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Association of Skeletal Facial Pattern With Treatment Response of Obstructive Sleep Apnoea Using Mandibular Advancement Devices – A Cluster Analysis

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ABSTRACT

Background: Mandibular advancement devices (MADs) are an effective treatment for obstructive sleep apnoea (OSA), though individual responses to therapy can vary.

Objectives: This study aims to: (1) examine how craniofacial characteristics are associated with MAD effectiveness to refine patient selection and improve outcomes; and (2) assess the association of skeletal facial patterns with treatment efficacy and mandibular advancement.

Methods: This retrospective study used data from a previous quasi-experimental study. Analysis was conducted with two-piece adjustable devices, following a standardised protocol. K-means clustering analysis categorised the sample into subtypes using clinical, polysomnographic, and anatomical data to evaluate MAD treatment response. Patients were also classified by growth pattern, and treatment response and mandibular advancement were compared across facial patterns.

Results: The study included 112 patients. Of these, 41 patients (36.61%) were assigned to Cluster 1 and 71 patients (63.39%) to Cluster 2. Cluster 1 patients had more severe OSA, with higher ESS, BMI, T90%, and AHI, along with a vertical facial pattern and narrower airways. Treatment response rates were significantly lower in Cluster 1 compared to Cluster 2. Among facial pattern groups, 32 patients were hyperdivergent, 46 were neutral, and 34 were hypodivergent. The responder rate was significantly lower in the hyperdivergent group, indicating reduced treatment effectiveness.

Conclusions: This study suggests that the efficacy of OSA treatment with MADs may be associated with anatomical subtypes. Cluster 1 patients showed a lower response rate compared to Cluster 2. Additionally, patients with hyperdivergent patterns may have a less favourable response to MAD treatment.

1 | Introduction

Obstructive sleep apnoea (OSA) is a complex and heterogeneous condition, with numerous risk factors, pathophysiological mechanisms, symptoms, and related comorbidities. This results in disparate prognoses and treatment outcomes among individuals [1–4].

The most recent recommendations from the European Respiratory Society regard continuous positive airway pressure (CPAP) therapy as being comparable to mandibular advancement device (MAD) therapy in patients with mild to moderate OSA. This equivalence also extends to patients with severe OSA who are unable to tolerate CPAP or decline surgical intervention [5]. However, the effectiveness of MAD

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therapy remains uncertain and unpredictable. According to the most commonly used success criterion, which is defined as achieving a reduction of at least 50% in the apnoea-hypopnea index (AHI) and a post-treatment AHI of fewer than 10 events per hour, approximately 40% of patients do not respond favourably to this treatment [6, 7].

The reasons for the observed variability in response rates remain unclear [8]. One strategy for addressing the complexity of OSA is to divide the disorder into smaller, more uniform subgroups, which are often referred to as 'phenotypes' [9]. Recently, cluster analysis has been employed as a means of classifying patients with OSA into subtypes. Some researchers have proposed that the identification of distinct OSA phenotypes in clinical practice could facilitate the implementation of more personalised treatment strategies, thereby enhancing therapeutic outcomes, quality of life, and patient adherence [2, 9].

Craniofacial morphology plays a crucial role in both the severity of OSA and the effectiveness of MAD therapy [10–15]. A substantial body of evidence highlights significant anatomical differences between responders and non-responders. Specifically, several studies have identified key features associated with a higher response rate to MAD treatment, such as a shorter maxillary length, reduced anterior and posterior facial height, a decreased hyoid-to-C3 distance, a shorter airway length, and a smaller minimum airway cross-sectional area [7, 10–16]. However, the significant variability among previous studies has prevented the achievement of consistent results, and these variables are seldom considered in comprehensive subtype analyses. A better identification of these subgroups will enable the development of more personalised treatments. Once identified, it will be essential to assess the efficacy, safety, and cost-effectiveness of available therapies targeting specific traits or phenotypes. This approach could help establish a new paradigm for managing OSA at all levels of care [17, 18].

Additionally, many of these characteristics are associated with facial patterns typically classified in orthodontics as brachyfacial, mesofacial, and dolichofacial. Patients with OSA have been observed to present with an increased mandibular plane angle and clockwise mandibular rotation, which have been identified as risk factors in the development of the condition [15]. Similarly, the vertical facial pattern may be associated with the degree of airway dilation during mandibular advancement [19]. It would therefore be valuable to investigate whether the facial pattern plays a role in the extent of mandibular advancement achieved by the device and the treatment response in OSA, as understanding these factors could enhance the ability to predict individual treatment outcomes, ultimately reducing the time to therapeutic success and optimising healthcare resource utilisation [17].

This study has two clear objectives. The first is to establish a response subtype to MADs in OSA patients based on a set of craniofacial characteristics, along with the most relevant clinical and polysomnographic features. The aim is to provide a clinically useful tool for certified dentists in dental sleep medicine in their decision-making processes. The second objective is to examine the role of skeletal facial patterns in treatment response to oral devices and to compare both the treatment response and the degree of mandibular advancement achieved by the device across the various facial patterns.

2 | Material and Methods

2.1 | Study Design and Setting

This retrospective analysis utilised data from a preceding quasi-experimental study, which was registered on ClinicalTrials.gov under the identifier NCT05596825 [20]. The article is in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for observational research.

The study was conducted at the Prosthodontics and Occlusion Unit of the University of Valencia. The patients were referred from the Respiratory Sleep Disorders Unit of the Otorhinolaryngology Department at the University Clinical Hospital of Valencia (Spain) and the Neurophysiology Department at La Ribera Hospital in Alzira (Spain). All participants provided written informed consent for the utilisation of their data for research purposes. This process received approval from the Ethics Committee of the University of Valencia, in accordance with the principles outlined in the Declaration of Helsinki (registration code: 7AU5SR7D350IY4LD) (Appendix S1).

2.2 | Study Population

The inclusion criteria were as follows: patients aged 18 years or above, referred to the sleep unit over a 6-year period, with an AHI of 5 or above per hour. MAD was regarded as the optimal treatment option for patients with mild to moderate OSA when CPAP or other therapeutic alternatives were not viable, particularly for those with minimal symptoms. Additionally, adults with any degree of OSA who were eligible for CPAP but were unable to tolerate it, sought alternative therapies, or declined surgery despite the presence of anatomical irregularities were also included in the study.

Exclusion criteria included individuals with incomplete data, those with sleep disorders other than OSA, pregnant women, patients with active periodontitis, participants with fewer than 10 teeth in each dental arch, and those on medications affecting sleep architecture. Additionally, individuals diagnosed with temporomandibular disorders (TMD) based on the Research Diagnostic Criteria were excluded [21].

2.3 | Oral Device Adjustment and Diagnostic Approach

Each participant was provided with a personalised, adjustable MAD featuring a restricted vertical dimension. The specific devices used were the DAM (Aditas, Spain), Orthoapnea Classic (Orthoapnea, Ortoplus, Spain), and NOA (Orthoapnea, Ortoplus, Spain).

Polysomnography (PSG) was the primary recommended method for diagnosing OSA. However, Type 3 home sleep apnoea testing

(HSAT) was employed for patients identified as high risk for moderate to severe OSA, although it was contraindicated for those with significant comorbidities. In instances where PSG was not a viable option, HSAT was used for both diagnosis and monitoring of responses to MAD treatment. Patients who were initially evaluated with PSG underwent subsequent follow-up tests using PSG, while those who were assessed with HSAT continued with HSAT for follow-up evaluations. This study was evaluated in accordance with the standards established by the American Academy of Sleep Medicine (AASM) [22].

The methodology for titrating the mandibular advancement appliance, along with the diagnostic and monitoring procedures for OSA, was previously delineated in our research [20].

2.4 | Treatment Success Rate

The success rate of MAD treatment was assessed based on a set of variables aligned with the severity definitions of OSA as outlined in the latest international consensus on OSA and the success criteria delineated in the SLEEP GOAL framework by Pang et al. [17, 23].

Patients who exhibited a reduction in their AHI of over 50% and achieved normalisation to fewer than 10 events per hour with the use of a MAD were classified as responders. Furthermore, these patients demonstrated enhanced oxygenation, as indicated by the percentage of time with oxygen saturation < 90% (T90%) value approaching zero, an Epworth sleepiness scale (ESS) score below 10, a 5-point increase on the Visual Analog Scale (VAS), and the absence of any cardiovascular risk factors (CVRFs) (definition 1). In contrast, non-responders were identified as individuals who failed to achieve a reduction in AHI of over 50%, exhibited a T90% exceeding 14, demonstrated an ESS score above 15, did not achieve a 5-point improvement in their VAS, or exhibited signs of CVRF or cardiovascular disease (CVD). Additionally, a second definition put forth by other researchers identified responders as individuals who demonstrated a reduction in AHI exceeding 50% yet still exhibited an AHI above 10 while using MAD, provided that their T90% remained below 14, their ESS was below 14, there was a 5-point improvement in VAS, and they did not have CVD (Figure 1) [17, 23].

2.5 | Measurements

All patients underwent a baseline cone-beam computed tomography (CBCT) scan, which was performed by the same experienced technician at the Radiology Unit of the Faculty of Medicine and Dentistry. The Master 3D equipment (E-WOO Technology), a cone-beam technology system with normal resolution and high quality, was utilised, emitting 90 kVp and 4 mA of radiation for approximately 30 s. To ensure consistency in the imaging data, the CBCT scans were performed with the patient in an awake, calm state, with the mandible in maximum intercuspation and the tip of the tongue touching the incisors, without swallowing or speaking.

The DICOM (Digital Imaging and Communications in Medicine) files were processed using Dolphin Imaging software (version 11.0, Chatsworth, CA, USA). Cephalometric measurements were obtained from the CBCT scans using the variables outlined in Table S1.

2.6 | Cluster Analysis

A K-means clustering analysis was performed to categorise all participants into distinct subgroups based on clinical characteristics (age, gender, body mass index (BMI), neck and waist circumference), polysomnographic data (AHI, minimum oxygen saturation ($minSaO_2$), T90%), and anatomical variables listed in Table S1.

K-means is an unsupervised clustering algorithm that partitions data into K clusters, grouping observations that share similar characteristics. The algorithm iteratively assigns data points to clusters and updates centroids until an optimal partitioning is achieved. To determine the most appropriate number of clusters, we applied the gap statistic, which evaluates the within-cluster variation relative to a reference null distribution.

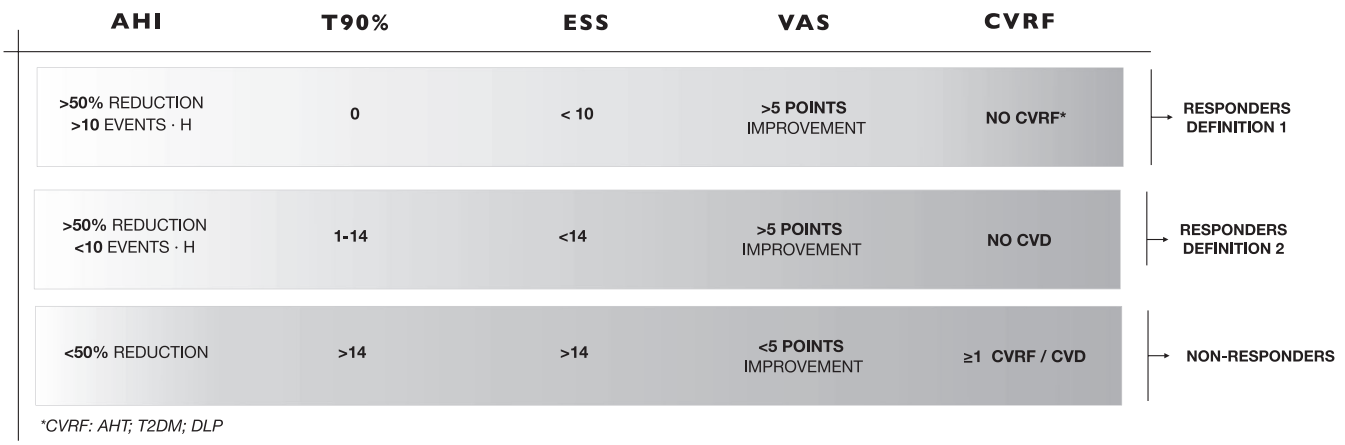

FIGURE 1 | Evaluation of the response to MAD treatment based on different parameters. AHI, apnoea-hypopnoea index; AHT, arterial hypertension; CVD, cardiovascular disease; CVRF, cardiovascular risk factors; DLP, dyslipidemia; ESS, Epworth sleepiness scale; T2DM, type 2 diabetes mellitus; T90%, percentage of time with oxygen saturation < 90%.

2.7 | Statistical Analysis

The statistical analysis was conducted using the SPSS Statistics software, version 28.0 (IBM Corporation). A parametric Student's *t*-test was employed to compare quantitative variables, with a significance threshold of $p < 0.05$. The chi-squared test was utilised to evaluate discrepancies in the distribution of proportions. To assess the differences between the hypodivergent, neutral growth, and hyperdivergent groups, variance homogeneity was evaluated, and one-way analysis of variance (ANOVA) was employed for variables that exhibited a normal distribution. Subsequently, all data were compared pairwise using Bonferroni post hoc analysis and the 2×2 chi-square test, with the objective of identifying specific differences between the groups.

A K-means clustering analysis was conducted to categorise all subjects into distinct subgroups based on their observed characteristics. The optimal number of clusters was determined through the application of the Gap statistic. Subsequently, the patients were grouped into homogeneous subtypes through the K-means clustering algorithm, and the resulting clusters were visualised. The K-means analysis was conducted using the R software, version 4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria).

To determine the sample size needed for a comparative analysis of the two groups with respect to the $minSaO_2$ variable, an effect size of $d = 0.8$ was assumed, with an alpha level of 0.05 and a power of 80%. Based on an estimated standard deviation of 1.5, it was calculated that 56 patients per group would be necessary, resulting in a total sample size of 112 patients.

Additionally, 10% of the data were subjected to independent assessment by two researchers to ascertain the extent of inter-observer error and subsequently reassessed by the principal investigator after 4 weeks to evaluate the potential for intra-observer error. The consistency of measurements for quantitative variables was determined by calculating the intraclass correlation coefficient (ICC) with 95% confidence intervals. The degree of agreement between observers was evaluated using the Fleiss-Cohen kappa statistic. In the case of categorical variables, the kappa statistic was applied in accordance with the Landis-Koch scale.

3 | Results

3.1 | Overall Baseline Demographic Characteristics and Polysomnographic Variables

STROBE patients flowchart for cohort studies is depicted Figure S1. The total sample consisted of 112 patients, of whom 52 were men and 60 were women (Table S2). No statistically significant differences were observed between men and women with regard to disease severity as measured by BMI ($p = 0.180$), ESS ($p = 0.100$), T90% ($p = 0.242$), and baseline AHI ($p = 0.160$). The mean age of the patients was 54.5 years [52.4; 56.6]. The mean BMI was 25.3 kg/m^2 [24.7; 26.0], the mean baseline AHI was 23.2 events/h [20.6; 25.9], and the mean T90% was 10.10% [8.0; 12.1]. The total follow-up for the patients included in the study ranged from a minimum of 1 year to an average of 4 [3.5–4.5] years.

Regarding baseline AHI, 37 patients presented with mild OSA, 47 with moderate OSA, 22 with severe OSA, and 6 with very critical OSA. This classification is in accordance with the severity criteria established by the latest International OSA Consensus [17].

All patients were treated with customised, adjustable devices: 51 with DAM, 23 with Orthoapnea Classic, and 38 with NOA. There were no statistically significant differences in response patterns or efficacy based on the type of device used ($p = 0.121$) nor in the severity of the patients treated with each device ($p = 0.209$) (Table S3). Moreover, there were no statistically significant differences observed in the mandibular advancement achieved with the devices between the groups: 74.1% [71.4; 76.9] for DAM, 72.2% [67.9; 76.5] for Orthoapnea Classic, and 73.9% [70.5; 77.4] for NOA (Table S4).

3.2 | Comparison of Variables Between Patient Clusters

The optimal number of clusters was determined using the Gap statistic, resulting in two distinct subtypes. Two homogeneous clusters were identified through the K-means clustering analysis (Figure 2). A total of 41 patients (36.61%) were assigned to Cluster 1, while 71 patients (63.39%) were assigned to Cluster 2.

Table 1 presents the clinical, polysomnographic, and anatomical differences observed between the two clusters. Patients in Cluster 1 exhibited more severe OSA, as indicated by higher levels of baseline daytime sleepiness, hypoxia, AHI, and BMI. Anatomically, individuals in Cluster 1 demonstrated more significant structural alterations compared to those in Cluster 2, which corresponded to a more vertical facial pattern. This was evidenced by a reduced Jarabak ratio ($p < 0.001$), an increased SN-MP angle ($p = 0.042$), and a larger gonial angle ($p = 0.049$). Furthermore, patients in Cluster 1 demonstrated a greater distance between the hyoid bone and the third cervical vertebra ($p = 0.049$). In terms of soft tissue characteristics, patients in Cluster 1 exhibited a longer and thicker soft palate than those in Cluster 2 ($p < 0.001$). Additionally, patients in Cluster 1 presented with a narrower airway space, particularly in oropharyngeal and hypopharyngeal volumes, as well as a reduced CSAmin ($p < 0.001$), along with an overall longer airway ($p < 0.001$).

The ICC values ranged from 0.9 to 1.0. According to Fleiss' criteria, this correlation is considered optimal since an ICC > 0.75 is deemed excellent (Table S5) [24].

3.3 | Variability in Treatment Response Among Clusters

A comparison of the treatment response for OSA using MAD among the different clusters is presented in Table S6. In

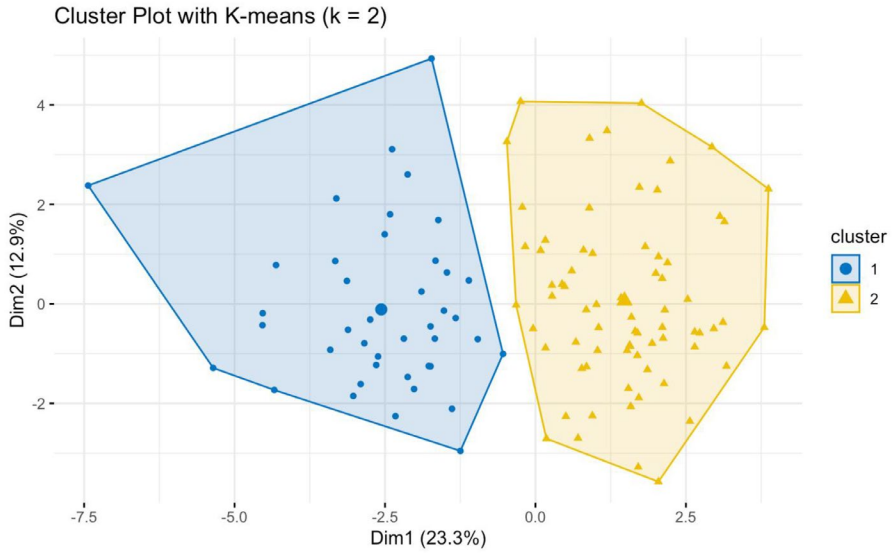

FIGURE 2 | K-means cluster plot illustrating two homogeneous clusters identified through cluster analysis, as determined by the Gap statistic evaluation. K-means clustering was performed to classify subjects into distinct subgroups based on craniofacial, clinical, and polysomnographic characteristics. The clustering algorithm grouped patients into homogeneous subtypes, and the results were visualised accordingly.

Cluster 2, 88.7% of patients exhibited a response to treatment according to the first response definition, while 11.3% did not. Regarding response definition 2, the response rate exhibited a notable improvement, with 93% of patients in Cluster 2 responding and only 7% failing to do so. Conversely, only 2.4% of patients in Cluster 1 met the criteria for response definition 1, while 36.6% responded according to response definition 2. The observed differences in response rates between the two clusters were statistically significant for both response definitions ($p < 0.001$).

3.4 | Relationship Between Facial Pattern and Craniofacial Variables

Patients were classified according to their growth pattern based on the Jarabak ratio, as follows: those exhibiting a hyperdivergent pattern, with a Jarabak ratio of < 59% and a downward and posterior facial rotation; those displaying a neutral growth pattern, with a ratio between 59% and 63%; and those demonstrating a hypodivergent growth pattern, which is characterised by horizontal growth and a ratio > 63% [25].

A total of 32 patients were included in the hyperdivergent growth pattern group, 46 in the neutral group, and 34 in the hypodivergent group. No significant differences were observed in the baseline clinical and polysomnographic characteristics among the three groups (Table 2).

It is frequently the case that growth patterns are associated with other craniofacial variables. In patients with a high facial angle, an increased gonial angle and SN-MP angle, a greater distance from the mandibular plane to the hyoid bone, a higher anterior facial height, and a reduced posterior facial height were observed ($p < 0.05$) (Table 2).

3.5 | Treatment Success and Therapeutic Mandibular Advancement Among Different Facial Growth Patterns

The results of the treatment are summarised in Table 3, which presents the outcomes across the different facial growth patterns. While all groups exhibited improvements in AHI, the hyperdivergent group exhibited a relatively lower reduction compared to the hypodivergent and neutral growth patterns. However, this difference was not statistically significant. Improvements in T90% and minSaO_2 were observed across all growth patterns, with no significant variation between them (p-values of 0.180 and 0.364, respectively). Regarding the ESS score, the hypodivergent group experienced the most substantial improvement, while the hyperdivergent group demonstrated the least reduction ($p = 0.084$). Notably, the responder rates based on both definitions were significantly lower in the hyperdivergent group compared to the other groups, indicating a reduced effectiveness of the intervention in patients with a high-angle growth pattern ($p < 0.001$).

Despite the observed discrepancies in treatment response, the extent of mandibular advancement required did not differ significantly among the groups (Pearson values of 0.112, 0.076, and 0.048 for the hyperdivergent, neutral growth, and hypodivergent patterns, respectively). However, it was observed to be slightly greater in the hyperdivergent group (Figure 3). Patients with hyperdivergent patterns required greater mandibular advancement to achieve a larger reduction in AHI compared to other patient groups; however, these differences were not statistically significant.

4 | Discussion

MADs are considered an alternative treatment to CPAP [3]. It has been demonstrated that these devices reduce airway

TABLE 1 | Comparative analysis of demographic, polysomnographic, and cephalometric measurements across patient clusters.

	Clusters				
	Cluster 1	Cluster 2	Mean difference [CI]	d Cohen	*p*
	n 41	*n* 71			
Age (years)	56.2 [52.9; 58.2]	54.1 [51.3; 55.6]	1.87 [−1.99; 4.81]	0.23 [−0.12; 0.41]	0.365†
Gender – men (%) *n* [25 C1/30 C2]	60.9 [45.7; 74.3]	73.2 [58.1; 84.3]	—	—	0.812‡
Initial BMI (kg/m^2)	30.2 [25.3; 34.7]	24.1 [23.5; 24.7]	3.40 [2.11; 4.71]	1.13 [0.71; 1.5]	< 0.001†,*
Neck circumference (cm)	41.2 [40.0; 42.3]	37.4 [36.6; 38.2]	3.78 [2.40; 5.16]	1.10 [0.68; 1.5]	< 0.001†,*
Waist circumference (cm)	97.1 [91.9; 102.4]	87.7 [85.2; 90.2]	9.44 [3.64; 15.2]	0.72 [0.32; 1.1]	< 0.001†,*
Baseline ESS	11.5 [9.98; 13.0]	8.83 [7.56; 10.1]	3.15 [2.10; 4.61]		0.003†,*
Initial AHI (events/h)	23.5 [20.3; 26.7]	20.5 [17.5; 22.5]	13.2 [8.2; 18.90]	1.05 [0.64; 1.4]	< 0.001†,*
Initial minSaO_2 (%)	81.5 [79.8; 83.2]	86.6 [85.3; 87.9]	−5.14 [−7.2; −3.0]	−0.9 [−1.3; −0.5]	< 0.001†,*
Initial T90%	20.8 [17.9; 23.8]	3.81 [2.47; 5.20]	17.0 [12.8; 20.3]	2.30 [1.84; 2.8]	< 0.001†,*
Mandibular length (mm)	75.4 [73.5; 77.3]	73.2 [72.1; 74.3]	2.21 [0.02; 4.40]	0.42 [0.03; 0.8]	0.024†,*
Maxillary length (mm)	57.2 [55.7; 58.6]	53.3 [52.6; 54.0]	3.86 [2.50; 5.22]	1.10 [0.69; 1.5]	< 0.001†,*
AF height (mm)	128.9 [127.7; 130.1]	125.6 [124.8; 126.4]	3.31 [1.86; 4.76]	0.92 [0.52; 1.3]	< 0.001†,*
PF height (mm)	87.4 [86.4; 88.3]	85.6 [84.4; 86.9]	1.71 [0.16; 3.27]	0.87 [0.49; 1.4]	0.015†,*
Jarabak's ratio (%)	58.5 [57.3; 59.7]	62.9 [62.0; 63.9]	−4.41 [−5.9; −2.9]	−1.1 [−1.5; −0.7]	< 0.001†,*
SN-MP (°)	36.4 [26.1, 45.42]	34.2 [31.7; 35.41]	−2.91 [−6.9; −10.6]	−0.5 [−0.9; −0.1]	0.042†,*
Gonial angle (°)	145.2 [109.0; 179.2]	134.2 [130.1, 136.2]	−12.1 [−27.1; −49.0]	−0.5 [−0.7; −0.3]	0.049†,*
SNA (°)	81.1 [80.2; 84.0]	81.20 [78.9; 82.5]	−0.21 [−1.99; 0.69]	−0.11 [−0.8; 0.4]	0.342†
SNB (°)	79.8 [78.5; 81.2]	77.4 [76.2; 78.49]	−1.81 [−2.98; −0.21]	−0.8 [−1.1; −0.6]	0.062†
ANB (°)	1.98 [1.86; 3.75]	3.76 [3.01, 4.87]	−1.76 [−0.19; 2.01]	0.4 [−0.21; 0.6]	0.051†
Overbite (mm)	3.56 [2.98; 4.75]	3.43 [2.99; 4.19]	−0.15 [−1.12; 0.69]	−0.3 [−0.5; 0.21]	0.091†
Overjet (mm)	3.45 [3.15; 4.35]	4.10 [3.45; 4.67]	0.62 [−0.241; 2.01]	0.5 [−0.21; 0.81]	0.062†
3rd cervical-H (mm)	46.7 [32.2; 57.6]	35.9 [32.9; 36.7]	−11.2 [−24.9; 4.02]	−0.6 [−0.9; −0.3]	0.049†,*
RGN-H (mm)	41.9 [39.9; 44.8]	43.2 [39.8; 44.3]	1.31 [−2.99; 3.151]	0.10 [−0.5; 0.51]	0.212†
MP-H (mm)	25.8 [19.9; 33.1]	24.7 [23.2; 27.4]	−1.10 [−4.12; 9.01]	0.3 [−0.40; 0.71]	0.092†
Soft palate length (mm)	42.4 [41.3; 43.4]	37.8 [36.9; 38.9]	4.62 [3.12; 6.11]	1.2 [0.78; 1.61]	< 0.001†,*
Soft palate width (mm)	12.6 [11.9; 13.4]	10.4 [10.0; 10.8]	2.21 [1.36; 3.06]	1.1 [0.69; 1.51]	< 0.001†,*
Tongue length (mm)	70.1 [68.1; 72.1]	69.4 [67.9; 70.9]	0.72 [−1.77; 3.2]	0.11 [−0.3; 0.50]	0.284†
Airway volume (mm^3)	16584.6 [15044.3; 18124.9]	22557.3 [20930.6; 24184.0]	−5972.7 [−8186.0; −3759.4]	−0.9 [−1.3; −0.52]	< 0.001†,*
Nasopharynx volume (mm^3)	4069.1 [3833.1; 4512.1]	4313.1 [3819.5; 4876.2]	48.9 [−499.2; 761.4]	0.09 [−0.12; 0.4]	0.502†
Oropharynx volume (mm^3)	8910.6 [7894.0; 9927.2]	12006.2 [10864.3; 13148.1]	−3095.6 [−4606.3; −1584.9]	−0.7 [−1.1; −0.32]	< 0.001†,*

(Continues)

TABLE 1 | (Continued)

	Clusters				
	Cluster 1	Cluster 2	Mean difference [CI]	d Cohen	*p*
	n 41	*n* 71			
Hypopharynx volume (mm^3)	4299.1 [3728.5; 5002.2]	6211.1 [5720.2; 6935.4]	1815.4 [816; 2814]	0.24 [0.19; 0.71]	< 0.001†,*
CSAmin (mm^2)	62.0 [54.3; 69.7]	89.1 [80.2; 98.0]	−27.1 [−38.7; −15.5]	−0.80 [−1.2; −0.4]	< 0.001†,*
CSAmin-AP (mm)	6.02 [5.21; 7.42]	6.23 [4.99; 6.33]	−0.21 [−0.79; 0.62]	−0.23 [−0.7; 0.42]	0.299†
CSAmin-lateral (mm)	17.7 [16.0; 19.4]	21.6 [20.2; 23.1]	−3.98 [−6.21; −1.74]	−0.69 [−1.1; −0.3]	< 0.001†,*
Airway length (mm)	92.1 [90.1; 94.1]	84.4 [82.7; 86.1]	7.68 [4.96; 10.41]	1.09 [0.68; 1.50]	< 0.001†,*

Note: All data are presented as mean difference or percentage and confidence interval (range).
Abbreviations: AHI, apnaea-hypopnoea index; AF, anterior facial; ANB, point A-nasion-point B; BMI, body mass index; C1, cluster 1; C2, cluster 2; CSAmin, minimum cross-sectional area of upper airway; CSAmin-AP, anteroposterior dimension of minimum cross-sectional area of upper airway; ESS, Epworth sleepiness scale; H, hyoid bone; $minSaO_2$, minimum oxygen saturation; MP, mandibular plane; *n*, number of participants; PF, posterior facial; RGN, retrognation point; SNA, sella-nasion-point A; SNB, sella point-nasion-point B; T90%, percentage of time with oxygen saturation < 90%.
*Significance accepted at $p < 0.05$. †*T*-student test. ‡Chi-squared test.

collapsibility by approximately 140%, as measured using the gold standard technique of critical closing pressure (Pcrit) [26]. Furthermore, the same technique has demonstrated that MADs reduce Pcrit by approximately 2 cm H_2O with a 50% advancement and by approximately 5 cm H_2O with a 100% advancement [27].

In crossover trials, patients tend to express a preference for oral devices over CPAP, and adherence rates are typically higher, by approximately 1.5 h per night. Additionally, numerous patients attain comparable health outcomes to those afforded by CPAP [28, 29]. However, it should be noted that there is considerable interindividual variability in response [28, 29].

Accordingly, one objective of this study was to establish a response subtype or phenotype for MAD in patients with OSA, based on a defined set of craniofacial characteristics and relevant clinical and polysomnographic features. An ideal phenotype represents an 'endotype', defined by a distinct disease subtype that includes a cohesive natural history, specific clinical and physiological traits, identifiable biomarkers, genetic factors, and a predictable treatment response that meaningfully impacts patient outcomes. However, the current classification systems for OSA have not yet advanced to the level of defining endotypes. The proposed definition of an OSA phenotype is limited to subgroups of patients differentiated by one or more clinically significant disease characteristics [9].

The application of Cluster analysis is a valuable tool for elucidating the heterogeneity that exists in the context of OSA. Subsequent to Ye et al.'s initial investigation into the clustering of patients with OSA, researchers have conducted analyses from a multitude of perspectives [2, 30–32]. It is noteworthy that some studies have indicated that different clusters demonstrate distinct therapeutic responses to CPAP therapy [33]. However, many of these analyses have failed to take into account the significant role played by craniofacial anatomical factors. Dysfunctional craniofacial anatomy remains a target for therapeutic intervention and is a determining factor in treatment strategies, including orthognathic surgery and MAD therapy [3, 34, 35]. Nevertheless, a notable gap remains in the literature concerning the use of CBCT to evaluate craniofacial anatomy and upper airway dimensions as key factors in OSA severity and treatment prognosis. To date, the majority of research in this field has focused primarily on cephalometric analysis [36, 37].

CBCT offers significant advantages over two-dimensional cephalometric radiography in the assessment of craniofacial and airway anatomy in OSA patients. Unlike cephalometric X-rays, which offer limited insight into three-dimensional structures and suffer from superimposition of anatomical landmarks, CBCT enables precise 3D reconstructions and volumetric measurements, facilitating the accurate capture the true cross-sectional areas and volumetric parameters of the upper airway [37, 38].

Cluster 1 patients exhibited a more pronounced severity of OSA in relation to the ESS, BMI, T90%, and AHI, accompanied by augmented skeletal alterations. This profile is characterised by a vertical facial pattern, greater prominence of soft tissues, and increased airway narrowness in comparison to Cluster 2. These features, particularly those associated with posterior rotation of the mandible, define a typical population of OSA patients who appear to be more susceptible to upper airway collapsibility [15]. The treatment response rates, based on both definitions analysed in this study, were found to be lower among Cluster 1 patients.

These findings may have clinical relevance, as although clinical characteristics alone do not serve as strong predictors, their association with other variables, such as anatomical traits or polysomnographic characteristics, could enhance patient selection to some extent [37, 39]. According to the results of this study, patients with more severe OSA, greater anatomical imbalance, a longer and wider soft palate potentially narrowing the airway, a more compromised airway, and a vertical facial pattern may benefit from alternative treatment options rather than MAD therapy [40]. Alternatively, a combined treatment approach should be considered for these patients. These findings are consistent with those previously reported in the literature [35, 36, 41].

TABLE 2 | Differences in baseline clinical, polysomnographic, and craniofacial variables among facial patterns.

	Hypodivergent pattern ($n=34$)[a]	Neutral growth pattern ($n=46$)[a]	Hyperdivergent pattern ($n=32$)	*p*
Gender—men (%) *n* [18/21/13]	52.94 [36.74; 68.66]	45.65 [32.15; 59.82]	40.63 [25.52; 57.74]	0.599[‡]
Age (years)	51.37 [47.32; 55.41]	56.66 [53.30; 60.02]	54.83 [51.07; 58.58]	0.114[†]
Initial BMI (kg/m^2)	24.54 [23.50; 25.58]	25.26 [24.34; 26.19]	26.29 [24.81; 27.78]	0.113[†]
Baseline ESS	9.05 [8.37; 10.98]	9.45 [8.79; 11.10]	10.09 [9.28; 11.09]	0.602[†]
Initial AHI (events/h)	21.04 [17.28; 24.80]	21.58 [17.81; 25.36]	27.90 [21.50; 34.49]	0.078[†]
Initial minSaO_2 (%)	85.97 [84.87; 88.07]	84.15 [82.32; 85.99]	84.25 [81.50; 85.01]	0.081[†]
Initial T90%	6.21 [2.69; 9.75]	8.37 [5.44; 11.30]	9.27 [5.25; 13.51]	0.067[†]
Gonial angle (°)	123.7 [119.9; 128.9]	130.1 [128.8; 131.4][b]	136.9 [135.9; 138.1][c]	0.039[†,*]
SN-MP (°)	30.55 [29.71; 32.24]	32.56 [31.72; 33.42]	35.05 [34.00; 36.10][c]	0.044[†,*]
Mandibular length (mm)	75.20 [73.23; 77.18]	73.22 [71.78; 74.65]	73.90 [71.86; 75.94]	0.258[†]
Maxillary length (mm)	53.56 [52.45; 54.66]	55.02 [54.07; 55.97]	55.49 [53.59; 57.40]	0.108[†]
SNA (°)	80.94 [79.84; 82.04]	80.18 [79.02; 81.34]	80.90 [79.22; 82.58]	0.619[†]
SNB (°)	77.94 [76.84; 79.04]	76.72 [75.45; 78.01]	78.44 [76.79; 80.10]	0.162[†]
ANB (°)	3.20 [2.17; 4.23]	3.72 [2.98; 4.45]	2.66 [1.65; 3.67]	0.242[†]
3rd cervical-H (mm)	34.86 [33.43; 36.29]	36.50 [35.26; 37.74]	48.42 [26.61; 70.23]	0.128[†]
RGN-H (mm)	42.43 [40.23; 44.63]	42.58 [41.01; 44.14]	41.11 [39.04; 43.18]	0.503[†]
MP-H (mm)	20.74 [19.21; 22.27]	22.72 [19.99; 25.98]	26.86 [24.78; 28.94][c]	0.047[†,*]
AF height (mm)	124.7 [123.5; 125.9]	126.1 [125.3; 127.0][b]	130.0 [128.7; 131.3][c]	<0.001[†,*]
PF height (mm)	88.89 [87.58; 90.19]	88.05 [87.37; 88.73][b]	82.54 [81.35; 83.77][c]	<0.001[†,*]

Note: All data are presented as mean difference or percentage and confidence interval (range).
Abbreviations: AHI, apnoea-hypopnoea index; AF, anterior facial; ANB, point A-nasion-point B; BMI, body mass index; ESS, Epworth sleepiness scale; H, hyoid bone; minSaO_2, minimum oxygen saturation; MP, mandibular plane; *n*, number of participants; PF, posterior facial; RGN, retrognation point; SNA, sella-nasion-point A; SNB, sella point-nasion-point B; T90%, percentage of time with oxygen saturation < 90%.
*Significance accepted at $p<0.05$. [†]ANOVA test; [‡]Chi-squared test. [a]$p<0.05$ after Bonferroni post hoc test between the hypodivergent and neutral growth patterns. [b]$p<0.05$ after Bonferroni post hoc test between the neutral growth and hyperdivergent patterns. [c]$p<0.05$ after Bonferroni post hoc test between the hypodivergent and hyperdivergent patterns.

Moreover, the present study sought to determine the association of facial pattern with the efficacy of MADs. The mandible is invariably retruded during mouth opening due to posterior rotation [42]. However, the extent of mandibular retrusion may vary depending on craniofacial morphology [19].

The present study demonstrated that hyperdivergent patterns exhibited a significantly inferior response to treatment with MAD compared to neutral and hypodivergent growth patterns ($p<0.001$). These findings align with those reported in previous research [43, 44]. One potential explanation for this finding is that patients with hypodivergent or neutral growth patterns experience a less negative impact on the oropharynx [45]. Furthermore, it has been observed that with maximum mandibular advancement, there is a diminished increase in vertical dimension, and the mandibular symphysis remains in a more anterior position relative to the posterior pharyngeal wall [45].

In brachyfacial patients, the mandible begins its trajectory during mouth opening in a position where the lower incisors are significantly more advanced. For the mandible to reach the point at which airway obstruction occurs, it must traverse a longer path. Conversely, in dolichofacial patients, the mandibular opening trajectory commences in a more posterior and downward position. Consequently, any increase in vertical dimension in these patients rapidly results in mandibular retraction, which may explain the differences observed in treatment response [19, 45]. Clinically, these findings suggest that patients with a vertical facial pattern may require alternative or adjunctive treatment strategies to improve therapeutic outcomes. Furthermore, these results have important implications for patient selection and device customisation. While the limitation of vertical dimension is already a key consideration in MAD design, it becomes even more critical for dolichofacial patients. For these individuals, ensuring minimal device thickness is essential to maintaining upper airway patency [19]. These findings are consistent with previous literature, highlighting the need for a more tailored approach to OSA management in patients with distinct craniofacial profiles [43, 44].

Similarly, the vertical facial pattern was identified as a factor influencing the dose-dependent relationship between the

TABLE 3 | Treatment success and mandibular protrusion comparison between facial patterns.

	Hypodivergent pattern ($n = 34$)	Neutral growth pattern ($n = 46$)	Hyperdivergent pattern ($n = 32$)	p
AHI improvement	−15.0 [−17.7; −12.3]	−15.9 [−18.9; −10.9]	−10.4 [−13.5; −6.2]	0.091[†]
T90% improvement	−4.63 [−7.23; −2.02]	−6.54 [−9.34; −3.75]	−3.62 [−5.26; −1.2]	0.180[†]
min SaO_2 improvement	3.356 [1.90; 4.81]	4.254 [3.01; 5.50]	3.088 [2.09; 4.10]	0.364[†]
ESS improvement	−5.68 [−7.15; −4.20]	−4.87 [−6.11; −3.62]	−3.50 [−4.67; −2.3]	0.084[†]
Responders – definition 1 – (%)	82.35 [66.5; 91.65]	60.87 [46.5; 73.61]	25.00 [13.3; 42.1]	<0.001[‡,*]
Non-responders – definition 1 – (%)	17.65 [8.35; 33.51]	39.13 [26.4; 56.54]	75.00 [57.9; 86.8]	
Responders – definition 2 – (%)	100.0 [89.9; 100.0]	69.57 [55.2; 80.92]	46.88 [30.9; 63.6]	<0.001[‡,*]
Non-responders – definition 2 – (%)	0	30.43 [19.1; 44.81]	53.13 [36.5; 69.1]	
Therapeutic MA (%)	71.47 [67.8; 75.10]	70.91 [68.8; 77.22]	75.31 [72.0; 78.6]	0.092[†]

Note: All data are presented as mean difference or percentage and confidence interval (range).
Abbreviations: AHI, apnea-hypopnea index; ESS, Epworth sleepiness scale; MA, mandibular advancement; minSaO_2, minimum oxygen saturation; T90%, percentage of time with oxygen saturation < 90%.
*Significance accepted at $p < 0.05$. [†]ANOVA test; [‡]Chi-squared test.

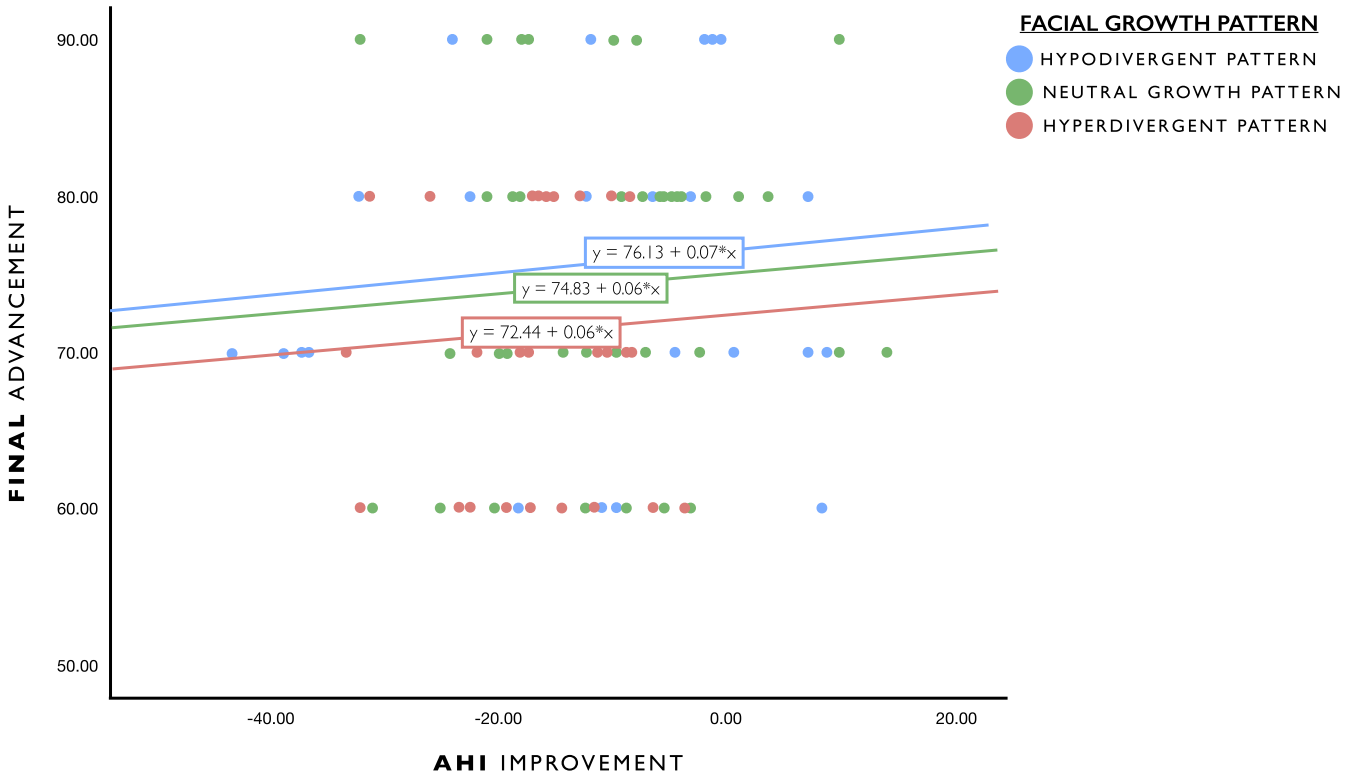

FIGURE 3 | The improvement rate of the apnoea-hypopnoea index (AHI) is depicted as change curves in relation to mandibular protrusion, expressed as a percentage of maximum mandibular protrusion. The data is categorised into hypodivergent pattern (blue), neutral growth pattern (green), and hyperdivergent pattern (red) groups. Patients with a hyperdivergent pattern required greater mandibular advancement to achieve a comparable reduction in AHI; however, these differences were not statistically significant.

extent of mandibular advancement and the reduction in AHI. Ma et al. [44] observed that in patients with high angles, mandibular protrusion from 70% to 80% resulted in an increase in vertical opening distance, which may have had unfavourable effects. Magnetic resonance imaging revealed that these patients exhibited a narrower baseline oropharyngeal dimension, and mandibular advancement resulted in a greater oropharyngeal cross-sectional area. Consequently, a greater degree of protrusion was necessary to achieve a 50% reduction in AHI in high-angle patients [44]. Although the results of the present study

were comparable, no statistically significant differences were observed between the groups.

The design of the MAD is a significant element in the interpretation of these results, as it affects the regulation of mandibular position during mouth opening, particularly in the supine position [46]. In some devices, the design allows for mandibular retrusion and posterior rotation during mouth opening, with the mandible returning to its resting position once the fin's limit is reached, thereby ensuring patient comfort [47]. In contrast, alternative device designs result in mandibular protrusion when the patient opens their mouth. In all three devices utilised in this study, despite a certain degree of mouth opening, there should be no reduction in device efficacy due to the protrusion of the mandible. Specifically, the NOA device is designed in accordance with the specific mandibular kinematics of each patient, given that the trajectory of the incisor tips varies among individuals who are using the same device [48].

The impact of mouth opening on treatment outcomes is a topic of ongoing debate in the literature. Some studies indicate that there is no significant difference between limiting or allowing mouth opening [49], while others suggest that minimising mouth opening may enhance treatment efficacy [50]. Such variability may be contingent upon the specific device employed. The first device employed was the Narval CC, which resulted in minimal mandibular retrusion during mouth opening. The second device utilised was the Somnodent, which caused an increase in retrusion with a greater vertical dimension. Thus, devices that maintain mandibular protrusion during mouth opening are crucial.

A limitation of this study is that the radiographic records of the patients were obtained while they were awake. Consequently, the results may not accurately reflect the actual conditions of sleep, due to changes in airway muscle tone that occur during sleep [51]. Moreover, although CBCT offers significant advantages in the assessment of craniofacial and airway anatomy in OSA patients, it is a static image [37, 38]. To understand upper airway collapse, it is necessary to go beyond passive components (such as soft tissues and airway) and consider active factors, such as muscle activity regulated by reflexes and central mechanisms, along with tissue deformation under breathing pressures, which collectively contribute to maintaining (or not) airway patency [52].

Another limitation is the relatively small sample size, which is attributable to the demanding and time-consuming processes involved in mandibular titration and home sleep evaluations. It should be noted that the sample of this study is limited to a Caucasian population, which may limit the generalisability of the findings to individuals of other racial backgrounds. Differences between ethnicities in soft and hard tissue proportions have been observed, which could influence the response to devices. For the same level of OSA severity, Caucasians have been shown to be more obese compared to Asians, while Asians exhibit smaller craniofacial skeletal measurements, such as a smaller, more posteriorly positioned maxilla, which is associated with OSA. Thus, both populations appear to have an anatomical imbalance contributing to upper airway collapsibility, with excess soft tissue in Caucasians and bone restriction in Asians [53].

Another important consideration is the retrospective nature of the study, which may introduce potential sources of bias. While efforts were made to minimise these biases through standardised data collection and analysis, prospective studies are needed to confirm these findings. Given the potential limitations of the study, the results could be interpreted in a way that extreme values of the combined parameters (clinical, anatomical, polysomnographic) identified as predictors of poor MAD treatment response may serve more effectively as contraindications or 'red flags' rather than predictive factors [37]. Furthermore, additional randomised clinical trials that incorporate non-anatomic factors into predictive models or assess treatment outcomes with MADs during sleep endoscopy could also provide valuable insights.

The use of different MAD devices represents another potential confounding factor. Although no statistically significant differences in treatment response were observed across devices, this does not entirely exclude the possibility of interactions between device characteristics and craniofacial morphology that could influence treatment outcomes [19]. Future studies should explore whether specific device designs better accommodate certain anatomical profiles to optimise therapy.

Notwithstanding the aforementioned limitations, this study has several notable strengths. Unlike many previous studies, it does not restrict its assessment of efficacy to a single parameter (AHI). Instead, it incorporates a set of parameters that align with the guidelines established by the most recent international consensus on OSA [17, 23].

5 | Conclusions

The findings of this study indicate that the anatomical subtypes may have different effects on the efficacy of OSA treatment utilising MADs. The data indicated that patients in Cluster 1 exhibited a less favourable response compared to those in Cluster 2. Patients in Cluster 1 not only displayed craniofacial anomalies but also exhibited soft palate imbalances and more severe OSA. Conversely, the findings of this study indicate that hyperdivergent patients may not respond favourably to MAD treatment. However, the vertical facial pattern was not identified as a significant factor influencing the dose-dependent relationship between the extent of mandibular advancement and treatment efficacy.

Author Contributions

Sara Camañes-Gonzalvo: investigation, writing – original draft. **Rocío Marco-Pitarch**, **Marina García-Selva**, and **Sara Camañes-Gonzalvo:** investigation. **Andrés Plaza-Espín:** writing – review and editing. **José María Montiel-Company:** data curation, statistical analysis. **Vanessa Paredes-Gallardo:** supervisor, review and editing. **Carlos Bellot-Arcís**, **Rocío Marco-Pitarch**, and **Marina García-Selva:** conceptualisation, methodology, writing – review and editing.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

Peer Review

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/joor.13956.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.