Online Supplement

Craniofacial Profile in Asians and Caucasians with Obstructive Sleep Apnea

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Statistical analysis

Framework for Statistical Analysis

Thorough preliminary data checks determined that the dataset of 239 patients was suitable for multivariate analyses (Tabachnick & Fidell, 2000). Spearman Rank Correlation was used to assess intra- and inter-observer reliability in the craniofacial measurements. SPSS Version 10.0.7 was used for all other analyses. Conservative significance levels were selected in all analyses to reduce error. The statistical strategy was to determine which dependent clinical and upper airway anthropometric variables could be broadly applied to predict which patients were likely to have obstructive sleep apnea (OSA). The dependent variables were age, body mass index (BMI), neck circumference (NC), Mallampati Score (MS), thyro-mental angle (TMA), thyro-mental distance (TD), Epworth Sleepiness Scale (ESS), and apnea-hypopnea index (AHI). Three sets of analyses were performed.

First we performed Hotelling's T^2 tests on three independent variables measuring subgroups of special interest – (i) OSA; (ii) gender; and (iii) ethnic group. The purpose of the Hotellings T^2 analyses was to examine the relationship between these three independent variables and the clinical dependent variables as a set without inflating error by the use of multiple t-tests.

Next, the sample of patients was divided into two groups of 120 and 119 patients, randomly selected from within groups of gender, ethnic status and OSA status to make two proportional groups. A discriminant function analysis was then applied to the first group of 120 patients to use the dependent set of variables as predictors of OSA and to thereby generate an equation for the prediction of OSA. Prior probabilities were based on actual group sizes to avoid spuriously increased specificity. A receiver operator characteristic curve (ROC) was also plotted to assess the utility of this prediction equation in terms of sensitivity and specificity and for comparison with other published prediction equations. The equation was then tested prospectively (cross-validation) in the other randomly selecting set of 119 patients to see how well the equation performed in a population other than that from which it was originally formulated.

Finally, an Analysis of Covariance (ANCOVA) was performed to effectively make all patients equivalent for BMI, NC and ethnic group, in order to determine whether the relationship between selected variables from the discriminant analysis was still significant when the patients were made equivalent on these three variables. In addition, several different cut-offs were used for the definition of OSA (AHI > 5, >10, >15, >30). Receiver operator characteristic curves were plotted to compare the accuracy of the predictive equations for the different cut-offs of OSA severity.

Hotelling's T^2 Analysis

Three T^2 analyses were conducted to determine the relationship between three independent variables, (i) OSA, (ii) ethnic group and (iii) gender, and the set of dependent clinical variables including age, weight, BMI, neck circumference, Mallampati score, thyro-mental angle, thyro-mental distance, ESS (Epworth Sleepiness Scale) and AHI (Table 1. in the manuscript). In the first analysis, OSA was found to be related significantly to the set of dependent variables, T^2 (9, 229) = 9.03, $p < 0.001$. Patients with OSA compared with Normals had larger Mallampati scores (mean=3.71 vs 3.37); greater thyro-mental angles (mean=161.12 vs 148.92°); and higher AHI (mean=31.68 vs 2.61/h). Caucasians and Asians differed significantly on the set of dependent variables, T^2 (9, 229)=20.67, $p <0.001$. Asians were lighter (mean=78.08 vs 92.18 kg) (data not included in the Table); had higher Mallampati scores (mean=3.85 vs 3.23); and shorter thyro-mental distances (mean=5.07 vs 5.62 cm) compared with Asians. In the analysis using gender as an independent variable, there was a significant relationship between gender and the set of dependent variables, T^2(9, 229)= 26.59, $p < 0.001$. Males had larger neck circumferences (mean=40.68 vs 36.27 cm) and higher AHI (mean=29.78 vs 13.56/h) compared with females.

Discriminant Function Analysis

The purpose of the discriminant analysis was (i) to see whether selected predictors from the Hotelling's T^2 analyses: age, BMI, NC, MP, TMA, and TMD, could be used to distinguish OSA patients from Normals; and (ii) to develop an equation whereby weights could be assigned to the predictor variables in order to be of use in predicting the presence of OSA in new patients. Discriminant analysis was selected in favor of logistic analysis because in conditions where the underlying variables such as age and BMI are normally distributed, discriminant analysis can be more powerful in detecting group differences; i.e. in this study, in predicting whether patients had OSA or not (Tabachnick & Fidell, 2000). The sample of 239 patients was divided into two groups of 120 and 119 patients based on random assignment to one group or the other in roughly equal proportions of OSA and Normals, males and females, Caucasians and Asians. Tests to ensure power was adequate to predict group membership with these group sizes were satisfactory (0.80). Variance-covariance matrices were examined prior to the analyses since, if they are not approximately even for each of the OSA and Normal groups, classification problems can occur where patients would be over-classified into the group with the biggest spread in variance. In this case, the variance-covariance matrices were proportional. Expected probabilities, also known as prior probabilities, were selected for the analysis to account for the difference between the Normal and OSA group sizes. With these important preliminary analyses and specifications accounted for, the main discriminant analysis was then performed. The main purpose in splitting the sample was to use the initial sample of 120 patients to see whether the selected predictors could be used to significantly distinguish OSA patients from Normals. The second reason was to see whether the prediction equation could be applied to the predictor variable set of the 119 patients and still retain the ability to distinguish between the OSA and Normal patients. OSA was defined as AHI ≥ 5. The results of the discriminant analysis indicated that the set of clinical predictors was able to discriminate well between Normal participants and those with OSA, $\chi^2(6) = 27.82$, $p<.05$; and 85.8% of patients were correctly classified. In order of importance (correlations with the discriminant function appear in brackets after each variable), the best predictors of OSA were MS(0.70), TMA (0.60), NC (0.54), BMI (0.53), age (0.53), and TMD (-0.13) (Table 2. in the manuscript). TMD was below the suggested cut-off of .30 (Tabachnick & Fidell, 2000) for inclusion as a significant predictor. Examination of the means for these variables demonstrated that (means for the group with OSA appear first in brackets after each variable and the means for the group without OSA appear after the colon) participants with OSA had a higher MS (M=3.71; M=3.37), a greater TMA (M=161.12; M=148.92), a larger NC (M=40.16; M=38.78), a higher BMI (M=29.42; M=27.29), and were of greater age (M=49.27; M=44.08) than Normals. When the equation derived from the initial sample of 120 patients (Table 3 in the manuscript) was applied to the predictor variable set from the sample of 119 patients, 82.4% of patients were correctly classified. In view of the positive results of the discriminant analysis, the data from 120 and 119 patients were again pooled for the final analysis of covariance (ANCOVA).

Analysis of Covariance (ANCOVA)

(i) Dependent Variables Grouped by Disease Classification and Ethnic Group with Effects of BMI and Neck Circumference Removed

An analysis of covariance (ANCOVA) of the 239 patients was conducted using age, MS, TMA and TMD as dependent variables, OSA and ethnic group as independent variables, and BMI and NC as covariates. The purpose of the ANCOVA was to examine the relationship between OSA and the four dependent variables while statistically removing prior differences in ethnic group, BMI and NC. The intent of removing the effects of BMI, NC and ethnic group was to increase the relationship between the four dependent variables and OSA by treating all scores for the sample of 239 patients as if they had the same ethnicity, BMI and NC. This procedure removes error from the ANCOVA due to the effects of ethnic group, BMI and NC so that one is left with a clearer picture of how well age, MS, TMA and TMD are related to OSA status. Additionally, by treating ethnic group as another independent variable rather than a covariate, this approach allows differences between ethnic groups to be examined separately after removal of the effects of prior differences in BMI and NC.

BMI was significantly related to the set of dependent variables, $F(4,230)=6.26$, $p<0.05$, as was NC, $F(4,230)=4.58$, $p<0.05$, and ethnic group, $F(4,230)=15.46$, $p<0.05$ These findings indicated that these three variables could be used to perform the desired function of rendering patients as if they had all scored equally on these variables. It is notable that there was no interaction between OSA and ethnic group. This indicated that the relationship between OSA and age, MP, TMA and TMD could be examined without regard to ethnic group; also investigation of ethnic group could proceed independently of OSA status.

OSA

The set of dependent variables was related significantly to OSA, $F(4, 230)=4.08$, $p<0.05$. Follow-up ANOVAs, with Bonferroni corrections to control the error rate, demonstrated that age, $F(1,233)=9.12$, p 0.<05, MS, $F(1,233)=7.59$, $p<0.05$, and TMA,

$F_{(1,233)}$=6.11, p<0.05, distinguished OSA patients from normals. These comparisons revealed that OSA patients compared with normals were older (M=49.27 vs 44.08), had larger TMA (M=161.17 vs 148.92), and had higher MS (M=3.71 vs 3.37).

Ethnic group

The significant relationship between ethnic group and the set of dependent variables was analysed to determine which of the dependent variables was related to ethnic group after adjustment for the effects of BMI and NC. ANOVAs, with Bonferroni corrections for the number of ANOVAs conducted, demonstrated that TMD, $F_{(1,233)}$=10.07, p<0.05, MS, $F_{(1,233)}$=57.05, p<0.05, and TMA, $F_{(1,233)}$=4.01, p<0.05, distinguished Caucasian and Asian groups. Ordering significant dependent variables by the magnitude of the F values indicates that the most important dependent variables separating ethnic groups were MS, TMD and TMA. These comparisons revealed that Asians compared with Caucasians had a higher MS (M=3.85 vs 3.23); larger TMA (M=160.51 vs 156.40); smaller TMD (M=5.07 vs 5.66).

(ii) Analysis of Age, Mallampati Score, Thyromental Angle, and Thyromental Distance for Different Cutoff Values of AHI.

Three ANCOVAs using different cutoffs of AHI to define OSA versus Normal were conducted to determine if there were similar effects of the dependent variables of age, MS, TMA and TMD (Table 4. in the manuscript).

AHI $\geq$ 10

In this ANCOVA, 168 had OSA patients while 71were Normal. The set of dependent variables was related significantly to OSA, F (4,232)=3.96, $p < 0.05$. Follow-up ANOVAs demonstrated that age, F (1,236)=5.52, $p < 0.05$), MS, F (1,236)=7.97, $p < 0.05$ and TMA, F(1,236)=9.52, p <.05, distinguished between OSA patients and Normals. The post hoc comparisons revealed that OSA patients compared with Normals were older (M=49.63 vs 45.64); had higher MS (M=3.73 vs 3.49); and larger TMA (M=161.45 vs 53.94).

AHI $\geq$ 15

In this ANCOVA, 143 patients had OSA and 96 were Normal. The set of dependent variables was significantly related to OSA, F(4, 232)=5.34, $p < 0.05$. Follow-up ANOVAs demonstrated that age F(1,236)=6.33, $p < 0.05$, MS, F(1,236)=17.12, p<.05 and TMA, F(1,236)=5.27, p<.05, distinguished between OSA patients and Normals. The follow-up comparisons revealed that patients with OSA compared with normals were older (M=50.04 vs 46.07); had higher MS (M=3.79 vs 3.46); and had larger TMA (M=161.33 vs 156.08).

AHI $\geq$ 30

In this ANCOVA, 88 patients had OSA and 151 were Normal. The set of dependent variables was significantly related to OSA, F(4, 232)=5.50, $p < 0.05$. Follow-up ANOVAs demonstrated that age, F(1,236)=5.09, $p < 0.05$, MS, F(1,236)=11.33, $p < 0.05$ and TMA, F(1,236)=4.13, $p < 0.05$, distinguished between OSA patients and Normals. The post hoc comparisons revealed that patients with OSA compared with Normals were older (M=50.75 vs 47.10); had higher MS (M=3.84 vs 3.55); and had larger TMA (M=163.88 vs 156.60).

References

Tabachnick BS, Fidell LS. Using multivariate statistics.(4th Edition) Boston: Allyn & Bacon 2001.