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WILEY
Predicting Obstructive Sleep Apnea Status With the Reflux Symptom Index in a Sleep Study Population

Meron Teklu, BA; Christopher J. Gouveia, MD; Amulya Yalamanchili, BS; Saied Ghadersohi, MD; Caroline P. E. Price, BA; Michiel Bove, MD; Hrayr P Attarian, MD; Bruce K. Tan, MD, MS

Objectives/Hypothesis: Otolaryngologic symptoms of obstructive sleep apnea (OSA) and their diagnostic utility are not well studied. We aimed to elucidate the prevalence of otolaryngologic symptoms among patients being evaluated for OSA. Given findings that the Reflux Symptom Index (RSI) was strongly associated with OSA status, we evaluated the diagnostic utility of the RSI for predicting OSA status.

Study Design: Cross-sectional.

Methods: We recruited 101 adults presenting for ambulatory polysomnograms to the Northwestern Sleep Disorders Center from July 2017 to July 2018. The Epworth Sleepiness Scale, Pittsburgh Sleep Quality Index, Leicester Cough Questionnaire (LCQ), RSI, Gastroesophageal Reflux Disease Questionnaire, Sino-Nasal Outcome Test-22, Nasal Obstruction Symptom Evaluation, Eustachian Tube Dysfunction Questionnaire 7, and Headache Impact Test were administered. Polysomnogram results were subsequently obtained. Patients with OSA (apnea-hypopnea index ≥ 5) and without OSA were compared.

Results: Of the 101 participants, 98 had valid sleep study results. Of those, 72 were diagnosed with OSA and 26 were not. The two groups differed significantly in age and body mass index (BMI). Of the questionnaires, only the RSI and LCQ means differed significantly, with worse symptoms in the OSA group (P = .003 and .014, respectively). Upon univariate regression, age, BMI, and RSI were associated with OSA status. Using regression coefficients, a clinical score of 2 (RSI) + 1.5 (BMI) + age yielded a diagnostic model (C-statistic = 0.807, P < .001). A threshold score of 104.21 was 76.4% sensitive and 73.1% specific.

Conclusions: Patients with OSA have worse symptoms of laryngopharyngeal reflux as measured by the RSI. The addition of the RSI to the recognized factors of age and BMI improves diagnostic utility for OSA.

Key Words: Obstructive sleep apnea, sleep apnea, reflux.

Level of Evidence: 2

INTRODUCTION

The prevalence of obstructive sleep apnea (OSA) has been estimated to be at least 2% to 4% in the adult population and is thought to affect approximately 9% of women and 24% of men in the United States.1,2 OSA is associated with comorbidities such as cardiovascular disease, insulin resistance, stroke, gastroesophageal reflux disease, and asthma.3–5 Given that symptoms of OSA include those associated with upper airway obstruction and management strategies can include otolaryngologic therapies, OSA is an important condition in the field of otolaryngology.6–9 Even with the high prevalence of OSA, it is estimated that in some populations 82% to 93% of those with clinically significant OSA remain undiagnosed.10,11 Treatment of OSA has been shown to improve both symptoms and comorbidities as well as quality of life.12–16 Thus, it is imperative for healthcare professionals to be able to accurately predict OSA status so as to refer patients for further evaluation and treatment.

The American Academy of Sleep Medicine recommends that a focused history and physical be performed to stratify patients based on risk of OSA before performing a sleep study for definitive results.1 The initial clinical evaluation for OSA using brief screening questionnaires can be important given the costs and time commitment required for a polysomnogram sleep study or portable monitoring.17–19 Currently, initial clinical evaluation of OSA often includes validated and widely used questionnaires such as the Epworth Sleepiness Scale (ESS), the Berlin questionnaire (BQ), and the STOP-BANG questionnaire1,20,21 despite prior findings that ESS and BQ have poor predictive value for OSA status.22–25 It has been estimated from various studies that the sensitivity of ESS, BQ and STOP-BANG are 0.54, 0.76, and 0.84, and the specificity 0.65, 0.59, and 0.56, respectively, when determining OSA status based on apnea-hypopnea index (AHI) ≥ 5 per hour.26,27 In addition, BQ and STOP-BANG include symptoms that need to be observed by an additional person, making them more difficult to administer than measures that rely purely on patient-reported symptoms. There is
ongoing need for assessment tools that are both easy to use in the clinical setting and able to predict OSA status reliably.

There are previous studies that have investigated associations between laryngopharyngeal reflux (LPR) or chronic cough and OSA, but until a recent study by our group, there had been no prospective analysis of this association. In our previous study, we analyzed data from the initial 52 patients of the cohort we currently report on and found that chronic cough, as measured by the Leicester Cough Questionnaire (LCQ), and LPR symptoms, as measured by the Reflux Symptom Index (RSI), were significantly more common among patients with OSA. In this study, we expanded the sample size to assess the stability of our conclusions and use this better-powered sample to evaluate the value of the prepolysomnogram RSI in predicting OSA status.

MATERIALS AND METHODS

One hundred one patients were prospectively recruited from the Northwestern Sleep Disorders Center in a tertiary medical center setting between July 2017 and July 2018. Patients 18 years and older presenting to a sleep clinic for a portable at home sleep test were included. Portable at home sleep tests were ordered by physicians throughout the medical center and are not limited to patients from any specific specialty. Those who had a previous diagnosis of OSA, other sleep disorders, and LPR disease were excluded. The Northwestern University Institutional Review Board reviewed this protocol and approved this study.

The ESS, Pittsburgh Sleep Quality Index (PSQI), LCQ, RSI, gastroesophageal reflux disease questionnaire (GerdQ), Sino-Nasal Outcome Test-22 (SNOT-22), Nasal Obstruction Symptom Evaluation (NOSE), Eustachian Tube Dysfunction Questionnaire 7 (ETDQ-7), and Headache Impact Test 6 (HIT-6) were administered to participants prior to their sleep study. The LCQ is a 19-item questionnaire validated for the assessment of the health-related quality of life of chronic cough. Each question is scored on a scale of 1 to 7, with an overall score range of 19–133, with higher scores indicating less severity. The RSI is a validated nine-item measure that assesses LPR symptom severity. Each question is scored on a scale of 0 to 5, with higher scores indicating increased severity. The ESS is an eight-item questionnaire that measures levels of daytime sleepiness. Each measure is scaled from 0 to 3, with higher scores indicating increased daytime sleepiness. The PSQI is a 19-item questionnaire that measures sleep quality over the past month. Scores range from 0 to 21, with higher scores indicating greater severity. The NOSE is a five-item patient-reported validated measure of nasal obstruction symptoms and related quality of life. Scores range from 0 to 20, with a higher score indicating more severe obstruction symptoms. The SNOT-22 is a 22-item questionnaire assessing symptoms of chronic rhinosinusitis, with scores ranging from 0 to 110. The ETDQ-7 is a validated seven-item eustachian tube dysfunction–specific questionnaire with scores ranging from 1 to 7 and higher scores indicating worse symptoms. The GerdQ is a six-item questionnaire that assesses symptoms of gastroesophageal reflux disease (GERD) on a scale of 0 to 18, with higher scores indicating more severe symptoms. The GerdQ was administered to only 45 of the 101 participants. The HIT-6 is as assessment tool that measures the impact of headaches on functional status and wellbeing. Scores range from 36 to 78, with higher scores indicating more severe headaches.

OSA status was retrieved from the home sleep study results, with an AHl ≥ 5 per hour used as the cutoff for the diagnosis of OSA based on the American Academy of Sleep Medicine criteria. Demographic information was collected from patients’ medical records. Portable polysomnogram results were interpreted by board-certified members of the Division of Sleep Medicine.

Statistical analysis

All statistical analysis was completed with SPSS Statistics 25 (IBM, Armonk, NY). A Shapiro-Wilk test of normality was performed on all measures. Age, AHl, ESS, RSI, SNOT-22, and HIT-6 were normally distributed (P > .05), whereas sex, body mass index (BMI), PSQI, NOSE, ETDQ-7, LCQ, and GerdQ were not normally distributed. Thus, all data were analyzed using nonparametric methods. Patient characteristics were compared using Mann-Whitney U test analysis. Mann-Whitney U tests were performed to assess differences between OSA and non-OSA groups. Logistic regressions were run against OSA status to assess significant predictors and build models for receiver operating characteristic (ROC) curves. All statistical significance is based on a P value < .05.

RESULTS

Of the 101 participants enrolled in the study, 98 had valid sleep study results. Of those, 72 were diagnosed with OSA and 26 were not. There was no difference in sex between the OSA and non-OSA groups (P = .777), but the two groups did differ significantly in age (P = .015), BMI (P = .023), and AHl (P < .014) (Table I). Of the administered questionnaires, only the RSI and LCQ mean scores differed significantly between the OSA and non-OSA groups (P = .003 and .014, respectively), confirming our previously reported findings on a smaller cohort (Table I).

Given that the LCQ had 22 questions, it was excluded from logistic regression due to a relatively small sample size for regression against 22 individual items. To evaluate whether the entire RSI instrument or specific questions on the RSI were associated with OSA status, individual RSI questions and the RSI total score were regressed against OSA status adjusting for age and BMI. Only “difficulty clearing your throat” on the RSI was a significant predictor upon stepwise regression (P = .009) without the RSI total. However, when the total RSI score was added to this stepwise regression, only the total RSI was a significant predictor (P = .008). When age, sex, and RSI total score were regressed together, the RSI total score, BMI (P = .033), and age (P = .024) were each significant predictors. The overall regression model with total RSI score, BMI, and age was highly significantly (P < .001) predictive of OSA status. The model explained 31.0% (Nagelkerke R²) of the variance in OSA status and correctly classified 76.5% of cases. The odds ratio was 1.14 for total RSI score, 1.09 for BMI, and 1.06 for age with 95% confidence interval (CI): 1.04-1.24, 1.01-1.17, 1.02-1.11, respectively.

Based on the findings from the logistic regressions, three models (termed model 1.1, 1.2, and 1.3) were created that assigned different weights to total RSI score, BMI, and age. Model 1.1 multiplied each variable by one. Model 1.2 multiplied each variable with its associated Exp (B). Model 1.3 considers the increase in the odds ratio contributed by each variable (RSI total score 0.14, BMI 0.09, and age 0.06). Given that these increases come
TABLE I.
Study Population Characteristics and Mean Comparison of OSA and Non-OSA Groups.

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>OSA</th>
<th>No OSA</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size, n (%)</td>
<td>101</td>
<td>72 (71.3%)</td>
<td>26 (25.7%)</td>
<td>.777</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>60 (59.4%)</td>
<td>42 (58.3%)</td>
<td>16 (61.5%)</td>
<td>.015</td>
</tr>
<tr>
<td>Female</td>
<td>41 (40.6%)</td>
<td>30 (41.7%)</td>
<td>10 (38.5%)</td>
<td>.023</td>
</tr>
<tr>
<td>Age, yr, mean ± SD</td>
<td>46.6 ± 13.2</td>
<td>48.2 ± 12.9</td>
<td>41.3 ± 12.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI, mean ± SD</td>
<td>32.4 ± 7.6</td>
<td>33.5 ± 7.8</td>
<td>29.7 ± 6.6</td>
<td>.003</td>
</tr>
<tr>
<td>AHI, mean ± SD</td>
<td>16.7 ± 17.1</td>
<td>22.1 ± 17.0</td>
<td>1.8 ± 1.6</td>
<td>.014</td>
</tr>
<tr>
<td>PSQI</td>
<td>8.5 ± 4.6</td>
<td>8.3 ± 4.7</td>
<td>9.0 ± 4.6</td>
<td>.094</td>
</tr>
<tr>
<td>ESS</td>
<td>7.4 ± 4.4</td>
<td>7.6 ± 4.5</td>
<td>7.3 ± 4.3</td>
<td>.916</td>
</tr>
<tr>
<td>RSI</td>
<td>9.2 ± 8.9</td>
<td>10.5 ± 9.3</td>
<td>4.9 ± 5.4</td>
<td>.003</td>
</tr>
<tr>
<td>LCQ</td>
<td>121.5 ± 16.2</td>
<td>119.3 ± 17.7</td>
<td>128.2 ± 16.7</td>
<td>.014</td>
</tr>
<tr>
<td>GerdQ</td>
<td>3.3 ± 4.2</td>
<td>3.4 ± 4.2</td>
<td>3.0 ± 4.2</td>
<td>.514</td>
</tr>
<tr>
<td>SNOUT-22</td>
<td>27.3 ± 18.2</td>
<td>28.2 ± 18.6</td>
<td>26.3 ± 17.9</td>
<td>.687</td>
</tr>
<tr>
<td>NOSE</td>
<td>32.5 ± 25.2</td>
<td>33.4 ± 25.8</td>
<td>30.2 ± 23.3</td>
<td>.660</td>
</tr>
<tr>
<td>ETDQ-7</td>
<td>1.8 ± 1.7</td>
<td>1.9 ± 1.1</td>
<td>1.8 ± 1.4</td>
<td>.370</td>
</tr>
<tr>
<td>HIT-6</td>
<td>48.5 ± 10.6</td>
<td>47.8 ± 9.7</td>
<td>48.7 ± 12.3</td>
<td>.682</td>
</tr>
</tbody>
</table>

Bold value indicates significance of results.

AHI = apnea-hypopnea index; BMI = body mass index; ESS = Epworth Sleepiness Scale; ETDQ-7 = Eustachian Tube Dysfunction Questionnaire 7; GerdQ = Gastroesophageal Reflux Disease Questionnaire; HIT-6 = Headache Impact Test 6; LCQ = Leicester Cough Questionnaire; NOSE = Nasal Obstruction Symptom Evaluation; OSA = obstructive sleep apnea; PSQI = Pittsburgh Sleep Quality Index; RSI = Reflux Symptom Index; SD = standard deviation; SNOT-22 = 22-item Sino-Nasal Outcome Test.

TABLE II.
Description of Models.

<table>
<thead>
<tr>
<th>Model</th>
<th>AUC</th>
<th>SE</th>
<th>Asymptomatic Significance</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI only</td>
<td>0.651</td>
<td>0.065</td>
<td>.023</td>
<td>0.523-0.778</td>
</tr>
<tr>
<td>BMI + age only</td>
<td>0.717</td>
<td>0.061</td>
<td>.001</td>
<td>0.598-0.836</td>
</tr>
<tr>
<td>RSI score only</td>
<td>0.699</td>
<td>0.058</td>
<td>.003</td>
<td>0.585-0.812</td>
</tr>
<tr>
<td>Model 1.1</td>
<td>0.798</td>
<td>0.051</td>
<td>&lt;.001</td>
<td>0.699-0.898</td>
</tr>
<tr>
<td>Model 1.2</td>
<td>0.800</td>
<td>0.051</td>
<td>&lt;.001</td>
<td>0.701-0.900</td>
</tr>
<tr>
<td>Model 1.3</td>
<td>0.807</td>
<td>0.048</td>
<td>&lt;.001</td>
<td>0.712-0.901</td>
</tr>
<tr>
<td>ESS score only</td>
<td>0.507</td>
<td>0.066</td>
<td>.917</td>
<td>0.377-0.637</td>
</tr>
</tbody>
</table>

Model 1.1, 1RSI + 1BMI + 1age; model 1.2, 1.138RSI + 1.088BMI + 1.061age; model 1.3, 2RSI + 1.5BMI + 1age.

AUC = area under the curve; BMI = body mass index; ESS = Epworth Sleepiness Scale; RSI = Reflux Symptom Index; SE = standard error.

Fig. 1. Receiver operating characteristic curves predicting obstructive sleep apnea status. BMI = body mass index; ESS = Epworth Sleepiness Scale.
out to an approximate relationship of 2:1.5:1 for RSI:BMI:age respectively, model 1.3 is adjusted with the multipliers of 2 for RSI total, 1.5 for BMI, and 1 for age. The areas under the curves were 0.798, 0.800, and 0.807 for models 1.1, 1.2, and 1.3, respectively. For reference, we calculated the area under the curve of BMI, BMI + age, RSI total, and ESS. In comparison, model 1.3 had the largest area under the curve (Table II and Fig. 1). Thus, a clinical score of $2(RSI) + 1.5(BMI) + age$ yielded a diagnostic model ($C$-statistic = 0.807, $P < .001$, 95% CI: 0.712–0.901). A threshold score of 104.21 was 76.4% sensitive and 73.1% specific for the diagnosis of OSA by an AHI $\geq 5$ per hour criteria.

**DISCUSSION**

This study assessed the presence of otorhinolaryngologic symptoms in a sleep study cohort and evaluated differences between those who were diagnosed with OSA and those who were not, using the PSQI, ESS, RSI, LCQ, GerdQ, SNOT-22, NOSE, ETDQ-7, and HIT-6. OSA and non-OSA groups differed significantly in age and BMI. However, of the symptom questionnaires, only the RSI and LCQ were significantly different between the two groups. Given that the RSI was strongly associated with OSA status, we further evaluated the diagnostic utility of the RSI for predicting OSA status, and found that a clinical score of $2(RSI) + 1.5(BMI) + age$ yielded a worthwhile diagnostic model that with a threshold score of 104.21 was 76.4% sensitive and 73.1% specific.

Several prior studies with small sample sizes or retrospective design have shown a high prevalence of LPR and sensitive and 73.1% specific effect size does appear smaller. It is also worth noting that the RSI has a greater focus on upper airway symptoms such as “difficulty clearing your throat,” and thus may be more mechanistically related to OSA than symptoms present in the GerdQ, which pertains more to esophageal concerns. In a similar vein, it is interesting to note the other symptomatic measures that did not differ between the two groups. For example, there appears to be no difference in sinonasal symptoms as measured by the SNOT-22 and NOSE between the two groups. There is some body of work that shows that nasal obstruction and chronic rhinosinusitis are associated with poor sleep quality and OSA, but to our knowledge, our study appears to be unique in examining this link in a prospective and well-controlled manner in a population not limited to those with chronic rhinosinusitis. Nevertheless, the treatment of nasal obstruction and sinusitis remain important in the management of OSA, as improvement in chronic rhinosinusitis in patients suffering from coexisting OSA has been shown to significantly improve quality of life and sleepiness. In addition, relieving nasal obstruction can significantly reduce the pressure of continuous positive airway pressure devices and increase compliance.

One of the more commonly inquired about symptoms of headache also does not appear to be different between these two groups. The association of headaches and OSA is quite controversial. Although headaches are clinically an important component of the evaluation for OSA, there are several bodies of work that indicate that the relationship between the two remains unclear, with some postulating whether the relationship exists at all. We believe our study’s findings that headache symptoms as measured by the HIT-6 are not significantly different between the OSA and control group add to the conversation about the true role headaches play in OSA. What we believe these findings on nasal obstruction, rhinosinusitis, and headache impact highlight is that although certain symptoms may be OSA- or upper airway–related, it may uniquely be the symptoms of cough and LPR that play a significantly different and predictive role for OSA.

Symptom evaluation and management strategies for OSA are an important part of the practice of otorhinolaryngology, and it is imperative for physicians to more accurately predict OSA status in a clinical setting to better assess which patients need sleep studies or further management. In addition, given the time and monetary costs associated with polysomnogram testing, it can be quite useful to better screen for patients in need of further evaluation. The ESS, BQ, and STOP-BANG are widely utilized questionnaires for the initial assessment of OSA. However, these tools have been shown to have poor sensitivities and/or specificities. We found that a clinical score accounting for RSI score, BMI, and age was able to predict OSA status with approximately 76% sensitivity and 73% specificity at a reasonable cutoff score. The RSI is a simple nine-item questionnaire containing information that is easy to elicit from the patient, whereas age and BMI are routinely updated in medical records. This makes our clinical score easy to administer while allowing for good diagnostic utility.

It has been widely reported that untreated sleep apnea can be costly, devastating to medical health, and worsen quality of life. Some have reported that untreated sleep apnea can have an impact up to $3.4
billion per year in additional medical costs.\textsuperscript{56} This, in addition to the large estimates for those who remain undiagnosed, makes finding reliable tools for OSA screening of paramount importance. Although overnight polysomnography (PSG) testing remains the gold standard for diagnosis, home sleep studies have been shown to be equally effective diagnostically amongst those with relatively high pretest probability while proving to be more cost-effective.\textsuperscript{57} One analysis found that the addition of a clinical questionnaire prior to PSG testing can be cost saving, and from this, one can postulate that the more accurate the clinical evaluation, the more cost that can be saved. Although cost varies by state and insurance coverage, even the more affordable home sleep testing can cost hundreds of dollars.\textsuperscript{58} We believe that our clinical score offers a sensitivity and/or specificity that are superior to the currently popular screening tools for OSA, especially in the otolaryngology setting. Our score, combined with clinical acumen, can help identify those most in need of sleep testing.

Given that our study population is a sleep study cohort, a limitation is that most of our patients already have some clinical suspicion for OSA. Whether this study population would be relevant to the population of patients being evaluated in otolaryngology offices for whom the chief complaint may be RSI component symptoms (e.g., throat pain) would require further investigation. In addition, the question of whether symptoms of chronic cough and LPR diminish with adequate treatment of OSA in our population is yet to be answered.

CONCLUSION

Patients with OSA have significantly worse symptoms of LPR as measured by the RSI and chronic cough as measured by the LCQ. The addition of the RSI to the recognized predictive factors of age and BMI improves diagnostic utility for evaluating OSA status.

BIBLIOGRAPHY


