h^{-1}), moderate (15 ≤ ODI < 30 events h^{-1}), and severe (ODI ≥ 30 events h^{-1}).

2.3 | Cephalometric analysis

A lateral cephalogram was routinely obtained in the sitting position during the end-expiration phase. The patients were asked to keep teeth in maximum contacted intercuspal position with tongue tip touching the incisors and without swallowing or speaking. A cephalostat was used to keep the subject's head in a position with the Frankfort horizontal line parallel to the floor during exposure.

Cephalometric measurements were accomplished by a single orthodontist (HLP) using the self-developed software. The cephalometric landmarks and measurements used in this study are outlined in Figure 1, which are based on the methods described previously by Lowe et al,[22] Tangugsorn et al,[23] and Liu et al.[24] The cephalometric variables used in this study were divided into four parts: craniofacial (14 variables), soft palate (2 variables), tongue (2variables), pharyngeal airway (7 variables) and hyoid bone (2 variables). Four weeks later, methodological evaluation was carried out by repeating the digitization process for 25 randomly selected radiographs. Differences calculated using Dahlberg's formula[25] ranged from 0.31 to 0.69 mm for the linear measurements and from 0.4 to 1.0 degrees for the angular measurements. Houston's coefficient of reliability[26] ranged from 90% to 99%, which showed a preferable consistency.

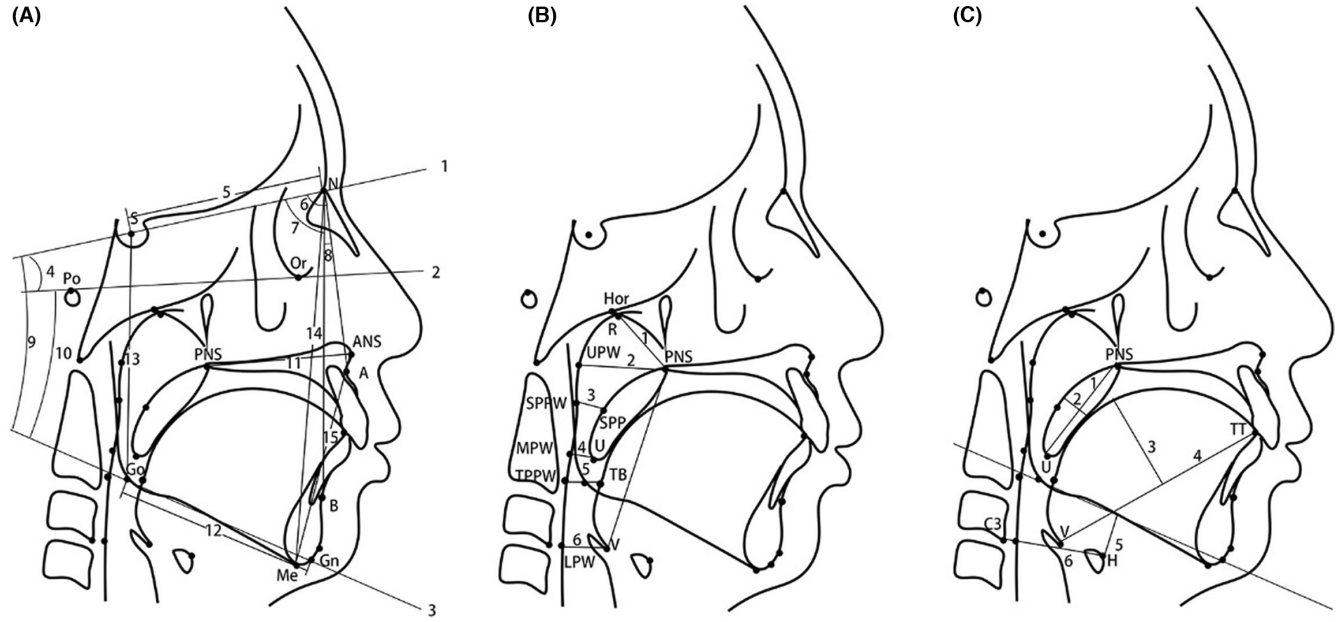


FIGURE 1 Cephalometric measurements. (A). Craniofacial hard tissue structure: S-Center of the sella turcica. N-Nasion, the deepest point in the concavity of the nasofrontal suture. Po-Porion, the most superior point of the bony external auditory meatus. Or-Orbitale, the most inferior point on the infraorbital margin. ANS, anterior nasal spine; PNS, posterior nasal spine. A-A point, the deepest point in the concavity of the anterior maxilla between the anterior nasal spine and the alveolar crest. B-B point, the deepest point in the concavity of the anterior mandible between the alveolar crest and pogonion. Me-Menton, the most inferior point on the body chin. Gn-Gnathion, the most anteroinferior point on the bony chin. Go-Gonion, the most posterior-inferior point on the angle of the mandible. 1. SN plane (the line between S and N); 2. FH plane (the line between Po and Or); 3. Mandibular plane (the line between Go and Gn); 4. Anterior cranial base inclination (the angle between SN and FH); 5. S-N; 6. SNA (The Angle between SN and NA); 7. SNB (The Angle between SN and NB); 8. ANB (The Angle between NA and NB); 9. MP/SN (The Angle between MP and SN); 10. MP/FH (The Angle between SN and FH); 11. Maxillary length (ANS-PNS); 12. Mandibular body length (Go-Gn); 13. Posterior facial height (S-Go); 14. Anterior facial height (N-Me); 15. Anterior lower facial height (ANS-Me) (B). Upper airway measurement: Hor-Hormion, the anterior border of the lateral pterygoid lamina intersects the lower border of the posterior skull base. R-The line between Hor and PNS intersects with the posterior pharyngeal wall. UPW-Upper pharyngeal wall point, the line between Ba and PNS intersects with the posterior pharyngeal wall. SPP-The intersection of a vertical line from the center of the soft palate to the posterior pharyngeal wall and the posterior margin of the soft palate. SPPW-The point perpendicular to the posterior pharyngeal wall through the center of the soft palate. U-The tip of the uvula. TB-Through the line between Go and B and the intersection of the tongue base. TPPW-Through the line between Go and B and the intersection of the posterior pharyngeal wall. V-Vallecula, the most posteroinferior base of the tongue. LPW-The point perpendicular to the posterior wall of the pharynx by V. 1. PNS-R. 2. PNS-UPW. 3. SPP-SPPW. 4. U-MPW. 5. PAS: posterior airway space (TB-TPPW). 6. V-LPW. 7. VAL: vertical airway length (PNS-V). (C). Surrounding tissue of upper airway: TT-Most anterior point of the tip of the tongue. H-The most superior and anterior point on the body of the hyoid bone. C3-anteroinferior limit of the third cervical vertebra. 1. SPL: Soft palate length (PNS-U). 2. SPT: Soft palate thickness (maximum thickness of soft palate measured on the line perpendicular to PNS-U line). 3. TGL: Tongue length (V-TT). 4. TGH: Tongue height (maximum height of tongue along the perpendicular line of V-TT line to tongue dorsum). 5. H-MP: Perpendicular distance from the MP to H. 6. C3-H.

2.4 | Cluster analysis

Among BMI, cephalometric measurements (as shown in Figure 1), complications (hypertension, diabetes, cardiovascular disease, and chronic obstructive pulmonary disease), symptoms and signs (snoring, recognizable apnea, difficulty falling asleep, slight sleep dry mouth, and Epworth Sleep Scale [ESS]), and then classification indicators were determined based on correlation analysis and regression analysis. Finally, the K-means cluster analysis was performed to categorize all the subjects into characteristic subgroups based on BMI, AHI, ANB (the angle indicating sagittal relationship of maxillary and mandible), MP/SN (the angle indicating inclination of mandible), PAS, H-MP (the distance indicating hyoid height), and soft palate length (SPL) to explore OSA anatomical phenotype. The procedure is as follows: First, the categorical variables were standardized to reduce the impact of different dimensions on the results of the cluster analysis. Next, the boxplot was used to detect the outliers, and in this study, no obvious outliers were found to deal with. Then, the optimal number of subtypes was determined based on average silhouette width (ASW)[27] and Gap statistic.[28] Finally, the patients were divided into homogeneous subtypes by K-means clustering analysis algorithm, and the results of the clustering analysis were visualized. K-means cluster analysis was performed using the software program R, version 4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria).

2.5 | Treatment outcome evaluation

There were 67 patients (60 males, 45.2 ± 12.8 years, 16 of cluster 1, 32 of cluster 2, 19 of cluster 3) who went to the general hospital for PSG evaluation and 33 patients (26 males, 52.7 ± 11.9 years, 16 of cluster 1, 32 of cluster 2, 19 of cluster 3) had side effects questionnaire after mandibular advancement device (MAD) therapy. They were used as response subjects for the clinical application of three clusters.

The improvement rate of AHI, AI, HI, and $LSaO_2$ of the patients can be calculated:

AHI improvement rate = (pre-treatment AHI − post-treatment AHI)/pre-treatment AHI.

AI improvement rate = (AI before treatment − AI after treatment)/AI before treatment.

HI improvement rate = (pre-treatment HI − post-treatment HI)/pre-treatment HI.

$LSaO_2$ improvement rate = ($LSaO_2$ after treatment − $LSaO_2$ before treatment)/$LSaO_2$ before treatment.

At the same time, the patients were classified into complete response, response, and non-response according to the following changes in AHI:

Complete response: AHI reduced to <5 events·h^{-1}.

Response: ≥50% reduction from baseline.

Non-response: <50% reduction from baseline.

2.6 | Statistical analysis

Normal distribution was analysed using the Kolmogorov-Smirnov test. Normally distributed data were expressed as a mean and standard deviation (mean ± SD), and non-normally distributed data were expressed as a median and interquartile range (median [interquartile range, IQR]). Categorical variables are expressed as numbers (percentages).

After the clusters were identified, their differences in patient demographics and other characteristics which include sex, age, BMI, AHI, and lowest oxygen saturation ($LSaO_2$) during the sleep study, cephalometric measurements, and treatment response were examined via Chi-squared, analysis of variance (ANOVA), or Kruskal-Wallis equality-of-populations rank tests, as appropriate. All data were then pairwise compared with Bonferroni post hoc analysis to determine specific differences between the groups.

All data were analysed using SPSS, version 26.0 (26.0; SPSS Inc., Inc., Chicago, IL, USA) and the software program R, version 4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria). The significance level was $P < .05$.

3 | RESULTS

3.1 | Overall polysomnographic characteristics

The patients aged 44.0 (36.0, 54.0) years old, predominantly of males (80.2%). The average BMI was 25.35 ± 3.00 kg·m^{-2}, and the average AHI was 23.20 (13.40, 39.40) events·h^{-1}.

3.2 | Determination of three clusters

According to average silhouette width (ASW) and Gap statistic (Figure 2), the optimal number of subtypes was determined and was equal to 3.

In addition, three homogeneous clusters were identified by K-means cluster analysis (Figure 3). Two hundred and thirty patients (31.9%) were characterized as cluster 1, 278 patients (38.5%) were characterized as cluster 2, and 214 patients (29.6%) were characterized as cluster 3.

3.3 | Differences among three clusters by comparison of cephalometric variables

The inter-cluster comparison of variables including demographic, polysomnographic, and cephalometric variables is shown in Table 1.

Patients in cluster 1 mainly represented moderate OSA without obesity and manifested obvious skeletal discrepancy, including severe Class II sagittal skeletal pattern (featured with maxillary protrusion and mandibular retraction) with a hyperdivergent pattern.

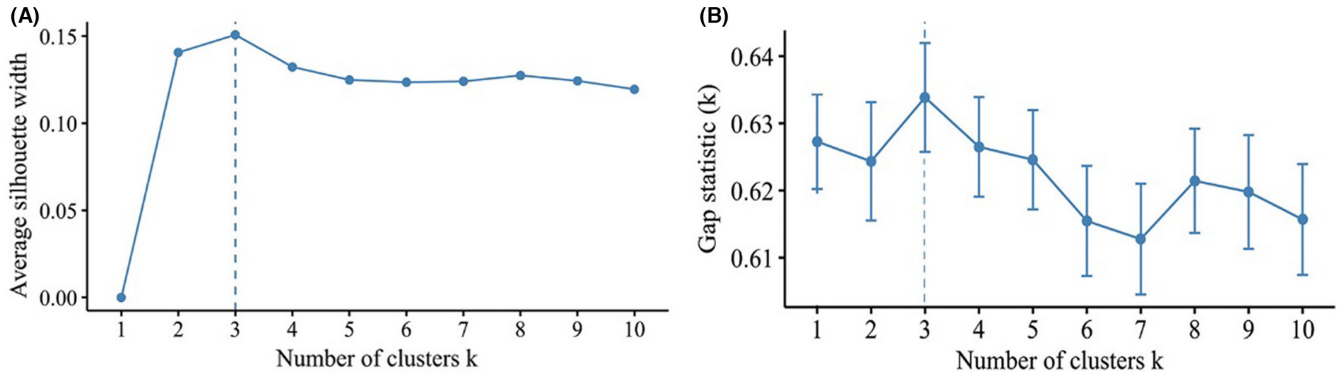
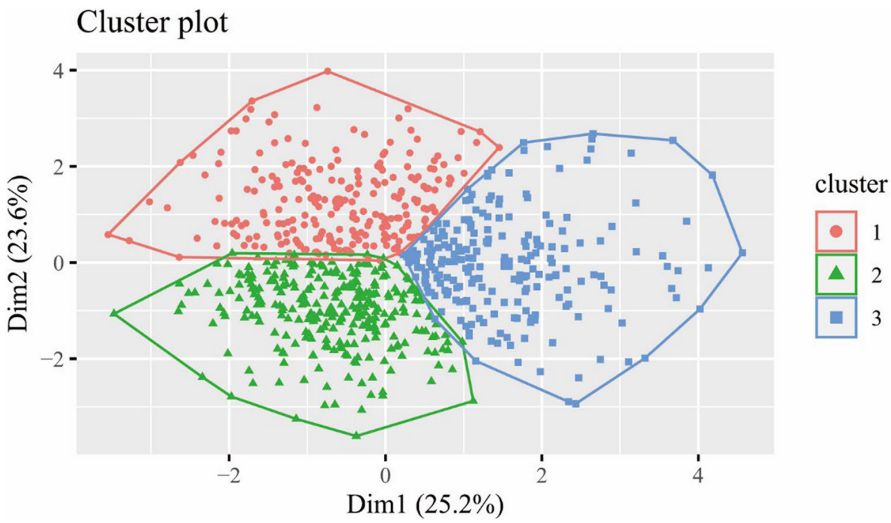


FIGURE 2 Two methods to determine the optimal number of clusters in cluster analysis. A, Average silhouette width; B, gap statistic.

FIGURE 3 Scatter plot for three clusters identified by cluster analysis.



Patients were characterized by the narrowest airway space. There is no obvious enlargement in the soft tissues.

While patients in cluster 2 exhibited moderate OSA and were overweight. Patients in this cluster showed less obvious skeletal abnormalities and the widest airway space among the three clusters. Patients had elongated soft palate in this cluster.

Patients in cluster 3 were characterized by severe OSA, obesity, and Class II malocclusion. Patients showed narrow airway space, obviously inferior hyoid bone displacement, and marked soft palate elongation.

3.4 | Treatment response of mandibular advancement device in patients among different clusters

Sixty-seven patients had PSG before and after mandibular advancement device treatment. The comparison among the efficacies of the mandibular advancement device on different clusters is shown in Table 2. After treatment, the improvement in AHI of cluster 3 was better than that of cluster 1. In addition, the improvement in AI of cluster 3 was better than that of cluster 1 and cluster 2. There was a statistical difference in response rate among the three clusters ($P = .02$). After Bonferroni pairwise comparison, patients with cluster 2 had the highest response rate (90.6%) after mandibular advancement device treatment. Differences of wearing frequency and discomfort feeling of mandibular advancement appliance in 33 patients are shown in Table 3.

4 | DISCUSSION

Since Ye et al[12] firstly conducted the cluster analysis of patients with OSA, researchers have attempted cluster analysis based on various aspects. An ad hoc working group of the European Respiratory Society and the European Sleep Research Society developed a new approach (beyond the AHI) to predict the disease, which integrated symptoms and cardiometabolic comorbidities.[29] In their study, the OSA patients were divided into four groups: A (minor symptoms and comorbidities), B (severe symptoms, minor comorbidities), C (minor symptoms, severe comorbidities) and D (severe symptoms and comorbidities), which were known as BAVENO classification criteria. Such cluster analyses were mainly based on subjective symptoms, PSG parameters and comorbidities. Since then, subtypes based on symptom experiences and the existence of major comorbidities are generally accepted.[5,12,13,30] Besides, Pien et al[15] found that the

TABLE 1 Comparison of demographic, polysomnographic, and cephalometric measurements among clusters.

Variables	Cluster 1 (n = 230)	Cluster 2 (n = 278)	Cluster 3 (n = 214)	*P* value	Multiple comparison		
					1 vs 2	1 vs 3	2 vs 3
					P value	*P* value	*P* value
Age[b] (years)	45.0 (35.0, 56.0)	41.0 (34.0, 50.0)	46.0 (39.0, 55.0)	.001**	.069	.478	.001**
Gender							
Male[c]	135 (58.7)	243 (87.4)	201 (93.9)	<.001***	<.001***	<.001***	.048*
Female[c]	95 (41.3)	35 (12.6)	13 (6.1)	<.001***	<.001***	<.001***	.048*
BMI[a] (kg/m^2)	23.65 ± 2.62	25.36 ± 2.53	27.57 ± 2.59	<.001***	<.001***	<.001***	<.001***
PSG							
AHI[b] ($events{\cdot}h^{-1}$)	17.65 (11.80, 30.42)	17.00 (11.00, 26.48)	45.35 (30.42, 62.53)	<.001***	.820	<.001***	<.001***
$LSaO_2$[b] (%)	83.00 (78.25, 88.00)	83.00 (78.00, 87.00)	76.00 (66.00, 82.00)	<.001***	1.000	<.001***	<.001***
Craniofacial							
SNA°[a]	81.16 ± 3.83	82.33 ± 3.70	81.53 ± 3.81	.002**	.002**	.907	.062
SNB°[a]	73.53 ± 3.39	77.99 ± 3.46	75.23 ± 3.82	<.001***	<.001***	<.001***	<.001***
ANB°[a]	7.63 ± 2.01	4.33 ± 2.00	6.30 ± 2.36	<.001***	<.001***	<.001***	<.001***
MP/FH°[b]	32.15 (27.85, 36.18)	23.70 (20.30, 27.50)	28.70 (24.85, 32.40)	<.001***	<.001***	<.001***	<.001***
MP/SN°[b]	38.35 (35.00, 42.55)	29.05 (25.20, 32.18)	35.00 (31.70, 39.00)	<.001***	<.001***	<.001***	<.001***
S-N[a] (mm)	63.30 ± 3.80	64.86 ± 3.41	66.03 ± 3.95	<.001***	<.001***	<.001***	.009**
SN-FH°[b]	8.00 (5.80, 1.67)	6.30 (4.10, 8.47)	7.30 (5.52, 10.10)	<.001***	<.001***	.670	<.001***
ANS-PNS[a] (mm)	45.84 ± 3.02	46.87 ± 2.94	47.73 ± 3.46	<.001***	.001**	<.001***	.015*
Go-Gn[a] (mm)	69.07 ± 4.60	74.78 ± 4.95	72.90 ± 5.16	<.001***	<.001***	<.001***	<.001***
PFH[a] (mm)	78.05 ± 7.18	86.01 ± 6.59	85.03 ± 6.46	<.001***	<.001***	<.001***	.335
AFH[b] (mm)	123.40 (118.32, 128.50)	123.00 (118.45, 127.88)	129.60 (123.82, 135.10)	<.001***	1.000	<.001***	<.001***
PFH/AFH[a]	0.63 ± 0.04	0.70 ± 0.04	0.66 ± 0.04	<.001***	<.001***	<.001***	<.001***
ALFH[b] (mm)	70.10 (66.82, 73.72)	68.80 (64.70, 71.97)	72.95 (69.30, 77.60)	<.001***	.002**	<.001***	<.001***
ALFH/AFH[a]	0.57 ± 0.02	0.56 ± 0.02	0.57 ± 0.02	<.001***	<.001***	1.000	<.001***
Pharyngeal airway space							
PNS-R[a] (mm)	22.16 ± 2.57	22.78 ± 2.65	23.23 ± 2.83	<.001***	.029*	<.001***	.195
PNS-UPW[a] (mm)	25.41 ± 2.84	26.21 ± 2.95	26.19 ± 3.02	.004**	.007**	.017*	1.000
SPP-SPPW[b] (mm)	8.10 (6.40, 9.67)	9.50 (7.23, 11.28)	8.20 (6.60, 9.90)	<.001***	<.001***	1.000	<.001***
U-MPW[b] (mm)	7.00 (5.60, 8.80)	8.90 (7.40, 11.00)	8.10 (6.40, 9.60)	<.001***	<.001***	.004**	<.001***
PAS[b] (mm)	7.70 (5.80, 9.70)	11.90 (9.00, 14.00)	9.05 (7.20, 11.67)	<.001***	<.001***	<.001***	<.001***
V-LPW[a] (mm)	18.06 ± 4.03	19.80 ± 4.55	19.74 ± 4.64	<.001***	<.001***	<.001***	1.000
VAL[a] (mm)	70.37 ± 7.09	71.60 ± 6.56	79.05 ± 6.12	<.001***	.113	<.001***	<.001***
Soft palate							
SPL[b] (mm)	37.85 (34.50, 40.10)	39.25 (36.12, 42.20)	42.45 (39.42, 45.10)	<.001***	<.001***	<.001***	<.001***
SPT[b] (mm)	11.20 (9.93, 12.40)	11.40 (10.03, 12.80)	12.40 (11.20, 13.90)	<.001***	.286	<.001***	<.001***
Tougue							
TGL[a] (mm)	77.17 ± 6.20	80.18 ± 6.21	85.91 ± 5.87	<.001***	<.001***	<.001***	<.001***

TABLE 1 (Continued)

Variables	Cluster 1 (n = 230)	Cluster 2 (n = 278)	Cluster 3 (n = 214)	*P* value	Multiple comparison		
					1 vs 2 *P* value	1 vs 3 *P* value	2 vs 3 *P* value
TGH[a] (mm)	35.43 ± 3.84	34.86 ± 3.80	36.83 ± 3.71	<.001***	.274	<.001***	<.001***
Hyoid bone							
H-MP[a] (mm)	20.36 ± 5.42	20.16 ± 5.25	27.49 ± 5.29	<.001***	1.000	<.001***	<.001***
C3H[a] (mm)	35.62 ± 4.37	39.76 ± 4.55	40.72 ± 4.44	<.001***	<.001***	<.001***	.053

Note: Data was expressed by mean ± SD or median (interquartile range, IQR).

Abbreviations: AFH, anterior facial height; AHI, apnea-hypopnea index; ALFH, anterior lower facial height; BMI, body mass index; $LSaO_2$, the lowest oxyhemoglobin saturation; PAS, posterior airway space; PFH, posterior facial height; SPL, soft palate length; SPT, soft palate thickness; TGH, tongue height; TGL, tongue length; VAL, vertical airway length.

*$P < .05$; **$P < .01$; ***$P < .001$.

[a]One-way ANOVA test was performed.

[b]Kruskal–Wallis test was performed.

[c]Chi-square test was performed.

TABLE 2 The differences in treatment response of mandibular advancement device in patients among different clusters.

Variables	Cluster 1 (n = 16)	Cluster 2 (n = 32)	Cluster 3 (n = 19)	*P* value
△AHI (events·h^{-1})	9.40 (1.87, 22.88)	15.40 (10.68, 23.20)	27.80 (14.20, 47.55)[d]	.015*
△AI (events·h^{-1})	5.06 (1.78, 16.87)	9.72 (4.97, 17.60)	20.60 (11.05, 28.35)[d,e]	.013*
△HI (events·h^{-1})	2.45 (−0.13, 6.47)	5.28 (2.69, 10.40)	4.80 (0.43, 19.36)	.33
△$LSaO_2$ (%)	5.00 (0.25, 8.00)	6.00 (1.00, 9.00)	7.00 (0.50, 16.00)	.619
AHI improvement rate (%)[a]	64.90 (22.30, 78.18)	73.72 (64.58, 89.70)	82.09 (40.79, 95.02)	.168
AI improvement rate (%)[a]	63.70 (37.39, 75.81)	81.31 (65.10, 91.35)	82.98 (54.31, 97.22)	.078
HI improvement rate (%)[a]	72.76 (−1.69, 81.73)	75.64 (50.82, 91.10)	68.92 (8.26, 93.71)	.622
$LSaO_2$ improvement rate (%)[a]	5.00 (0.25, 8.00)	6.00 (1.00, 9.00)	7.00 (0.50, 16.00)	.512
Complete response rate (%)[b]	8 (50.0)	18 (56.3)	6 (31.6)	.229
Response rate (%)[c]	9 (56.2)	29 (90.6)[f]	13 (68.4)	.02*
Non-response rate (%)[c]	7 (43.8)	3 (9.4)	6 (31.6)	.02*

Note: Continuous variables were expressed as Median (interquartile range, IQR); categorical variables were expressed as n (percentage).

Abbreviations: AHI, apnea hypopnea index; AI, apnea index; HI, hypopnea index, low ventilation index; $LSaO_2$, the lowest oxyhemoglobin saturation.

[a]Kruskal-Wallis test was used.

[b]Chi-square test is used.

[c]Fisher's exact test is used.

[d]Comparison between cluster 3 and cluster 1 $P < .05$.

[e]Comparison between cluster 3 and cluster 2 $P < .05$.

[f]Comparison between cluster 2 and cluster 1 $P < .05$.

*$P < .05$, **$P < .01$, ***$P < .001$.

patients in the different clusters had different therapeutic responses toward CPAP. Their research plays an important role in the identification of the heterogeneity of OSA. However, the important craniofacial anatomy is excluded from the above cluster analyses.

In fact, work on the craniofacial factors could lay the groundwork for possible benefits of mandibular advancement device therapy and orthognathic surgery on OSA. Impaired anatomy remains a key target for therapy and the focus of most existing treatments, while research that based on craniofacial features to identify patient subgroups is scant.[1,31,32] An et al[32] have identified three clusters in 89 cephalograms of patients with mild or moderate OSA, categorizing them into obesity type, skeletal type and complex type. Furthermore, Kim et al[31] yielded three clusters in 421 patients with OSA according to ANB and MPA and labelled them as noncraniofacial phenotype, craniofacial skeletal phenotype and complicated phenotype.

Present studies have collected as far as possible the complications, symptoms, signs, sleep monitoring data in medical records and comprehensive cephalometric indicators for cluster analysis in a large East Asian sample. In our study, we analysed the efficacy

TABLE 3 The differences in wearing frequency and discomfort feeling of mandibular advancement device in patients among different clusters.

Variables	Cluster 1 (n = 8)	Cluster 2 (n = 9)	Cluster 3 (n = 16)	*P* value
Wearing frequency (%)				
Every day	7 (87.5)	6 (66.7)	10 (62.5)	.447
A few times a week	0 (0.0)	2 (22.2)	1 (6.3)	
Occasionally	1 (12.5)	1 (11.1)	5 (31.3)	
Tolerance (%)	7 (87.5)	8 (88.9)	16 (100.0)	.258
Saliva stimulation (%)	4 (50.0)	1 (11.1)	6 (37.5)	.251
Dry mouth (%)	3 (37.5)	3 (33.3)	4 (25.0)	.794
Pain in some teeth (%)	3 (37.5)	3 (33.3)	8 (50.0)	.733
Pain in all teeth (%)	3 (37.5)	0 (0.0)[a]	0 (0.0)	.010*
Pain in cheek joints (%)	5 (62.5)	1 (11.1)	5 (31.3)	.088
Discomfortable bite in the morning (%)	5 (62.5)	1 (11.1)	8 (50.0)	.069

*$P < .05$.

[a]Comparison between cluster 2 and cluster 1 $P < .05$.

of mandibular advancement device treatment among the three subtypes to search for tailored approaches for patients with OSA. Using cluster analysis, the present study identified three clinical subtypes of OSA adults based on OSA-related craniofacial variables, OSA severity and obesity.

Patients in cluster 1 (n = 230, 31.9%) primarily exhibited a skeletal deformity with vertical facial excess, which is manifested by several classical features, including an increased ANB angle, reduced mandibular length, and clockwise rotation of the mandible. In addition to influencing the upper oropharyngeal dimension, this long-face syndrome, or facial hyperdivergence, also represents the deficient development of the cranio-maxillary complex, especially in the sagittal direction.[33] These traits are typical of patients with OSA founded by Neeplau et al,[16] and could severely affect the dimension of the upper airway. Banhiran et al[34] pointed out that PAS < 10 mm would increase the possibility of moderate to severe OSA. In normal weight patients, the narrower the width of the posterior airway space is associated with an increased incidence of OSA.

However, the mandibular advancement device did not show an advantage as expected in treatment with patients of cluster 1, which may attribute to the fact that the expansion of the airway by mandibular protrusion is partially counteracted by the posterior rotation of the mandible during the vertical mandibular opening.[35]

Cluster 2 (n = 278, 38.5%) was characterized by generally normal skeleton, the widest airway space, slightly obese and mild abnormality at the soft tissue level, with AHI similar to cluster 1. Previous studies have supported that nonobese patients exhibit more skeletal limitations invading airway opening, whereas obese patients have relatively larger parapharyngeal soft tissues associated with fat deposition and less skeletal limitations.[17,36–38] Furthermore, our study found that adults with OSA without mandibular retraction had better MAD efficacy and lower side effects, thus serving as an indication for MAD.

Cluster 3 (n = 214, 29.6%) presented not only skeletal deformities but also soft tissue enlargement, making its severity much more serious than the other clusters. The low location of hyoid bone, especially H-MP, reflects the severity of OSA. The position of the tongue is closely related to the size of oropharynx and the treatment changes, which has received extensive attention from scholars.[39] Lam et al[40] found that hyoid bone position was still an independent risk factor for the development of OSA after controlling the neck circumference.

Our study has some limitations. First, the samples came from the patients referred for MAD therapy, which might have the bias of mild PSG indicators, obvious skeletal characteristics, and few severe complications. Second, East Asians exhibited more craniofacial bony restriction and less obesity, thus making them more susceptible to the effect of obesity on OSA severity. Therefore, the results of the present study may not be referred to other races, other therapies, or the more severe and heavier patients. Third, our study was based on lateral cephalogram, a two-dimensional imaging method that could not provide three-dimensional information, and the upright lateral cephalogram did not reflect dynamic characteristics of the upper airway during sleep. Fourth, the response data was limited, and a larger post-treatment sample is preferred to study the differences among phenotypes. Besides, considering the complexity of OSA, more serious complications in a larger sample size, and with other therapies should also be taken into consideration. Finally, future research should delve into the bioinformatic characteristics between clusters to link phenotypes to endotypes.

Although it is observed that anatomical subtypes may have different effects on treatment, the specific degree, range and applicable population need to be further studied in the future.

5 | CONCLUSIONS

To conclude, adult OSA treated with MAD was clustered into three subtypes based on AHI, BMI, and anatomical features. Those nonobese patients with mild to moderate OSA and mild skeletal dysmorphology tended to have favourable results.

AUTHOR CONTRIBUTIONS

Liping Huang contributed to data collection, data analysis, and manuscript writing. Ying Xu contributed to data collation and manuscript revision. Xuemei Gao and Xu Gong contributed to study design, manuscript editing, providing content expertise, and supervising the work.

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest related to the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Carberry JC, Amatoury J, Eckert DJ. Personalized management approach for OSA. *Chest*. 2018;153(3):744-755.
2. Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of sleep apnea. *Physiol Rev*. 2010;90(1):47-112.
3. Chen X, Wang R, Zee P, et al. Racial/ethnic differences in sleep disturbances: the multi-ethnic study of atherosclerosis (MESA). *Sleep*. 2015;38(6):877-888.
4. Bjorvatn B, Lehmann S, Gulati S, Aurlien H, Pallesen S, Saxvig IW. Prevalence of excessive sleepiness is higher whereas insomnia is lower with greater severity of obstructive sleep apnea. *Sleep Breath*. 2015;19(4):1387-1393.
5. Keenan BT, Kim J, Singh B, et al. Recognizable clinical subtypes of obstructive sleep apnea across international sleep centers: a cluster analysis. *Sleep*. 2018;41(3):zsx214.
6. Ayas NT, Owens RL, Kheirandish-Gozal L. Update in sleep medicine 2014. *Am J Respir Crit Care Med*. 2015;192(4):415-420.
7. Kushida CA, Littner MR, Morgenthaler T, et al. Practice parameters for the indications for polysomnography and related procedures: an update for 2005. *Sleep*. 2005;28(4):499-521.
8. Veasey SC, Rosen IM. Obstructive sleep apnea in adults. *N Engl J Med*. 2019;380(15):1442-1449.
9. Korotinsky A, Assefa SZ, Diaz-Abad M, Wickwire EM, Scharf SM. Comparison of American Academy of Sleep Medicine (AASM) versus Center for Medicare and Medicaid Services (CMS) polysomnography (PSG) scoring rules on AHI and eligibility for continuous positive airway pressure (CPAP) treatment. *Sleep Breath*. 2016;20(4):1169-1174.
10. Edwards BA, Redline S, Sands SA, Owens RL. More than the sum of the respiratory events: personalized medicine approaches for obstructive sleep apnea. *Am J Respir Crit Care Med*. 2019;200(6):691-703.
11. Zinchuk AV, Gentry MJ, Concato J, Yaggi HK. Phenotypes in obstructive sleep apnea: a definition, examples and evolution of approaches. *Sleep Med Rev*. 2017;35:113-123.
12. Ye L, Pien GW, Ratcliffe SJ, et al. The different clinical faces of obstructive sleep apnoea: a cluster analysis. *Eur Respir J*. 2014;44(6):1600-1607.
13. Kim J, Keenan BT, Lim DC, Lee SK, Pack AI, Shin C. Symptom-based subgroups of Koreans with obstructive sleep apnea. *J Clin Sleep Med*. 2018;14(3):437-443.
14. Gagnadoux F, Le Vaillant M, Paris A, et al. Relationship between OSA clinical phenotypes and CPAP treatment outcomes. *Chest*. 2016;149(1):288-290.
15. Pien GW, Ye L, Keenan BT, et al. Changing faces of obstructive sleep apnea: treatment effects by cluster designation in the Icelandic Sleep Apnea Cohort. *Sleep*. 2018;41(3):zsx201.
16. Neelapu BC, Kharbanda OP, Sardana HK, et al. Craniofacial and upper airway morphology in adult obstructive sleep apnea patients: a systematic review and meta-analysis of cephalometric studies. *Sleep Med Rev*. 2017;31:79-90.
17. Sutherland K, Lee RW, Cistulli PA. Obesity and craniofacial structure as risk factors for obstructive sleep apnoea: impact of ethnicity. *Respirology*. 2012;17(2):213-222.
18. Lowe AA, Santamaria JD, Fleetham JA, Price C. Facial morphology and obstructive sleep apnea. *Am J Orthod Dentofacial Orthop*. 1986;90(6):484-491.
19. Lowe AA, Fleetham JA, Adachi S, Ryan CF. Cephalometric and computed tomographic predictors of obstructive sleep apnea severity. *Am J Orthod Dentofacial Orthop*. 1995;107(6):589-595.
20. Tangugsorn V, Skatvedt O, Krogstad O, Lyberg T. Obstructive sleep apnoea: a cephalometric study. Part I. Cervico-craniofacial skeletal morphology. *Eur J Orthod*. 1995;17(1):45-56.
21. Kapur VK, Auckley DH, Chowdhuri S, et al. Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: an American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med*. 2017;13(3):479-504.
22. Lowe AA, Ono T, Ferguson KA, Pae EK, Ryan CF, Fleetham JA. Cephalometric comparisons of craniofacial and upper airway structure by skeletal subtype and gender in patients with obstructive sleep apnea. *Am J Orthod Dentofacial Orthop*. 1996;110(6):653-664.
23. Tangugsorn V, Skatvedt O, Krogstad O, Lyberg T. Obstructive sleep apnoea: a cephalometric study. Part II. Uvulo-glossopharyngeal morphology. *Eur J Orthod*. 1995;17(1):57-67.
24. Liu Y, Zeng X, Fu M, Huang X, Lowe AA. Effects of a mandibular repositioner on obstructive sleep apnea. *Am J Orthod Dentofacial Orthop*. 2000;118(3):248-256.
25. Dahlberg G. *Statistical Methods for Medical and Biological Students*. George Allen & Ulvin Ltd.; 1940:123-132.
26. Houston WJ. The analysis of errors in orthodontic measurements. *Am J Orthod*. 1983;83(5):382-390.
27. Lovmar L, Ahlford A, Jonsson M, Syvänen AC. Silhouette scores for assessment of SNP genotype clusters. *BMC Genomics*. 2005;6:35.
28. Tibshirani R, Hastie WT. Estimating the number of clusters in a data set via the gap statistic. *J R Stat Soc B*. 2001;63(2):411-423.
29. Randerath W, Bassetti CL, Bonsignore MR, et al. Challenges and perspectives in obstructive sleep apnoea: report by an ad hoc working group of the sleep disordered breathing Group of the European Respiratory Society and the European Sleep Research Society. *Eur Respir J*. 2018;52(3):1702616.
30. Mazzotti DR, Keenan BT, Lim DC, Gottlieb DJ, Kim J, Pack AI. Symptom subtypes of obstructive sleep apnea predict incidence of cardiovascular outcomes. *Am J Respir Crit Care Med*. 2019;200(4):493-506.
31. Kim SJ, Alnakhli WM, Alfaraj AS, et al. Multi-perspective clustering of obstructive sleep apnea towards precision therapeutic decision including craniofacial intervention. *Sleep Breath*. 2021;25(1):85-94.
32. An HJ, Baek SH, Kim SW, Kim SJ, Park YG. Clustering-based characterization of clinical phenotypes in obstructive sleep apnoea

using severity, obesity, and craniofacial pattern. *Eur J Orthod*. 2020;42(1):93-100.
33. Zhong Z, Tang Z, Gao X, Zeng XL. A comparison study of upper airway among different skeletal craniofacial patterns in nonsnoring Chinese children. *Angle Orthod*. 2010;80(2):267-274.
34. Banhiran W, Wanichakorntrakul P, Metheetrairut C, Chiewvit P, Planuphap W. Lateral cephalometric analysis and the risks of moderate to severe obstructive sleep-disordered breathing in Thai patients. *Sleep Breath*. 2013;17(4):1249-1255.
35. Vroegop AV, Vanderveken OM, Van de Heyning PH, et al. Effects of vertical opening on pharyngeal dimensions in patients with obstructive sleep apnoea. *Sleep Med*. 2012;13(3):314-316.
36. Hou HM, Hägg U, Sam K, et al. Dentofacial characteristics of Chinese obstructive sleep apnea patients in relation to obesity and severity. *Angle Orthod*. 2006;76(6):962-969.
37. Kim SJ, Ahn HW, Hwang KJ, Kim SW. Respiratory and sleep characteristics based on frequency distribution of craniofacial skeletal patterns in Korean adult patients with obstructive sleep apnea. *PLoS One*. 2020;15(7):e0236284.
38. Yu X, Fujimoto K, Urushibata K, Matsuzawa Y, Kubo K. Cephalometric analysis in obese and nonobese patients with obstructive sleep apnea syndrome. *Chest*. 2003;124(1):212-218.
39. deBerry-Borowiecki B, Kukwa A, Blanks RH. Cephalometric analysis for diagnosis and treatment of obstructive sleep apnea. *Laryngoscope*. 1988;98(2):226-234.
40. Lam B, Ooi CG, Peh WC, et al. Computed tomographic evaluation of the role of craniofacial and upper airway morphology in obstructive sleep apnea in Chinese. *Respir Med*. 2004;98(4):301-307.

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