Tufts UNIVERSITY | School of Dental Medicine

Predictors Of Success For Oral Appliance Therapy In Obstructive Sleep Apnea Patients Based On Initial Craniofacial Characteristics: An Exploratory Study

A Thesis

Presented to the Faculty of Tufts University School of Dental Medicine

in Partial Fulfillment of the Requirements for the Degree of

Master of Science in Dental Research

by

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June 2016

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ABSTRACT

Aim: 1. To evaluate the association of Obstructive Sleep Apnea (OSA) severity with age, BMI and certain craniofacial characteristics. 2. To compare these characteristics among the three different categories of OSA severity. 3. To investigate whether any of these characteristics could predict the success of oral appliance (OA) therapy. **Hypotheses:** 1. There is a positive association between the increase in OSA severity and cephalometric variables, age and BMI. 2. The success of OAs in treating OSA can be predicted by evaluating certain craniofacial characteristics on lateral cephalographs. 3. There is a significant difference in craniofacial hard and soft tissue characteristics between mild, moderate and severe OSA cases. **Materials & Methods:** Records of 108 OSA patients, consecutively treated with OAs in the Dental Sleep Medicine Clinic at Tufts University School of Dental Medicine, were reviewed retrospectively. Fifty-two subjects were included. We studied BMI, age, gender and seven cephalometric measurements: 1. Mandibular plane angle (MP), 2. Vertical distance between MP and the most superior point of the hyoid bone (MP-H), 3. ANB angle (ANB), 4. Soft tissue ANB angle (S.T. ANB), 5. Upper lip position to a true vertical line (UL-VL), 6. Lower lip position to a true vertical line (LL-VL), and 7. Soft tissue chin position to a true vertical line (C-VL). Three different definitions of success were evaluated: 1. At least 50% reduction in initial AHI, 2. Residual AHI ≤ 10 after treatment, and 3. Residual AHI ≤ 5.

Results: The sample was classified into: Mild (n=16, 30.8%), moderate (n=26, 50%) and severe (n=10, 19.2%) OSA groups. No statistically significant differences were found between the three groups ($P>0.05$). Median initial AHI = 17.1 (IQR = 15.5), was reduced on follow-up to 9.2 (IQR = 13.8). BMI (median= 28.3, IQR = 5.9) had a weak association with the increased AHI; $r_s = 0.28$, $P = 0.045$. OA therapy resulted in 51.9%, n= 27, 55.7%, n= 29 and 30.7%, n= 16 successful outcomes, using the first, second and third methods of defining success, respectively. Two cephalometric parameters were positively associated with success: MP (1^{st} and 3^{rd} definition) and C-VL (3^{rd} definition). Area under the curve (AUC) statistics were MP = (0.67 & 0.68), C-VL = (0.71), respectively.

Conclusion: A weak positive correlation was found between BMI and OSA severity. The MP and C-VL were significantly associated with the outcome of OA therapy. These two cephalometric characteristics showed poor and fairly modest predictability for the success of OA therapy, respectively. However, these results should be interpreted with caution and their clinical significance should be investigated further in future studies.

DEDICATION

“Challenges are what make life interesting. Overcoming them is what makes it meaningful”

- Joshua J. Marine

This thesis is dedicated to my parents and my little family, for their unconditional love and support, throughout my journey.

I also dedicate this to the angelic soul of my youngest brother “Mohannad”.

Missing you now and always.

ACKNOWLEDGMENTS

The profound thanks first and foremost to God “Allah” for blessing my journey of education and my whole life.

My sincere appreciation to my principle investigator Dr. Georgios Kanavakis and my committee members, Dr. Leopoldo Correa, Dr. Matthew Finkelman and Dr. Carroll Ann Trotman for teaching, guiding and supporting me.

I am grateful to all faculties, staffs and colleagues at Tufts Dental School, especially the front desk staff at the Dental Sleep Medicine Clinic at Tufts University School of Dental Medicine, for their help and patience during data collection.

I would like to express my gratitude to Umm Alqura University for sponsoring my postgraduate education, under the umbrella of my beloved country.

Last but not least, I am thankful to my little family; my little hero “Ibrahim”, loving husband “Asaad” whose decisions in life changed not only his future, but also mine. I am also highly thankful to my parents “Monawar and Zakarya Khojah”, my sisters, my brother and my friends. Without their love, support, and prayers it would have been more difficult to achieve this.

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LIST OF ABBREVIATIONS

AHI	Apnea-hypopnea index
AUC	Area under the curve
BMI	Body mass index
CBCT	Cone beam computed tomography
CI	Confidence interval
C-VL	Soft tissue chin position relative to a true vertical line
EEG	Electroencephalogram
ENHP	Estimated natural head position: A patient's radiograph or photograph has been taken and then rotated to their natural head position.
FHP	Frankfort horizontal plane
Go	Gonion
H	Hyoid bone
IQR	Interquartile range
LL-VL	Lower lip position to a true vertical line
Me	Menton
MP	Mandibular plane angle

MP-H	The vertical distance between MP and the most superior point of the hyoid bone
N	Nasion
NHP	Natural head position
OA	Oral appliance
OSA	Obstructive sleep apnea
PSG	Polysomnography
RNHP	Registered natural head position: The head of the subject is oriented to his or her NHP and a mark is used on their radiograph or photograph as a registration point.
ROC	Receiver operator curve
S	Sella
TUSDM	Tufts University School of Dental Medicine
UL-VL	Upper lip position to a true vertical line

Predictors of success for oral appliance therapy in sleep apnea patients

based on initial craniofacial characteristics:

An exploratory study

Introduction

Obstructive Sleep Apnea (OSA) is a form of sleep-disordered breathing, characterized by the presence of repetitive upper airway obstruction during sleep. It could manifest as partial (hypopnea - reduction in airflow ≥ 30% from baseline) or complete (apnea - reduction in airflow greater than 90% of baseline) obstruction of airflow, resulting in blood oxygen desaturation, increased inspiratory effort and sleep fragmentation.[1] The condition is known to be associated with a number of other symptoms, such as snoring, excessive daytime sleepiness, morning headache, fatigue, impaired alertness and reduction in cognitive function.[1-3]

In a recently published systematic review about the epidemiologic aspects of OSA in the US, Garvey et al. reported that OSA associated with daytime sleepiness has a prevalence of 3-7% in adult males and 2-5% in adult females. Those prevalence estimates are similar to data reported worldwide.[4,5] OSA has been linked to increased road traffic accidents, a number of morbid conditions such as stroke, hypertension, cardiovascular disorders, secondary depression, anxiety, sexual dysfunction, and overall mortality; thus, it is now considered a crucial health hazard that requires careful evaluation and proper management by healthcare providers.[1,6]

The mechanism by which obstructive sleep apnea condition develops is believed to be multifactorial and complex. A common explanation of OSA etiology is the narrowing of the upper airway, due to the presence of excessive bulk of soft tissues; for example, an enlarged tongue, inflamed adenoids/tonsils or excessive accumulation of adipose tissue in the neck area inducing pressure on the dimensions of the upper airway.[1] It also has been emphasized in the literature that the condition may arise due to structural abnormalities in the head and neck area, such as a mandible that is diminished i.e. micrognathia or retrognathia.[2] The American Academy of Sleep Medicine recognizes the condition as an intrinsic sleep disorder, since the disorder is believed to originate within the body and progresses due to intrinsic factors already established in the body. Although it can be induced by an external factor such as alcohol consumption[7], the development of the sleep disorder syndrome would not be possible without the presence of internal factors.

Diagnosis of OSA starts with a comprehensive sleep history followed by a full-night comprehensive sleep evaluation known as polysomnography (PSG).[8] The latter is considered the standard of reference for diagnosis of OSA.[9] One way of assessing the severity of sleep apnea is through evaluating the apnea-hypopnea index (AHI), which is the number of complete (apneas) or incomplete (hypopneas) obstructive events per hour of sleep. An AHI $\geq$ 5 events/hour is needed to diagnose a case with OSA, while an AHI score less than 5 is considered to be normal. Furthermore, obstructive sleep apnea condition can be classified as mild for AHI $\geq$ 5 and $<$15, moderate for AHI $\geq$ 15 and $\leq$ 30, and severe for AHI reading beyond 30/h. [2,8] Respiratory disturbance index (RDI) is another commonly used parameter in evaluating OSA and has its specific scale for classification. It quantifies the number of apneas, hypopneas and respiratory effort-related arousals per hour of sleep, confirmed by EEG.[10]

Treatment options for such a condition may involve behavioral and lifestyle modifications[11,12], continuous positive airway pressure devices (CPAP)[3,13,14], oral appliances (OAs)[15-18], orthognathic surgery (e.g. bimaxillary advancement)[19,20] and pharmacotherapy (e.g. Protriptyline and Acetazolamide)[21]. CPAP is considered a "gold standard" in the treatment of OSA[14]; however, in patients with mild or moderate OSA, oral appliances may provide positive therapeutic results by protruding the mandible, advancing the tongue, and thereby increasing pharyngeal space.[17] Although CPAP has been considered the standard treatment option for OSA, its major limitations such as poor patient tolerance and cumbersome fitting of the device should not be overlooked. The use of OAs has evolved as a practical alternative to CPAP, especially in cases with mild to moderate OSA.[17] This treatment modality has been shown to be effective in clinical practice.[16,18,22,23] Gjerde *et al.* found an overall OA treatment success rate to be 75% and they did not find a significant difference in success rates between patients in the moderate and severe categories (69% and 77%, respectively). Therefore, depending on the severity of the condition and its etiology, treatment options may vary and also may rely on the clinical judgment of the health care provider.[2] It is important to distinguish and recognize which patients would benefit from OA therapy in order to determine whether it would serve as a suitable treatment option.

When using OAs in clinical practice, a common advancement protocol is lacking in the literature. Some investigators suggest a mild amount of advancement, others prefer high amount of protrusion, while some clinicians titrate the appliances progressively. A meta-regression analysis of moderate quality RCTs, carried out by Bartolucci *et al.*, revealed that advancement beyond 50% does not significantly influence the success rate (Q = 0.373, P = 0.541) and that improvement in AHI scores were not proportional to the increase in the amount of mandibular advancement. Furthermore, It was suggested that the amount of mandibular protrusion is not the unique factor influencing the effectiveness of OA therapy, it is rather a combination of multiple factors, including the inter-individual variability. Thus, it is vital to consider customized and progressive amount of mandibular advancement.[24]

Numerous studies have attempted to establish a direct correlation between craniofacial structures and OSA, and many suggested that different cephalometric features might contribute a risk factor for OSA. The position of the hyoid bone, posterior to anterior facial height ratio, gonial and mandibular plane angles are all among the most reported cephalometric parameters linked to sleep apnea. [9,25,26] The focus of these cephalometric studies has been generally directed towards studying the hard tissues of the head and neck and to a great extent towards evaluating the airway. Yet, there has not been much emphasis on evaluating soft tissue parameters in sleep apnea sufferers.[27] Lee R.W. *et al*. focused their studies on the craniofacial phenotyping in obstructive sleep apnea patients, and studied surface facial measurements obtained by simple two-dimensional digital photography. They found that certain facial measurements such as face width correctly classified 76.1% of subjects with and without OSA (sensitivity 86.0%, specificity 59.1%, area under the receiver operating characteristics curve [AUC] 0.82).[28]

Relationships between facial phenotype and upper airway anatomy are likely to exist as a result of the shared embryological origins of craniofacial components. Hence, identification of potential anatomic predictors for OSA treatment, including soft tissue measures obtained from the facial profile, is of great value and should be explored. Capistrano *et al*. found that patients' facial morphology influences OSA. Interestingly, they found that brachyfacial types had higher apnea-hypoxia indices, as opposed to the common finding, which implies that dolicofacial form is more related to OSA. [29]

While facial photographs are simple, less invasive and convenient for identifying facial characteristics; lateral cephalometric films are also very simple, standardized and widely available diagnostic records in pediatric, orthodontic and maxiollofacial surgeon offices. Despite their two-dimensional assessment of anatomical structures in the head and neck when compared to the three-dimensional imaging of cone beam computed tomography (CBCT), cephalometric radiographs serve various diagnostic purposes effectively with less amount of exposure to radiation. [30] It was concluded by Guarda-Nardini *et al.* that both the mandibular plane angle and the distance between hyoid bone and the mandibular plane were positively correlated with OSA treatment outcome. [9] A retrospective study carried by Sakamoto *et al.* to identify the cephalometric factors associated with OSA severity and their predictability for OA treatment outcome, suggested that cephalometric analysis is useful for predicting OSA severity and the efficacy of OA therapy. Both ANB angle and the distance between the mandibular plane and hyoid bone (MP-H) were found to be predictive factors of OSA severity.[31]

Aim and Hypothesis

Objectives of the project:

We utilized age, gender and BMI of OSA subjects, along with their lateral cephalographs that were taken at their baseline clinical evaluation in order to:

1. Evaluate the association of Obstructive Sleep Apnea (OSA) severity with age, BMI and certain craniofacial characteristics of OSA patients.

2. Compare these characteristics among the three different categories of OSA severity.

2. Investigate whether any of these characteristics could predict the success of oral appliance (OA) therapy.

Hypotheses:

1. There is a positive association between the increase in OSA severity and cephalometric variables, age and BMI.

2. The success of OAs in treating OSA can be predicted by evaluating certain craniofacial characteristics on lateral cephalographs.

3. There is a significant difference in craniofacial hard and soft tissue characteristics between mild, moderate and severe OSA cases:

Severe OSA group is expected to have higher values for the mandibular plane angle, and hyoid bone distance to the mandibular plane. Higher ANB angle, soft tissue ANB angle and protrusive lips are all indicative of a convex facial profile. Thus, severe cases may show higher values for those parameters, along with lower values for the soft tissue chin position, which is indicative of a retrusive mandible.

Significance:

Our data could potentially help clinicians categorize sleep apnea patients based on their craniofacial morphology. Identifying predictors of success for OSA therapy may provide clinicians with insight about proper candidates for the oral appliance treatment option. Moreover, they could facilitate case selection and treatment planning for OSA therapy, especially when the less invasive treatment modality (oral appliance option) is considered. To date, soft tissue parameters had not been investigated on lateral cephalographs and it would be interesting and valuable to explore such parameters within existing lateral cephalographs for OSA patients.

Research Design

This was a retrospective cohort study design, utilizing the records of OSA patients treated in the Dental Sleep Medicine Clinic at Tufts University School of Dental Medicine (TUSDM). The sample was a convenience sample of 108 adult patients, diagnosed with OSA, who were consecutively treated with OAs within the period between July 1, 2014 and February 29, 2015 in the Dental Sleep Medicine Clinic at Tufts University School of Dental Medicine.

The following inclusion criteria were applied:

- Adult patients (≥18 years old)
- Diagnosed with OSA i.e. AHI ≥ 5 indicated by a PSG study on initial evaluation and treated by OAs.
- Those presented with natural complete or partial dentition.
- Patients with complete records:

1. Complete demographic information (age, gender and BMI).
2. PSG study on initial evaluation with Apnea-hypoxia index (AHI) reported.
3. Lateral cephalometric radiograph recorded on initial evaluation exhibiting clearly identifiable soft and hard tissue structures.
4. Follow up sleep study, reporting post-treatment AHI score.

The exclusion criteria were as follows:

- Those who were prescribed OAs for an indication other that OSA, such as snoring only or myofacial pain.

Materials and Methods

One of the investigators (L.C.) provided a list of the patients' names and chart numbers who were consecutively treated with OAs in the Dental Sleep Medicine Clinic at Tufts. This list was created as part of the standard practice by that investigator. All patients were treated by the same clinician (L. C.) under the same treatment protocol. This involved the use of adjustable and custom fabricated mandibular advancement oral appliances. His protocol implicated progressive increase in mandibular protrusion, ranging between 70-80-% of initial maxilla-mandibular relation i.e. around 5 mm of advancement as maximum. All subjects' lateral cephalographs were recorded at their baseline clinical visit when the demographic information was entered into the electronic/paper charts.

IRB approval was sought from Tufts IRB office at the dental school. Researcher (M.K.) had axiUm research access (provided by Tufts IT team) to the electronic records of the indicated subjects for data collection and organization. AxiUm records' numbers were used for initial identification of the cases. Both electronic and paper charts of 108 subjects were reviewed for inclusion criteria. Fifty-two subjects qualified to be included as the study sample (N = 52). The same researcher collected the demographic information of each subject (age, gender and BMI) and tabulated the information on an Excel spreadsheet, which was kept password protected on Tufts Box. The BMI was calculated for a number of subjects as the only information provided by those patients on initial evaluation were height and weight. After converting weight into kilograms and height to meters, BMI was calculated in Kg/m^2.

AxiUm records' numbers of the study sample were replaced with unique study identifying numbers (generated through an online randomization website: www.random.com. The identification numbers were used from that point on, to label the cases and identify them.

Lateral cephalometric radiographs of the 52 subjects were exported and saved on Tufts Box as well, prior to uploading them to the cephalometric analysis software: ViewBox (dHAL Software, Kifissia, Athens-Greece). Once the radiographs were uploaded to ViewBox software, they were adjusted to be in natural head position and facing towards the right side. The natural head position, was used in order to establish a reliable and reproducible true vertical reference line, from which the needed linear measurements can be calculated. According to the estimated natural head position (ENHP), the heads were adjusted subjectively by both researcher (M.K.) and the P.I. (G.K.), based on their consensus for the head to be oriented as if the subject was looking straight to the horizon. After orienting the radiographs into ENHP and following identification of point "subnasale", a true vertical line through subnasale was created automatically in the software.

The cephalometric radiographs were traced by researcher (M.K.). Prior to tracing, the magnification error in the radiographs was controlled/adjusted digitally within the Viewbox software. This was accomplished by marking the standardized ruler - incorporated on the cephalometric film when it was initially taken - and entering the measured length into the established magnification tab on the software. All angular and linear measurements were calibrated accordingly.

The following soft and hard tissue landmarks were identified on each radiograph:

Landmark	Definition
1- Soft tissue Nasion	The deepest point of the soft tissue superior to the bony pyramid of the nose.
2- Subnasale	The junction where the base of the columella of the nose meets the upper lip.

3- Soft tissue A point	The most concave (deepest) point between the vermilion border of the upper lip and subnasale.
4- Soft tissue B point	The most concave (deepest) point between the vermilion border of the lower lip and the prominence of soft tissue covering the chin i.e. soft tissue pogonion.
5- FA of the upper lip	The most anterior point of the upper lip.
6- FA of the lower lip	The most anterior point of the lower lip.
7- Soft tissue pogonion	The most prominent point of the soft tissue structure of the chin.
8- Sella (S)	the center of the hypophyseal fossa or the saddle (sella tursica).
9- Nasion (N)	The most anterior point at the junction of the nasal and frontal bones (nasofrontal suture).
10- A point (subspinale)	The deepest point of the anterior surface of the maxilla.
11- B point (supramentale)	The most concave point on mandibular symphysis.
12- Menton (Me)	The lowest point on the symphysis of the mandible.
13- Gonion (Go)	The most posterior inferior point on angle of mandible.
14- (H) point	The most superior point on the greater horn of the hyoid bone.

Seven different cephalometric linear and angular measurements were determined on Viewbox for each subject. Values of those seven cephalometric variables were exported to the same Excel sheet that included the demographic information – Refer to figures 1-4:

1. Soft tissue ANB angle (S.T. ANB).
2. Skeletal ANB angle (ANB).
3. Upper lip position to a true vertical line through subnasale (UL-VL).
4. Lower lip position to a true vertical line through subnasale (LL-VL).
5. Soft tissue chins position to a true vertical line through subnasale (C-VL).
6. Mandibular plane angle (MP): formed between the anterior cranial base SN and the mandibular plane.
7. Vertical distance between the most superior point of the hyoid bone to the mandibular plane (MP-H).

Following completion of cephalometric tracing, the error in identification of cephalometric landmarks was assessed via intra-examiner and inter-examiner reliability testing:

A- Intra-examiner reliability:

Twenty percent of the total sample size (n=11) was randomly selected to create duplicates of their cephalometric radiographs in order to be retraced by researcher (M.K.). This was done after two weeks of her previous tracing of the total sample. The Dahlberg formula was used to determine the amount of error in identifying cephalometric landmarks that examiner M.K. might have experienced in tracing the subjects. This is illustrated below:

Cephalometric Variable	Amount of measured error	Original measurement by M.K.		SD	IQR	N
	Inter-examiner	Mean	Median			
UL-VL	0.4	1.48	-	2.61	-	11
LL-VL	0.44	0.71	-	3.47	-	11
C-VL	0.29	-	-1.4	-	6.9	11
S.T. ANB	0.37	5.84	-	2.13	-	11
ANB	0.41	-	3.3	-	2.7	11
MP	0.88	30.66	-	6.38	-	11
MP-H	0.43	-	17.5		8.5	11

B- Inter-examiner reliability:

The P.I. traced a group of 11 randomly selected subjects. The Dahlberg formula was used to determine the amount of error in identification of cephalometric landmarks between the two examiners for these 11 subjects. This is illustrated in the following table:

Cephalometric Variable	Amount of measured error	Original measurement by M.K.		SD	IQR	N
	Intra-examiner	Mean	Median			
UL-VL	0.35	1.48	-	2.61	-	11
LL-VL	0.22	0.71	-	3.47	-	11
C-VL	0.46	-	-1.4	-	6.9	11
S.T. ANB	0.68	5.84	-	2.13	-	11
ANB	0.39	-	3.3	-	2.7	11
MP	0.71	30.66	-	6.38	-	11
MP-H	0.57	-	17.5		8.5	11

Following that step, researcher M.K. evaluated the OA treatment outcome for each case to determine successful cases and exported the findings to the excel spreadsheet. Three different definitions of success were used. Thus, for each subject, follow-up AHI score was evaluated for satisfaction of any of the following criteria in defining successful treatment:

- At least 50% reduction of baseline AHI score.
- Post-treatment residual AHI ≤ 10 events/hour.
- Post-treatment residual AHI ≤ 5 event/hour.

This was followed by statistical analysis of all exported data.

Statistical Analysis

Descriptive statistics were computed and presented as counts and percentages for categorical variables. Means and standard deviations were used for normally distributed continuous variables, while medians and inter-quartile ranges (IQR) were reported for those which were not normally distributed. Spearman's correlation was used to evaluate the association between age, BMI and the seven cephalometric measurements with initial AHI scores of the subjects (OSA Severity). The Kruskal-Wallis test was conducted to compare the distribution of the age, BMI and the cephalometric values between the three different categories of initial OSA condition. Bivariate associations between gender and each definition of success or failure of treatment were explored via the chi-square test. The association between the efficacy of OA (the success of OA therapy) and our specified cephalometric variables, age and BMI was determined by simple logistic regression analysis. Receiver operating characteristic (ROC) curve analysis was conducted to calculate area under the curve (AUC) statistics. Dahlberg's formula[32] was utilized to assess the degree of measurement error. Data were analyzed using SPSS software version 24. Statistical significance was set at $p < 0.05$.

Variables studied:

I. First aim:

We studied the association between age, BMI and the following seven craniofacial characteristics (upper lip position to a vertical line through subnasale, lower lip position to a vertical line through subnasale, soft tissue chin position to a vertical line through subnasale, hyoid bone distance to the mandibular plane, soft tissue ANB, skeletal ANB and mandibular plane angle), with OSA severity i.e. the initial AHI scores of the subjects. We looked at the differences in craniofacial characteristics among mild, moderate and severe Obstructive Sleep Apnea (OSA) patients, where OSA severity served as the dependent variable, while subjects' gender, age, BMI and the seven different cephalometric variables acted as the independent variables.

II. Second Aim:

To test the predictability of success of oral appliance therapy, the seven craniofacial characteristics (upper lip position to a vertical line through subnasale, lower lip position to a vertical line through subnasale, soft tissue chin position to a vertical line through subnasale, hyoid bone distance to the mandibular plane, soft tissue ANB, skeletal ANB and mandibular plane angle) were used as independent variables, while the dependent variable was the outcome of OA therapy (success/failure).

Results

Descriptive Statistics:

Demographic information of the study sample is summarized in Table 1. The study sample was comprised of 52 subjects; 34 males (65.4%) and 18 females (34.6%), Figure 5. The mean age for the study sample was 56.06 years (SD = 9.65) and it ranged between 36 and 87 years. The mean body mass index (BMI) was 28.76 (SD = 4.36). Nine subjects had a normal BMI <25 while 43 subjects had a BMI ≥ 25; within those, 21 subjects were deemed obese (BMI ≥ 30). On initial evaluation, the AHI score in this sample displayed a median of 17.1 (IQR = 15.5). There were 16 cases (30.8%); 13 males and 3 females diagnosed with mild OSA, 26 cases (50%); 14 males and 12 females diagnosed with moderate OSA and 10 cases (19.2%); 7 males and 3 females diagnosed with severe OSA, Figure 6. AHI scores reduced generally on follow up to exhibit a median of 6.9 (IQR = 12.2). Following the use of OAs in our study sample, 27 cases (51.9%) out of 52 exhibited at least 50% reduction of their initial AHI score. Twenty-nine subjects (55.8%) fulfilled the second definition of success i.e. having residual AHI reading equal to or less than 10, while only 16 cases (30.8%) qualified for the stricter definition of success and had an AHI score that was less than or equal to 5. The distribution of successful subjects based on gender is demonstrated in Figures 7-9.

The median value for ANB angle was 3.3 (IQR = 2.7) indicating a central tendency of mild skeletal class II pattern. Correspondingly, the soft tissue ANB angle (reflecting the soft tissue profile) was 5.8 ± 2.1 degrees on average. The upper lip average position was 1.48 mm ahead of the true vertical line through subnasale with a standard deviation of ± 2.60 mm, however, the lower lip was 0.7 ± 3.47 mm away from the same line. We also evaluated the prominence of the soft tissue chin relative to the true vertical line passing through subnasale, and we found that its median value was -1.4 mm (IQR = 6.9). The median value for hyoid bone was found to be 17.5 mm (IQR = 8.5) away from the mandibular plane (Go-Me). The latter formed an angle with the anterior cranial base that was on average equal to 30.6 degrees (SD = 6.38) indicating an average normo-divergent skeletal pattern. Summary of cephalometric values are reported in Table 2.

Correlation/Association:

Based on univariate analysis, only BMI showed a weak positive statistically significant correlation with initial AHI severity, Spearman's coefficient $r_s = 0.28$, $P = 0.045$, Figure 10. Results for Spearman's correlation are indicated in Table 3.

Simple logistic regression analysis:

This test revealed that the mandibular plane angle (SN-GoMe) could statistically significantly predict success - considering at least 50% reduction in AHI score - of OSA therapy $P = 0.03$, OR= 1.12, 95% C.I. [1.10,1.24]. Under the stricter definition of success, both the mandibular plane angle and soft tissue chin position relative to the vertical line through subnasale were found to be statistically significantly associated with success which implies a post-therapy AHI score of less than 5 events per hour ($P = 0.02$, OR= 1.14, 95% C.I. [1.02,1.27] and $P = 0.03$, OR = 0.83, 95% C.I. [0.71,0.99], respectively). (Tables: 4-6).

Kruskal-Wallis test:

The Kruskal-Wallis test was conducted to determine if there were differences in age, BMI and the seven cephalometric variables we studied, between the mild OSA group (n=16), moderate OSA group (n=20) and severe OSA group (n=10). The difference in age between the three groups was not statistically significant (P =0.94). The median age for the mild, moderate and severe groups was: 57, 56.5 and 58, and their IQR was:16,12 and 10, respectively. Similarly, the difference in BMI between groups was not statistically significant (P =0.35). The median BMI for the mild, moderate and severe groups was: 26.7, 28.5 and 30.4 and their IQR was 5.8, 5.8. 7.4, respectively. The difference in craniofacial characteristics among the three categories of sleep apnea was not statistically significant $P >$ 0.05. Results are illustrated in Table 7 and Figures 11-19.

Receiver operating characteristic (ROC) curves and area under the curve statistics:

Receiver operating characteristic (ROC) curves were used to obtain area under the curve (AUC) statistics in order to evaluate each of the variables' ability to predict those cases that were successful after OSA therapy with the use of oral appliances – Table 8. Under the first definition of success, the mandibular plane angle was the only cephalometric measurement that was statistically significant $P = 0.03$ with an AUC statistic of 0.67, 95% CI [0.52, 0.82] indicating poor predictability.[33] The same measurement was statistically significant to predict success $P = 0.03$, AUC statistic = 0.68, 95% CI [0.53, 0.84] under the third definition, indicating its poor predictability as well.[33] The soft tissue chin position had an AUC statistic of 0.71, 95% CI [0.60, 0.81] in predicting success within the third definition of success ($P = 0.02$). A rough guide for classifying the accuracy of a diagnostic test is the traditional academic point system.[33]

Discussion

Mandibular advancement OAs are increasingly used in treating patients with OSA. They have gained more popularity and patients' acceptance since they provide a less costly and more comfortable therapeutic option. The aim of mandibular advancement OA therapy is to increase the dimensions of the upper airway and reduce its collapsibility by holding the mandible in an advanced position during sleep. It works by increasing the activity of genioglossus muscle, thus preventing retraction of the tongue and negative airway pressure. It also pulls the geniohyoid muscle forward causing an anterior movement of the hyoid bone, which, in turn, would widen the space at the junction point of the tongue with the posterior wall of the pharynx. [4,24]

A number of studies have shown the effectiveness of OA therapy in treating OSA.[16-18,22,23]. Different authors reported variable indications for OA therapy, based on the severity of OSA condition. Lim *et al* concluded in their systematic review that "it is appropriate to recommend OA therapy to patients with mild symptomatic OSAH, and those patients who are unwilling or unable to tolerate CPAP therapy".[15] Furthermore, Doff *et al.* indicated that OAs can be used as a substitute to CPAP when treating mild to moderate OSA conditions.[17] Alternatively, other investigators have used mandibular advancement oral appliances in managing severe OSA cases and proved their effectiveness.[18,34] Thus, it is interesting and helpful to identify OSA patients who would actually benefit from OA therapy.

Several significant cephalometric characteristics have been correlated with obstructive sleep apnea, including: inferiorly positioned hyoid bone, posterior to anterior facial height ratio, gonial angle and mandibular plane angle.[9,30,35] The current study attempted to add to the understanding of craniofacial characteristics related to OSA;

however, similar to the findings of Cillo *et al.*[26], no skeletal or soft tissue measurement we explored was found to be correlated to the severity of sleep apnea. Additionally, we did not find any statistically significant differences between the mild, moderate and severe OSA subjects with regards to their craniofacial characteristics, BMI or age. An explanation for such a finding could be attributed to the complex and heterogeneous nature of the OSA condition being affected by variable contributing factors. While the exact etiology for OSA remains unknown, it is attributed, generally, to the reduction in pharyngeal patency as a consequence to the interaction between anatomic and neuromuscular factors. Although compromised craniofacial structures and the excessive deposition of soft tissues within the neck area have been implicated in OSA, impaired upper airway mechanoreceptor sensitivity, airway edema and reduced lung volume have been reported as predisposing factors to pharyngeal incompetency.[8,24,36] Moreover, neurologic disturbance in the balance between the factors maintaining airway patency and those promoting airway collapse is a plausible cause for OSA. The contribution of any one factor or a combination of different factors to airway collapsibility also varies from person to person, endorsing the complexity in determining specific characteristics that are consistently related to such a multifactorial condition. [37]

The baseline clinical characteristics of our study sample appear to be generally similar to those reported in other studies; however, we did not compare our study sample to a control group. Banhiran *et al*[37] investigated BMI and a number of physical measurements, including chin length (measured during physical examination of the subjects, and was identified as the distance from the lowest point of the chin to the lower vermilion border) in a group of OSA patients and control subjects. They found statistically significant differences in BMI, neck circumference, chin length and several physical measures between the control group and OSA patients. Most of these differences were found between the controls and patients with moderate to severe OSA. The mild group differed only in their BMI and neck circumference [37]

Obesity, which is highly prevalent in the United States and is increasingly becoming epidemic, has been correlated with OSA.[26] Peppard *et al.*[38] found that the increase in body weight was positively correlated with AHI; that is, patients who gain 10% of their weight leads to a 32% increase in AHI score; conversely, a 10% reduction in body weight leads to a 26% reduction in AHI. In our study, a correlation was seen between OSA severity and BMI, which was only weak and could be related to the range of BMI values of our subjects. Within our sample, obese subjects i.e. those with BMI $\geq$ 30 kg/m^2 (n = 21, 40,4% of the total sample) had a mean AHI of 28 events/hour, while the average AHI for non-obese subjects was 18.5 events/hour. Both fall under the moderate level of sleep apnea and that could explain the weak association. We relied on BMI only in verifying the status of obesity in our subjects, and we should keep in mind that BMI does not represent the distribution of fat in the body. In a recently published systematic review by Cho *et al.,* the authors found no difference in BMI, waist circumference, and waist to hip ratio between patients with OSA and controls. Only neck circumference was greater and statistically significant among OSA patients regardless of their ethnicity. [36] Intuitively, more fat accumulation in the neck area predisposes the upper airway volume to more compression, compromising air flow and complicating the OSA condition.

Cephalometry is a low-cost, simple and widely available diagnostic technique. Previous studies have suggested that lateral cephalometry can identify craniofacial structures that might have an impact on treatment response of OSA cases.[39] Among the seven cephalometric variables we explored, we found that the mandibular plane angle was associated with success (under two different definitions of success in OSA therapy: at least 50% reduction in AHI score and having a residual AHI ≤ 5) while the soft tissue chin position relative to a true vertical line through subnasale was associated only with success defined by an AHI score ≤ 5. To date, this is the first study that looked at soft tissue chin position as a measurement on lateral cephalograph and associated that with success in OSA treatment. It should be noted that these two measurements were not statistically significantly associated with AHI severity.

If a number of structures identified on lateral cephalographs could provide a good level of prediction for OSA treatment outcome, this would turn such a simple radiographic procedure into a valuable screening and predictive tool, when managing OSA patients. We tested the ability of the mandibular plane angle and soft tissue chin position relative to the vertical line through subnasale, in predicting success of OSA treatment, and we found that the soft tissue chin position showed only fairly modest potential in its prediction (AUC = 0.71). Yet, the ability of the mandibular plane angle in predicting success was not adequate as it showed low AUC statistics. Within a study similar in design to ours, Sakamoto *et al.* analyzed retrospectively the records of 67 subjects with a mean age of 68.9. With a multivariate logistic regression analysis (controlling for confounders such as systematic health condition of the subjects, age, gender, etc.), they found that both ANB angle and the hyoid bone distance to the mandibular plane were predictive factors of OSA severity. Patients who had a high position of the hyoid bone had a poor response to OA therapy.

Guarda-Nardini *et al.*[9] reviewed the literature and summarized the data related to the predictive value of anatomical parameters identified on lateral cephalographs. They showed that both the mandibular plane angle and the distance between hyoid bone and the mandibular plane were found to have a predictive value for the effectiveness of mandibular advancement devices in treating OSA patients. However, they also noted that decisions based solely on these factors are not recommended due to the relative weak and somewhat inconsistent cephalometric data found in the literature. Likewise, both Alessandri-Bonetti *et al.*[40] and Saffer *et al.*[41], in their systematic reviews, found no clear predictors of OA treatment success and that the current available evidence is inconclusive for identification of cephalometric parameters capable of reliably discriminating between good and poor responders to OA devices. It can be inferred that the clinical applicability of cephalometric characteristics in predicting OA treatment outcomes remains controversial. This is due to the high inter-individual variability in response to OSA therapy in general, and, again, the complex nature of the condition of interest.

The chosen method to evaluate/quantify OA treatment response is usually based on the clinicians' goals and their clinical practice. With the lack of consensus around the definition of a successful treatment outcome when managing OSA, we utilized three different ways of defining success; all have been reported in the literature.[42] Okuno *et al.*[43] found that the predictive accuracy of different clinical and experimental tests for predicting OA treatment outcomes in OSA varied depending on the definitions of treatment success used as well as the type of index test used. They also reported that while many clinicians use PSG data as their main assessment tool to recommend an OA, studies using PSG variables have shown lower predictive accuracy. It is also important to consider the intra-individual night-to-night variability in AHI. Moreover, Ahmadi *et al.* reported a difference in AHI score >5 between two consecutive PSGs. Likewise, White *et al.* described a difference > 10 events/ hour in 35% of their sample.[24]

Our study did not detect any significant differences in the craniofacial characteristics of different OSA groups and none of the variables we tested were significantly correlated to OSA severity (the increase in AHI score), except for BMI. The presence of a condition like asthma could affect the upper airway and influence AHI values and OSA severity. Such a systemic health condition and many others were not reported in our investigation.

The sample size was restricted by the available data (convenience sample), thus limiting the study power and making this study exploratory in nature. In addition, a large portion of the original sample was excluded from further analysis due to missing information - either part of the subject records was missing or the sleep studies were not available at the time of analysis. This is a practical limitation of most retrospective studies, and, as such, caution is required when the results of this study are interpreted. It is worth mentioning that six subjects were excluded because the indication for OSA treatment was either snoring or myofacial pain i.e. initial AHI values were not diagnostic for OSA. Power calculation and a prospective approach comparing subjects with OSA to a control group may provide more profound results and conclusions.

Certain drawbacks related to the use of cephalometric radiographs were controlled in our study. This includes the error in measurement and identification of landmarks: inter-examiner and intra-examiner reliability testing were performed, and the adjustment for magnification error. However, we should always consider that lateral cephalograms are performed in an awake state and in an upright position whereas the pathology of OSA arises with the patient lying down during sleep, and such a factor is important when interpreting findings related to lateral cephalographs.

The natural head position (NPH) was defined by Moorrees as "a standardized and reproducible orientation of the head in space when one is focusing on a distant point at eye level".[44] It has better reproducibility compared to Frankfort horizontal plane, moreover, its stability and reproducibility has been proven by many research works.[45-47] In preparation for tracing the cephalographs and to develop an accurate reference line for cephalometric measurements, with consensus of two researchers (an experienced orthodontist and an orthodontic resident) the ENHP was utilized to adjust the orientation of the cephalographs. Despite the perceived possibility for error when using the ENHP as compared to RNHP, Jiang, Xu and Lin found a strong correlation between the two methods when orienting subjects' head position.[48]

After orienting the cephalographs into the ENHP, we analyzed three unique soft tissue parameters that can be easily evaluated from a standard cephalograph: upper lip, lower lip and soft tissue chin position relative to a true line through subnasale. Soft tissue chin position had a fairly modest ability in predicting success and was statistically significantly associated with OSA treatment outcome. The mandibular plane angle (SN-GoMe) was also correlated to success in treatment but showed weak predictability. These findings must be interpreted with caution, considering the limitations of the study. Additionally, we should not overlook the possibility of obtaining these findings just by chance due to the use of multiple statistical tests.

Conclusion

Based on the findings presented, the following conclusions can be drawn:

- No significant differences in craniofacial characteristics were found between the mild, moderate and severe OSA patients whom we studied.
- A weak positive correlation was found between BMI and OSA severity.
- In our exploratory study, the mandibular plane angle (SN-GoMe) and the soft tissue chin position relative to a true vertical line through subnasale were both associated with success in OSA therapy using mandibular advancement OA.
- These two variables have some potential in predicting success of OSA treatment. However, they both did not show a high predictive ability. Therefore, they must be interpreted with caution and their clinical significance should be investigated further in future studies with improved designs.
- Future studies accounting for confounding factors within the statistical analysis, and with a larger sample size are recommended to take the results beyond an exploratory level.

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APPENDICES

Appendix A: Tables 1-8

Appendix B: Figures 1-19

Appendix A: Tables

Table1: Demographic characteristics of the study sample.

Characteristic	N	Mean	Percentage	SD	Range
Age (Year)	52	56.06	-	9.65	36 – 87
BMI (kg/m^2)	52	28.76	-	4.36	19.2 – 41.2
Gender (no.)					
Male	34		65.4%		
Female	18		34.6%		
Baseline AHI (no. of respiratory events per hour)					
Mild (≥ 5 AHI <15)	16		30.8%		
Moderate (≥ 15 AHI ≤ 30)	20		50%		
Severe (AHI>30)	10		19.2%		

Table 2: Central tendency of the seven cephalometric variables.

Cephalometric Variable	Measurement		SD	IQR	N
	Mean	Median			
UL-VL	1.48	-	2.61	-	11
LL-VL	0.71	-	3.47	-	11
C-VL	-	-1.4	-	6.9	11
S.T. ANB	5.84	-	2.13	-	11
ANB	-	3.3	-	2.7	11
MP	30.66	-	6.38	-	11
MP-H	-	17.5		8.5	11

Table 3: Spearman's correlation - Association between initial AHI score and cephalometric variables, age and BMI.

Initial AHI	Age	BMI	UL-VL	LL-VL	C-VL	MP	ANB	S.T. ANB	MP-H
Spearman's Rho	0.17	0.28	0.05	0.08	0.15	-0.025	-0.25	-0.10	-0.16
P-value	0.23	0.04*	0.73	0.56	0.28	0.86	0.07	0.46	0.25
N	52	52	52	52	52	52	52	52	52

* $P < 0.05$

Table 4: Association between age, BMI and seven cephalometric measurements with success in OA therapy (1st definition: at least 50% reduction in AHI): Simple logistic regression analysis

Variable	Definition 1	
	Odds Ratio (95% C.I.)	*P*-value
UL-VL	0.85 (0.68,1.09)	0.22
LL-VL	0.94 (0.78,1.11)	0.45
C-VL	0.96 (0.85,1.10)	0.47
S.T. ANB	0.85 (0.65,1.12)	0.25
ANB	0.98 (0.76,1.27)	0.89
MP	1.12 (1.10,1.24)	0.03*
MP-H	0.96 (0.88,1.06)	0.47
Age	0.99 (0.93,1.05)	0.69
BMI	0.98 (0.87,1.12)	0.78

* $P < 0.05$

Table 5: Association between age, BMI and seven cephalometric measurements with success in OA therapy

(2nd definition: residual AHI ≤ 10): Simple logistic regression analysis

Variable	**Definition 2**	
	Odds Ratio (95% C.I.)	*P*-value
UL-VL	0.87 (0.67,1.09)	0.23
LL-VL	0.94 (0.80, 1.11)	0.45
C-VL	0.92 (0.81,1.04)	0.19
S.T. ANB	0.99 (0.76,1.28)	0.93
ANB	1.13 (0.86,1.47)	0.37
MP	1.04 (0.95,1.32)	0.43
MP-H	0.98 (0.89,1.10)	0.71
Age	0.96 (0.90,1.02)	0.20
BMI	0.89 (0.78,1.02)	0.11

Table 6: Association between age, BMI and seven cephalometric measurements with success in OA therapy

(3rd definition: residual AHI ≤ 5): Simple logistic regression analysis

Variable	Definition 3	
	Odds Ratio (95% C.I.)	*P*-value
UL-VL	0.93 (0.73,1.17)	0.51
LL-VL	0.93 (0.77,1.11)	0.39
C-VL	0.83 (0.71,0.99)	0.03*
S.T. ANB	1.11 (0.84,1.45)	0.49
ANB	1.16 (0.86,1.58)	0.33
MP	1.14 (1.02,1.27)	0.02*
MP-H	0.97 (0.87,1.08)	0.56
Age	0.99 (0.93,1.05)	0.71
BMI	0.87 (0.74,1.01)	0.07

* $P < 0.05$

Table 7: Differences in age, BMI and the seven cephalometric variables between OSA severity groups (Kruskal-Wallis test results)

Variables	Groups	N	OSA Severity		P-value
			Median	IQR	
Age	Mild	16	57.0	16.0	0.94
	Moderate	26	56.5	12.0	
	Severe	10	58.0	10.0	
BMI	Mild	16	26.7	5.8	0.35
	Moderate	26	28.5	5.8	
	Severe	10	30.4	7.4	
UL-VL	Mild	16	0.9	2.8	0.5
	Moderate	26	1.5	2.4	
	Severe	10	1.1	5.6	
LL-VL	Mild	16	0.3	3.5	0.61
	Moderate	26	1.1	4.2	
	Severe	10	0.3	6.0	
C-VL	Mild	16	-2.0	5.5	0.66
	Moderate	26	-0.45	6.7	

	Severe	10	-2.5	9.4	
MP	Mild	16	30.2	8.1	0.99
	Moderate	26	30.3	8.4	
	Severe	10	28.5	15.0	
ANB	Mild	16	3.8	1.2	0.39
	Moderate	26	2.4	2.9	
	Severe	10	2.5	2.6	
S.T. ANB	Mild	16	6.5	2.9	0.67
	Moderate	26	5.4	2.9	
	Severe	10	5.7	2.1	
MP-H	Mild	16	22.7	7.3	0.11
	Moderate	26	16.3	5.2	
	Severe	10	1.1	5.6	

Table 8: The predictability of success of OSA therapy based on cephalometric variables, Area under the curve statistics (AUC).

Variables	Definition 1		Definition 2		Definition 3	
	AUC	*P*-value	AUC	*P*-value	AUC	*P*-value
UL-VL	0.57	0.40	0.55	0.51	0.56	0.51
LL-VL	0.53	0.69	0.52	0.79	0.59	0.32
C-VL	0.55	0.52	0.61	0.19	0.71	0.02*
S.T. ANB	0.58	0.34	0.53	0.73	0.59	0.32
ANB	0.52	0.82	0.61	0.19	0.64	0.11
MP	0.67	0.03*	0.55	0.53	0.68	0.03*
MP-H	0.54	0.64	0.52	0.81	0.52	0.80

* $P < 0.05$

Appendix B: Figures

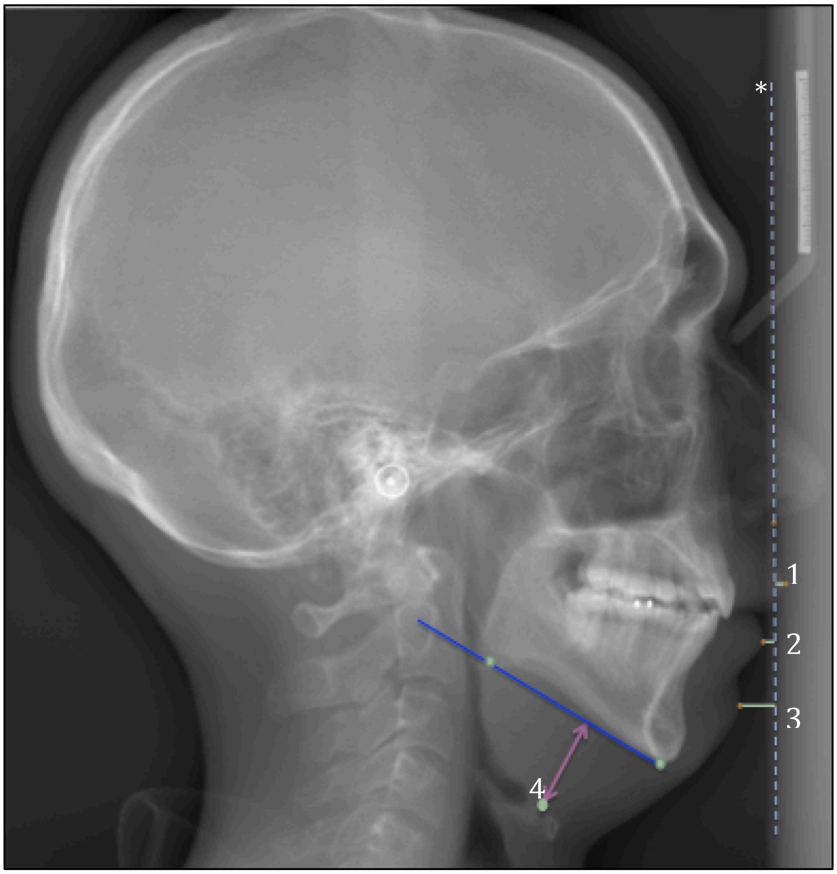


Figure 1: Cephalometric parameters:

1. Upper lip position to the vertical line (UL-VL).
2. Lower lip position to the true vertical line (LL-VL).
3. Soft tissue chin position the true vertical line (C-VL).
4. Vertical distance between the most superior point of the hyoid bone to the mandibular plane (MP-H).

   * True vertical line through subnasale.

Figure 2: Cephalometric parameter: Skeletal ANB angle (ANB).

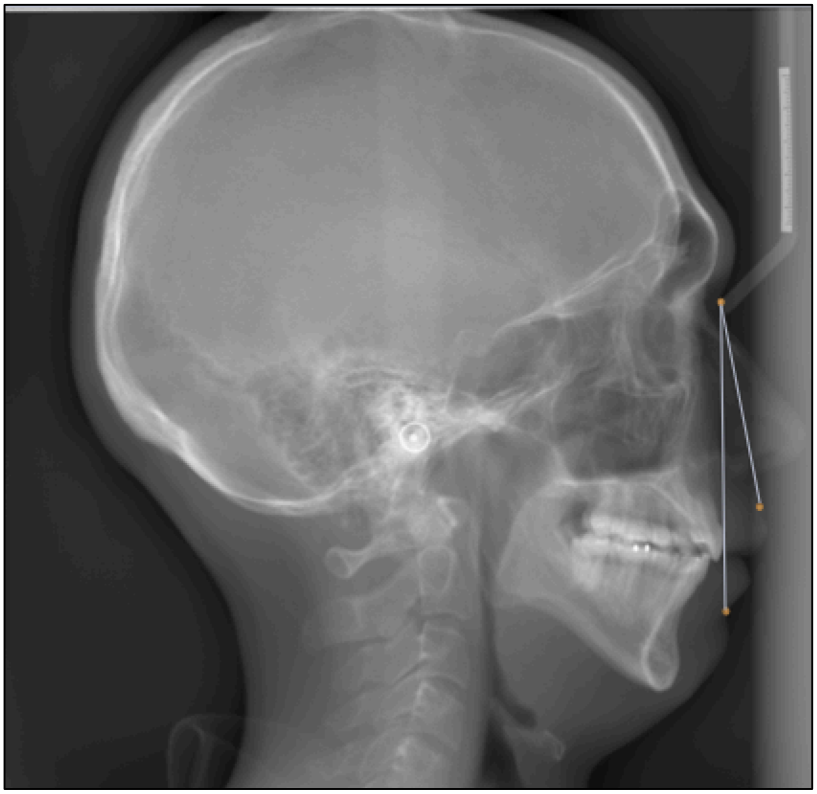


Figure 3: Cephalometric parameter: Soft tissue ANB angle (S.T. ANB).

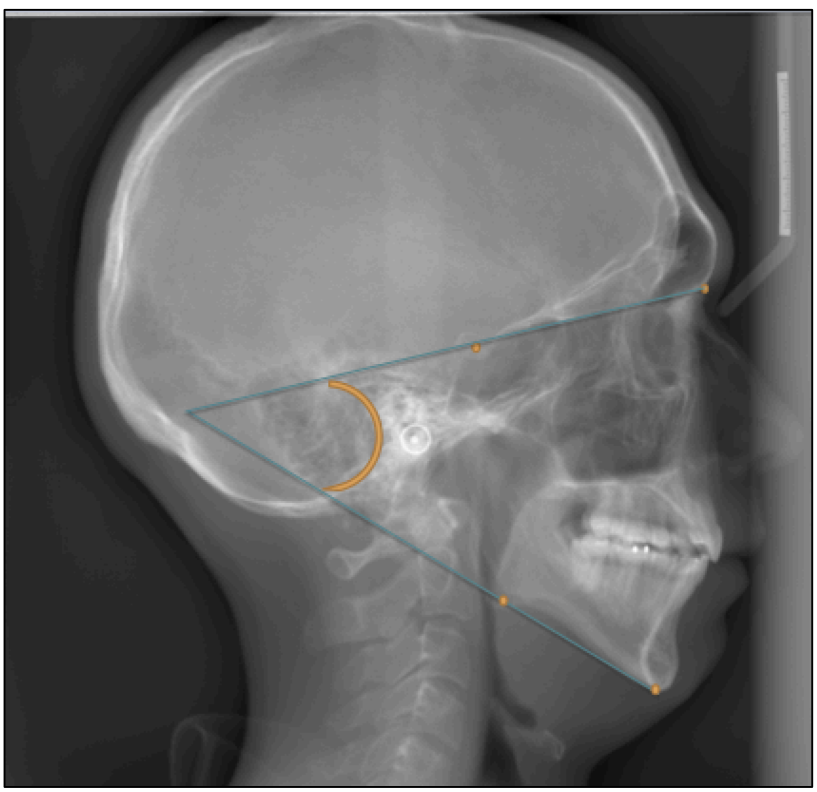
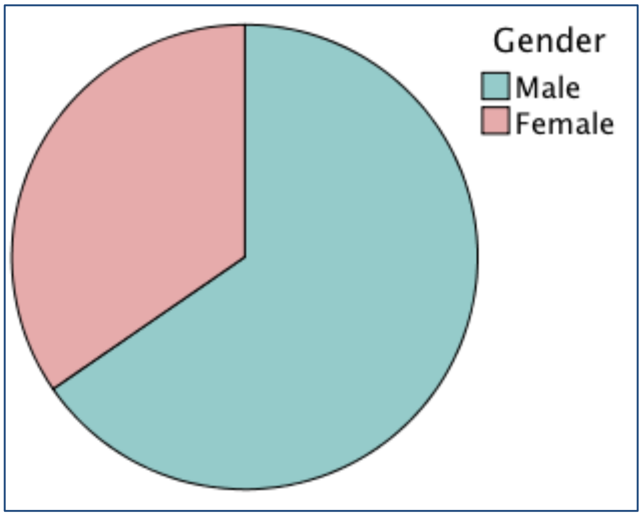
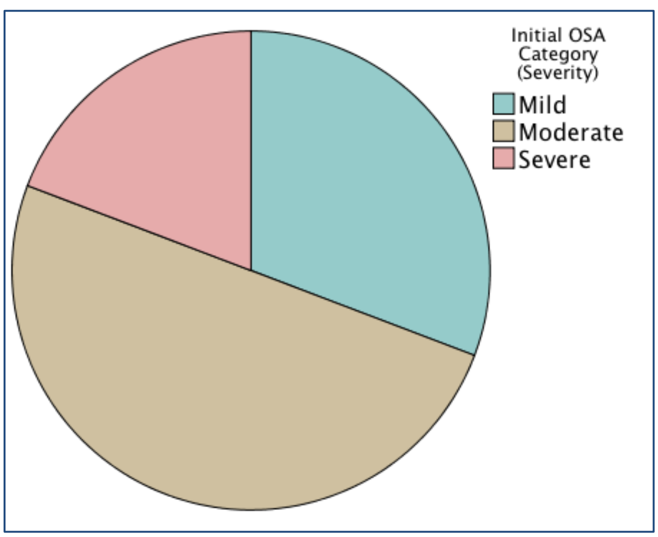


Figure 4: Cephalometric parameter: Mandibular plane angle (MP).



Gender	N	Percentage
Males	34	65.4%
Females	18	34.6%
Total	52	100%

Figure 5: Gender distribution in the study sample



OSA Category	N	Percentage
Mild	**16**	**30.8%**
Moderate	**26**	**50.0%**
Severe	**10**	**19.2%**
Total	**52**	**100%**

Figure 6: Distribution of mild, moderate and severe subjects in the study sample.

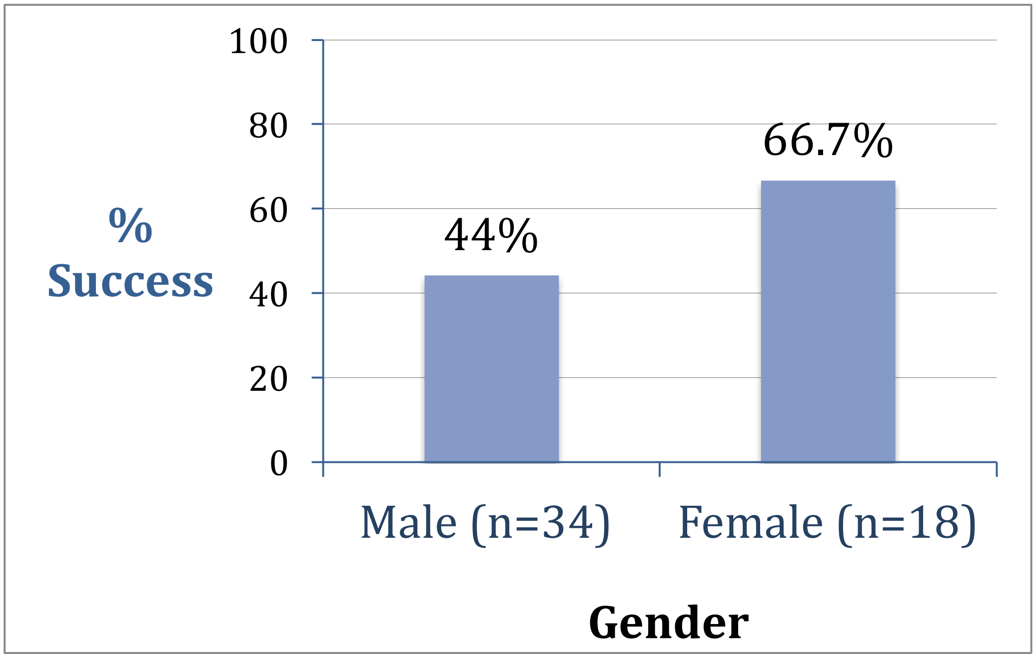


Figure 7: Association between gender and 1st definition of success (at least 50% reduction in AHI)

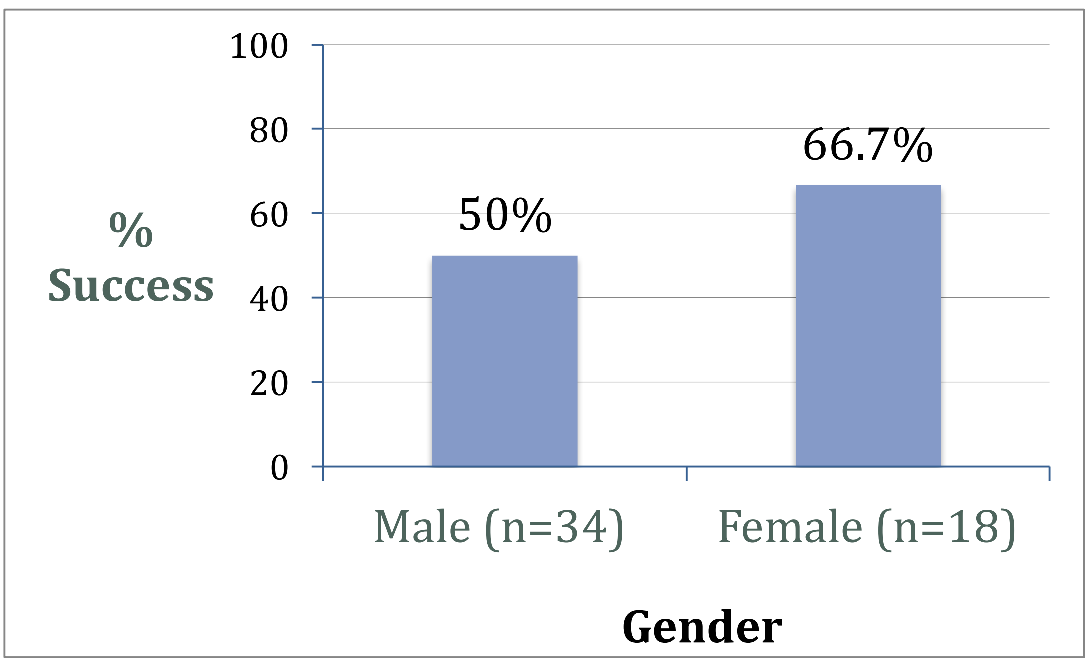


Figure 8: Association between gender and 2nd definition of success (residual AHI ≤10)

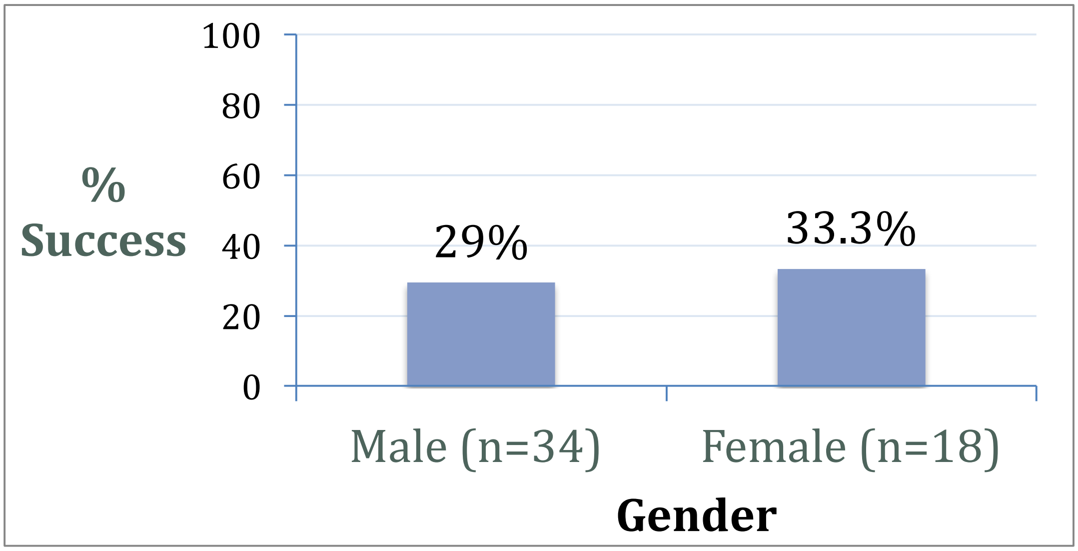


Figure 9: Association between gender and 3rd definition of success (residual AHI ≤5)

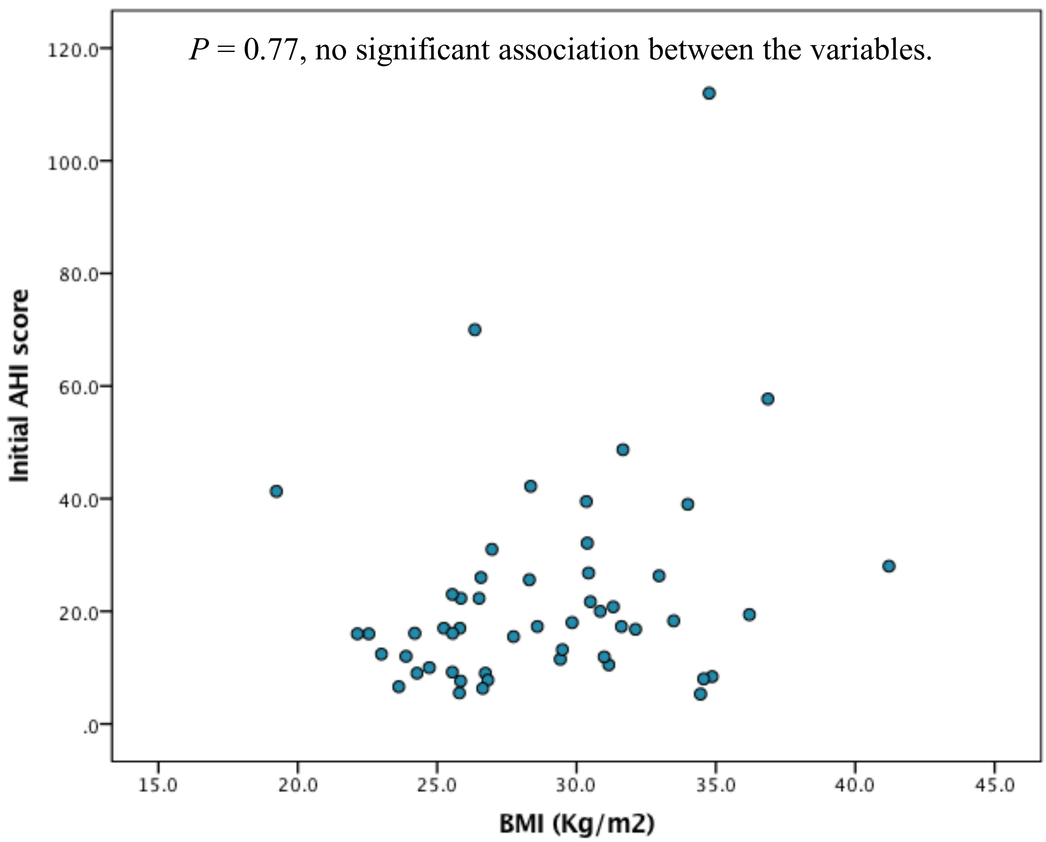


Figure 10: Spearman's correlation between BMI and initial AHI severity.

Figures 11-19: Distribution of variables within mild, moderate and severe groups

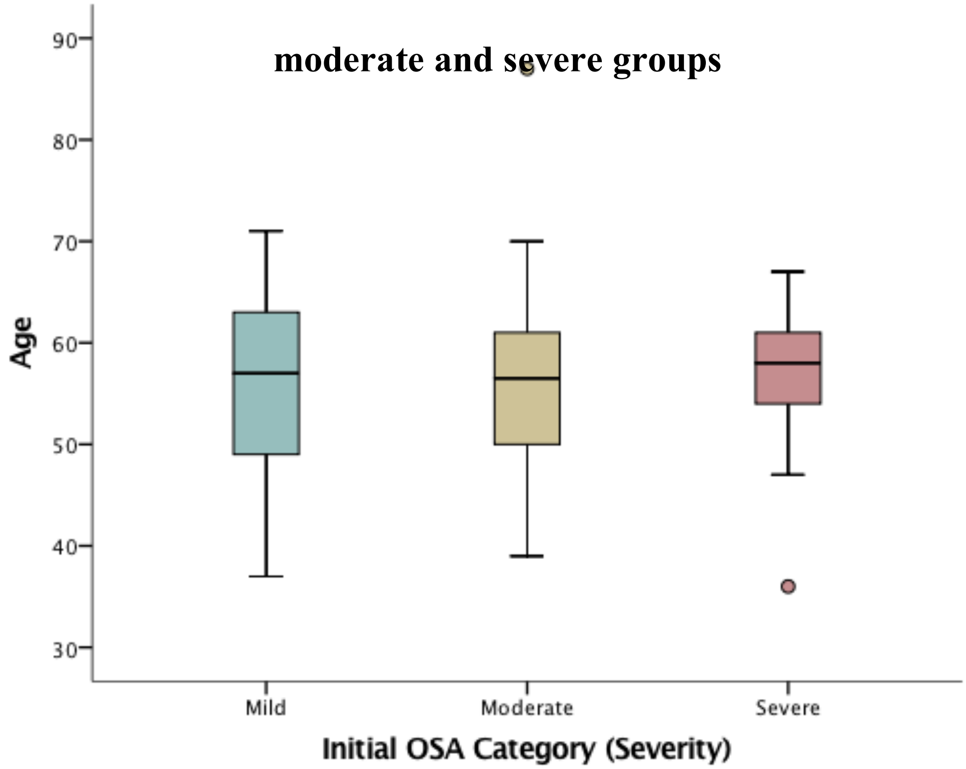


Figure 11: Distribution of age within mild, moderate and severe OSA cases P = 0.94, no significant differences in age between the groups.

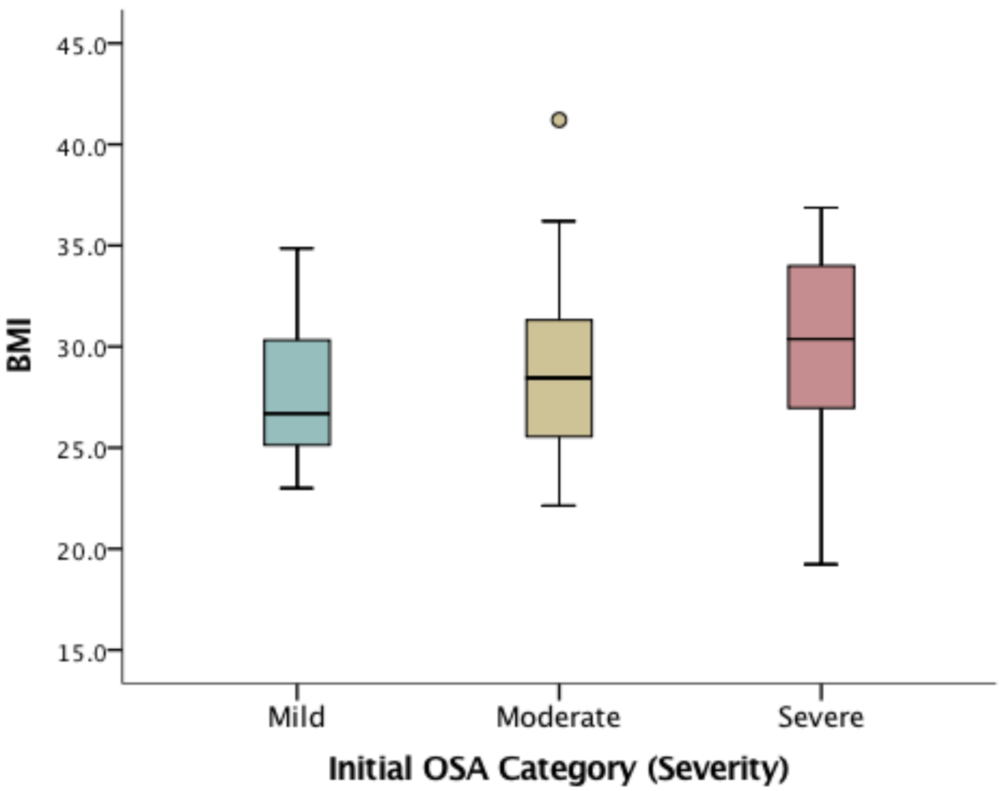


Figure 12: Distribution of BMI within mild, moderate and severe OSA cases P = 0.35, no significant differences in BMI between the groups.

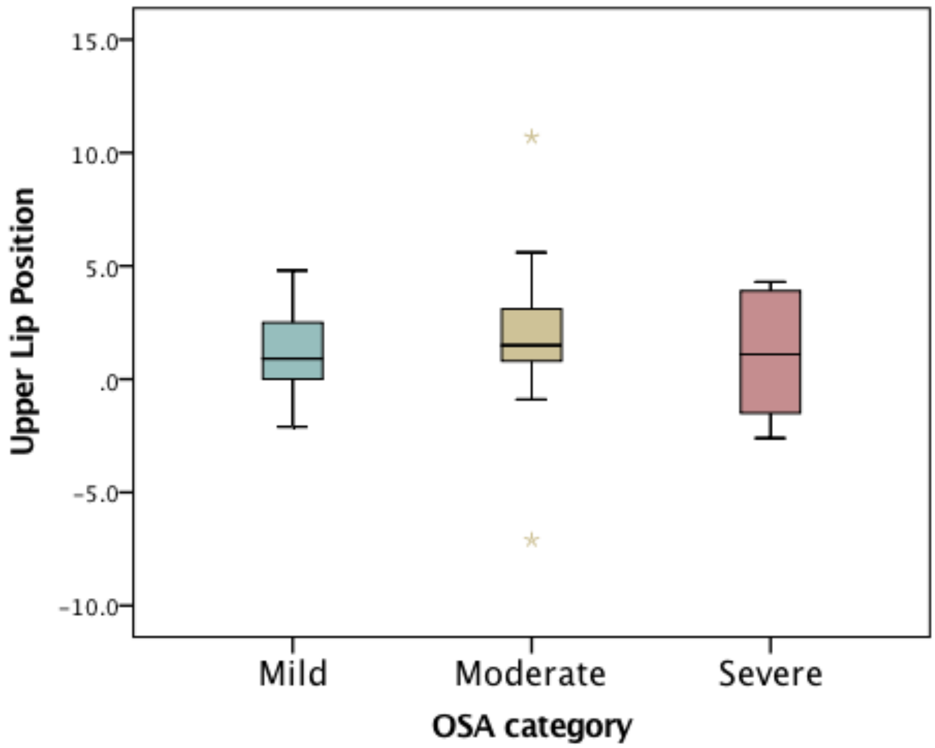


Figure 13: Distribution of Upper lip position within mild, moderate and severe OSA cases *P* = 0.51, no significant differences in UL-VL between the groups.

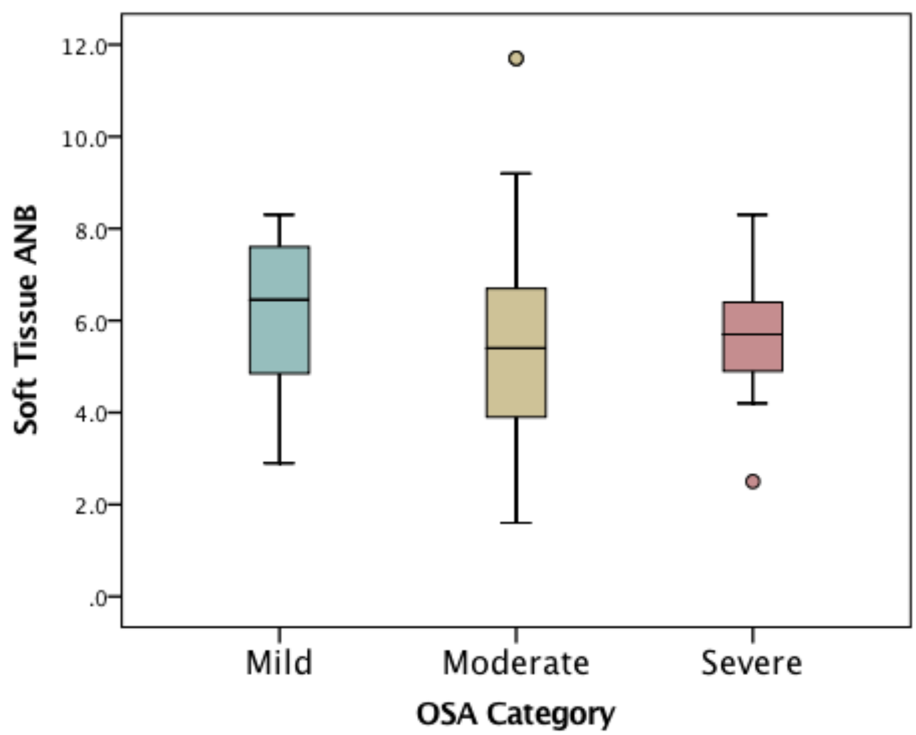


Figure 14: Distribution of soft tissue ANB within mild, moderate and severe OSA cases *P* = 0.67, no significant differences in S.T. ANB between the groups.

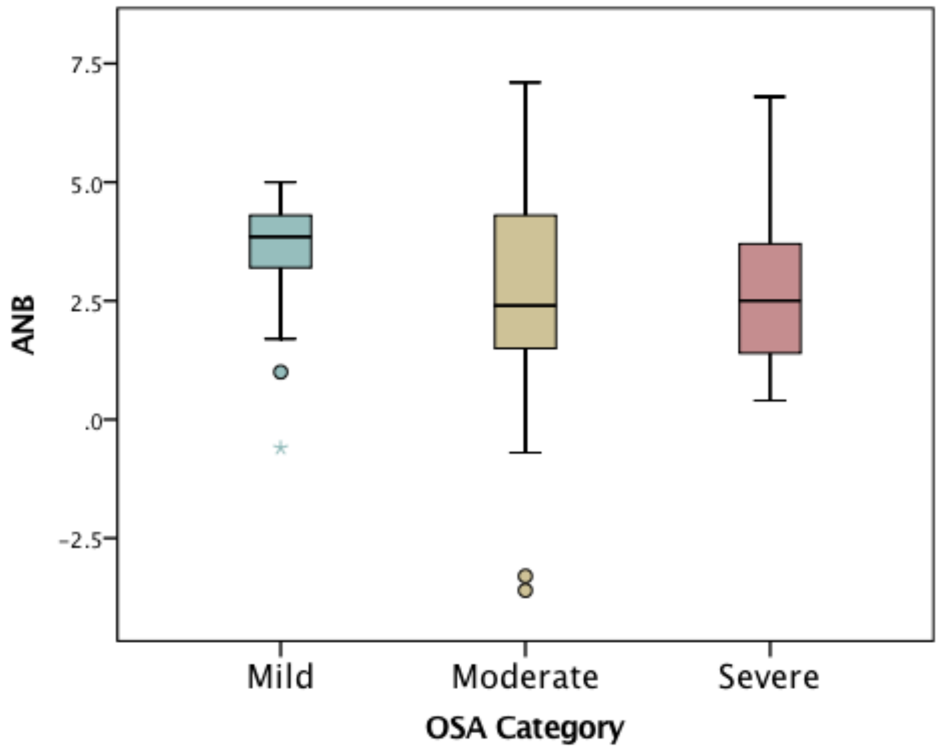


Figure 15: Distribution of skeletal ANB within mild, moderate and severe OSA cases P = 0.39, no significant differences in ANB between the groups.

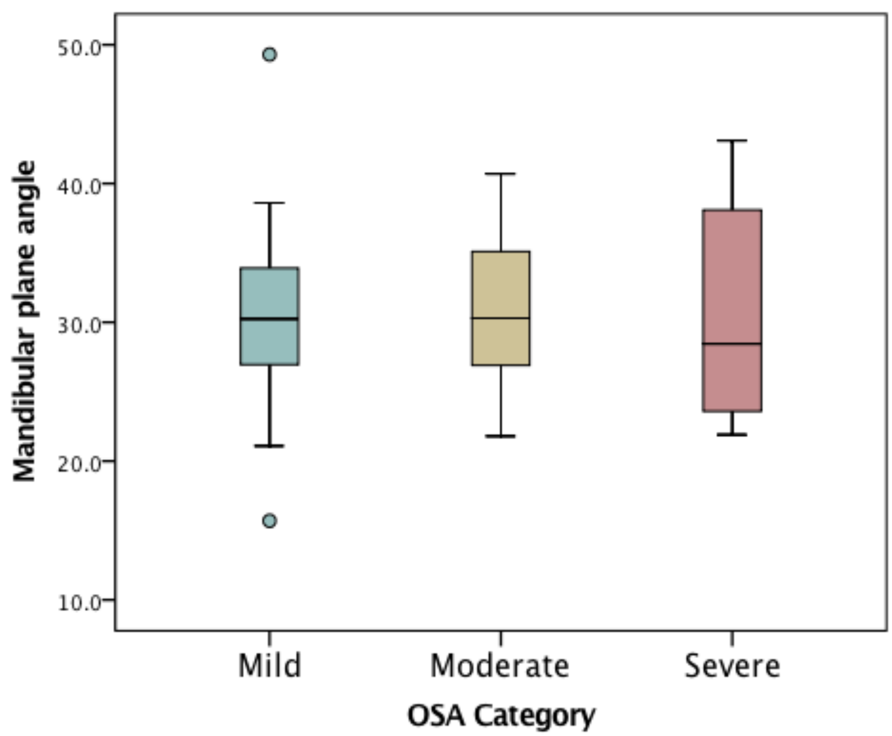


Figure 16: Distribution of mandibular plane angle within mild, moderate and severe OSA cases P = 0.99, no significant differences in MP between the groups.

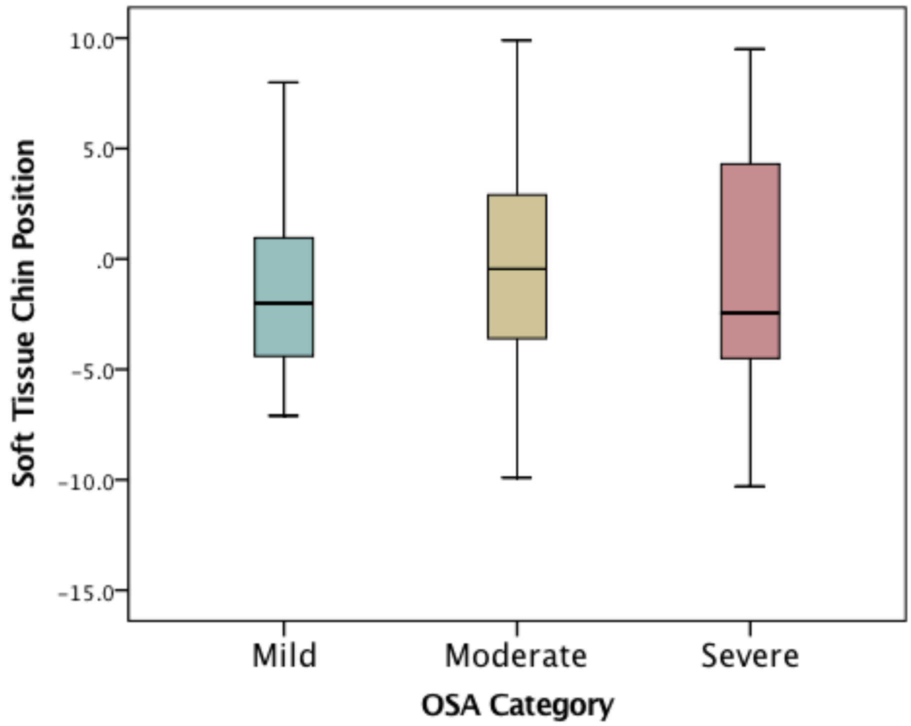


Figure 17: Distribution of soft tissue chin position within mild, moderate and severe OSA cases P = 0.66, no significant differences in C-VL between the groups.

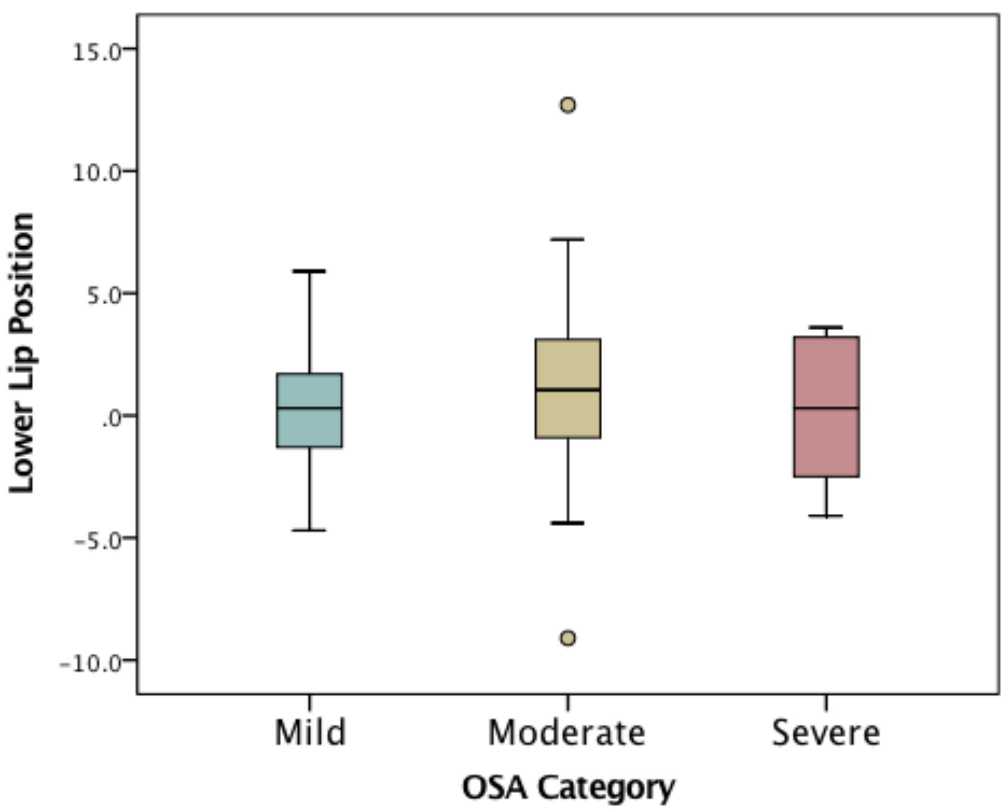


Figure 18: Distribution of upper lip position within mild, moderate and severe OSA cases P = 0.99, no significant differences in UL-VL between the groups.

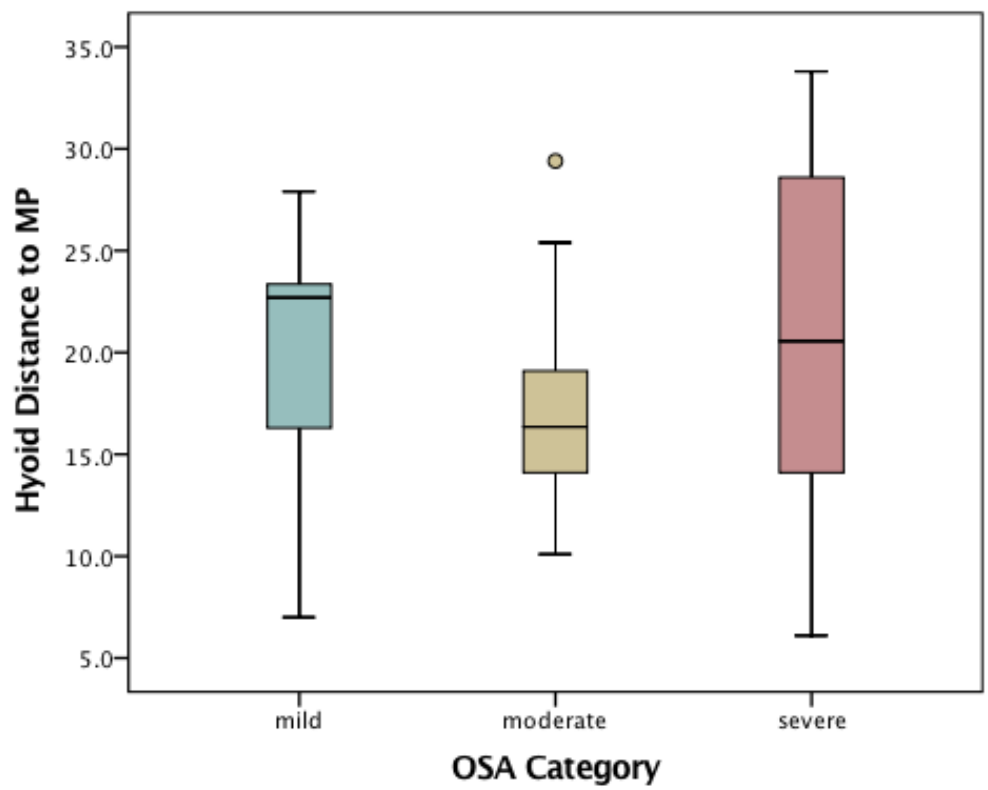


Figure 19: Distribution of hyoid bone distance to MP within mild, moderate and severe OSA cases $P = 0.11$, no significant differences in MP-H between the groups.