Development, Validation, and Assessment of an Ischemic Stroke or Transient Ischemic Attack-Specific Prediction Tool for Obstructive Sleep Apnea

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Abstract

Background—Screening instruments for obstructive sleep apnea (OSA), as used routinely to guide clinicians regarding patient referral for polysomnography (PSG), rely heavily on symptomatology. We sought to develop and validate a cerebrovascular disease-specific OSA prediction model less reliant on symptomatology, and to compare its performance with commonly used screening instruments within a population with ischemic stroke or transient ischemic attack (TIA).

Methods—Using data on demographic factors, anthropometric measurements, medical history, stroke severity, sleep questionnaires, and PSG from 2 independently derived, multisite,

randomized trials that enrolled patients with stroke or TIA, we developed and validated a model to predict the presence of OSA (i.e., Apnea-Hypopnea Index 5 events per hour). Model performance was compared with that of the Berlin Questionnaire, Epworth Sleepiness Scale (ESS), the Snoring, Tiredness, Observed apnea, high blood Pressure, Body mass index, Age, Neck circumference, and Gender instrument, and the Sleep Apnea Clinical Score.

Results—The new SLEEP Inventory (Sex, Left heart failure, ESS, Enlarged neck, weight [in Pounds], Insulin resistance/ diabetes, and National Institutes of Health Stroke Scale) performed modestly better than other instruments in identifying patients with OSA, showing reasonable discrimination in the development (c-statistic .732) and validation (c-statistic .731) study populations, and having the highest negative predictive value of all in struments.

Conclusions—Clinicians should be aware of these limitations in OSA screening instruments when making decisions about referral for PSG. The high negative predictive value of the SLEEP INventory may be useful in determining and prioritizing patients with stroke or TIA least in need of overnight PSG.

Keywords

Introduction

Obstructive sleep apnea (OSA) occurs commonly in the post-ischemic stroke or transient ischemic attack (TIA) population, affecting 60%–80% of persons after their cerebrovascular event.[1,2] Untreated OSA is an independent risk factor for future vascular events (e.g., stroke, myocardial infarction), may complicate management of vascular risk factors (e.g., hypertension, atrial fibrillation), and increases the risk for mortality in patients with cerebrovascular disease.[3–6] Despite the potential treatment and prognostic implications of discovering whether patients with cerebrovascular disease have comorbid OSA, the condition frequently goes undiagnosed.[5,7] This situation may be due, in part, to the observation that hallmark features of OSA (e.g., excessive daytime sleepiness) can occur less commonly among patients with cerebrovascular disease than in the general population.[5] Several well-validated sleep instruments used in the general population to screen for OSA and perceived somnolence, such as the Berlin Questionnaire (BQ)[8] and Epworth Sleepiness Scale (ESS) score,[6] rely heavily on symptomatic features of OSA, but have not been predictive of OSA (as defined by an Apnea-Hypopnea Index [AHI] 5 on polysomnography [PSG]) in mixed stroke populations (ischemic and hemorrhagic).[5,7] A modified version of the Snoring, Tiredness, Observed Apnea, high blood Pressure-Body mass index, Age, Neck circumference, and Gender (STOP-BANG) was only moderately predictive of OSA compared with home sleep testing equipment among patients with a cerebrovascular event, [9,10] whereas the Sleep Apnea Clinical Score (SACS) has not been studied among patients with cerebrovascular disease. Given the suboptimal performance of commonly used OSA screening instruments within the stroke or TIA population, authors have suggested that the development of models based on medical comorbidity should be pursued.[10]

The most recent American Heart Association/American Stroke Association ischemic stroke or TIA prevention guidelines provide new recommendations addressing OSA, noting that PSG might be considered for patients with an ischemic stroke or TIA and, that once diagnosed, treatment of OSA might be considered, given its association with improved post-cerebrovascular event outcomes.[2] The guidelines do not, however, specify which patients should be considered for PSG referral. Because universal OSA screening with PSG may not be feasible based on the worldwide prevalence of stroke, we sought to (1) develop and validate a cerebrovascular disease-specific instrument that would be less reliant on patient symptomatology and anthropometric features, and; (2) determine how well the new instrument, and the BQ, ESS, SACS, and STOP-BANG, predicted the presence and absence of OSA in an exclusively post-ischemic stroke or TIA population (rather than a mixed ischemic and hemorrhagic stroke population). These analyses could then help identify which patients are most (i.e., high positive predictive value [PPV]) or least (i.e., high negative predictive value [NPV]) in need of PSG referral.

Methods

Overview

Participants in 2 separate, multisite, 1-year randomized controlled trials examining the utility of unattended PSG to identify and treat OSA in the post-ischemic stroke or TIA populations with continuous positive airway pressure (CPAP) were used as the study population; the methods of each trial are described elsewhere.[11,12] A clinical prediction model was developed and validated. Results across different OSA prediction instruments were compared.

Patient Populations

From 1 study,[11] Veterans with an ischemic stroke within either 30 days of recruitment or any time after developing a TIA were included as the development cohort, whereas patients (non-Veterans and Veterans) from the second study who had an ischemic stroke or TIA within 1 week of enrollment were included as the validation cohort.[12] Patients enrolled into the study used as the development set had either a history of hypertension or a blood pressure 140/90 mm Hg. Both studies used the same exclusion criteria: known history of OSA, suspected sleep disorder other than OSA (e.g., narcolepsy, given that such patients have another indication for formal PSG), life expectancy less than 6 months, inability to use either a nasal or a face mask (as continuous positive airway pressure could not be administered), non–English-speaking patients, and inability to provide informed consent. Patients were not excluded based on stroke severity, or if they had language impairments secondary to their event. The BQ, ESS, STOP-BANG, SACS, and National Institutes of Health Stroke Scale (NIHSS) scores were calculated for patients after their cerebrovascular event.

Definitions

Type 2, full unattended PSG was performed using Safiro Compumedics in both studies. Apnea was defined as airflow cessation lasting 10 seconds; hypopnea was defined as reduction in airflow for 10 seconds or decrease in amplitude of breathing by 30%,

followed by oxygen desaturation 3% or arousal from sleep.[13] Obstructive events were defined as those accompanied by thoracic or abdominal wall movements; central events had no associated wall movements. An AHI was calculated from the number of apneas and hypopnea per hour; an AHI 5 events per hour was used to identify patients with sleep apnea.[13,14] Excessive daytime sleepiness was defined as an ESS 10. "High risk" for OSA was defined as scoring positive on 2 or more categories, a SACS 15, and by a score 5 on the STOP-BANG questionnaire.[15] As recommended by the Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine, a large neck was defined as neck circumference >17 inches for men and >16 inches for women.[16]

Development and Validation of Clinical Prediction Model

Rather than dividing a single cohort into a random two-third sample for development and retaining the other one-third sample for validation, we used separate, independently derived development and validation cohorts. Plots of the logit of sleep apnea by classes of continuous predictors were examined to assess the best form of the predictor for modeling. Weight, NIHSS, and ESS scores were determined to be modeled as quadratic, whereas Personal Health Questionnaire-8 scores had a cubic relationship. Bivariate logistic models were then used to assess the strength of each predictor variable. Six variables thought to be clinically important were included in the multivariable model: gender, weight, large neck, history of congestive heart failure, history of diabetes, and NIHSS score. Six other variables (ESS, "high-risk" BQ, chronic obstructive pulmonary disease, Personal Health Questionnaire-8, Charlson Comorbidity score, and age) were significant at the .25 level in bivariate logistic models and were included in initial models, but were removed by backward variable selection if they were not statistically significant at the .05 level. Given the lack of association between infarct location and OSA, radiographic data were not included in the model.[17] Regression diagnostics were performed, and 5 patients were removed from the development sample because they proved to be highly influential.

Model performance was evaluated using the c-statistic.[18] The optimal cut point for predicting OSA was selected as the probability that maximized sensitivity and specificity. Resulting classification tables were used to obtain sensitivity, specificity, percentages of correctly classified and misclassified, false-positive and false-negative rates, PPVs and NPVs, and likelihood ratios for all models.

Missing data were rare; imputation was not used. We used SAS/STAT software, Version (9.3) of the SAS system for Windows (Cary, NC). Institutional review board approval was obtained for this research.

Results

OSA occurred frequently in the development (119 of 194; 61%) and validation (84 of 109; 77%) cohorts, as shown in Table 1. Associations between predictor variables and OSA are shown in Table 2. The final model included an indicator for female (sex), congestive or left heart failure, the ESS, an indicator for having an enlarged neck, weight (in pounds) and weight squared, insulin sensitivity or diabetes, and NIHSS score; these factors can be combined as the SLEEP INventory, with the NIHSS score and ESS also including squared

terms. Although model sensitivity was high in both development (91.4%) and validation (100%) cohorts, model specificities were low (development, 43.8%; validation, 12.5%). Using the optimal cut point, the percent classified correctly was 73.2% in the development sample and 80.2% in the validation sample (data not shown).

As shown in Table 3, the SLEEP INventory, BQ, ESS, STOP-BANG, and SACS had similar PPVs; in comparison, the NPV was greatest for the SLEEP INventory (76.2%–100.0%) than for the BQ (43.3%), ESS (51.9%–46.2%), STOP-BANG (40.0–41.7), and SACS (12.5%–44.1%). Alternative models using only the BQ, ESS, STOP-BANG, and SACS typically had lower sensitivities, higher specificities, lower rates of classifying cases correctly, and lower NPVs. The SLEEP INventory c-statistics were similar between the development and the validation sets in modeling the presence of OSA (.732 and .731, respectively).

In examining receiver operator curves for each model, although the SLEEP INventory had the best discrimination of any model, none of the models showed strong discrimination (Figure 1). Whereas the clinical threshold for treating OSA is an AHI 5 events per hour,[19] we also examined how well the SLEEP INventory and other models predicted an AHI index 30 events per hour (i.e., severe OSA)[20]; the models had similar sensitivities, specificities, and predictive values regardless of AHI threshold used (data not shown).

Discussion

This study demonstrates that the BQ, ESS, STOP-BANG, and SACS did not strongly predict the presence of OSA on formal PSG in an exclusively post-ischemic stroke or TIA population. We also demonstrated that a clinical prediction rule combining patient symptomatology with readily available and routinely collected patient demographic, anthropometric, medical history, and stroke severity data could be derived from and applied to a population of patients with ischemic stroke or TIA. Although the SLEEP INventory performed somewhat better than the BQ, ESS, STOP-BANG, and SACS, it too did not strongly predict the presence of OSA. Nonetheless, a strength of the SLEEP INventory is in its NPV, and it could be used to help prioritize which patients are least in need of PSG referral. Our study also confirmed the high rate of OSA in post-stroke or TIA patients, occurring in 60%–80% of this population[1,21]; by comparison, 20%–26% of the general population has OSA.[22,23]

Underdiagnosis of OSA leads to untreated OSA, which is itself a risk factor for stroke, and may make other vascular risk factors (e.g., hypertension) more difficult to control. [1,3,4,22,24,25] Given the importance of identifying individuals at risk for OSA, several screening questionnaires have been developed and validated within the general population. [6,8] The BQ categorized patients as being "high risk" for OSA based on patient-reported symptoms (e.g., snoring, tiredness in various settings), body mass index 30 kg/m^2, and a history of hypertension.[8] The BQ accurately predicts the presence of OSA on PSG among patients in primary care setting (sensitivity 86.0%, specificity 77.0%, PPV 89.0%). The accuracy of the BQ was even higher in cardiology clinics (sensitivity 86.0%, specificity 89.0%, PPV 97.0%).[8] When applied to the stroke population (mixed ischemic and hemorrhagic), the BQ correlated less well with PSG-defined OSA (sensitivity 68.0%,

specificity 59.0%, PPV 59.0%).[7] Prediction of OSA was not improved with the addition of the ESS (as a measure of daytime somnolence) to the BQ (sensitivity 50.0%, specificity 88.0%, PPV 57.0%), likely because the BQ already contains questions regarding sleepiness.[7] Srijithesh et al noted that none of the clinical indicators in the BQ were sufficient to diagnose OSA in the post-stroke population.[7] Boulos et al similarly reported that the BQ did not predict the presence of OSA among patients with stroke (mixed ischemic and hemorrhagic) or TIA.[10] Our current study confirms the lower sensitivity, specificity, and predictive values in a study population exclusively with ischemic stroke or TIA, rather than a mixed ischemic and hemorrhagic stroke population.

The STOP-BANG has increasingly been used to screen patients for OSA, especially within the surgical population. Among preoperative obese patients, a STOP-BANG score of 4 identified the presence of severe OSA found on PSG with both high sensitivity (87.5%) and NPV (90.5%), with a higher score being associated with increased specificity.[26] When applied to patients with cerebrovascular disease, lower sensitivity (35.3%) and NPV (41.7%) were observed in the development and validation sets. Severine et al screened 300 prospective patients during an admission for a cerebrovascular event for OSA with STOP-BANG, but information about whether patients were ultimately referred for PSG, and if STOP-BANG was associated with the presence of OSA on formal PSG, was not reported.[9] Boulos et al assessed the utility of a modified version of the STOP-BANG (the STOP-BAG, which excluded the neck circumference) in detecting the presence of OSA among patients with stroke, either ischemic or hemorrhagic, or TIA receiving screening via home sleep testing equipment.[10] Using cutoffs that maximized sensitivity, the authors reported that the STOP-BAG was only moderately predictive of OSA. They also noted that objective sleep testing would still be important in diagnosing patients with stroke or TIA with OSA until a more accurate instrument was developed, and that future work should focus on developing OSA screening instruments that use patient-level comorbidities.[10]

Like the STOP-BANG, the SACS is another sleep instrument used to make determinations about PSG referral that has its origins in perioperative OSA assessment. The SACS includes patient symptomatology, neck circumference, and a history of hypertension; it has been found to have a sensitivity of 76% and a PPV of 77% when applied to patients presenting to a sleep disorders center.[15,27] To our knowledge, the SACS has not been used to predict OSA on PSG for patients with cerebrovascular disease. Our findings suggest that the SACS likely has limited utility in the stroke or TIA population.

As described above, the BQ, ESS, STOP-BANG, and SACS rely heavily on patient symptomatology and anthropometric features, but excessive daytime sleepiness and obesity may occur less commonly among patients with ischemic stroke than in a community sample of patients without a stroke. In a case-control study, Arzt et al sought to determine whether post-ischemic and hemorrhagic stroke patients reported less daytime sleepiness, and had lower body mass indexes, than did a community sample of persons with a similar degree of OSA.[5] Patients with stroke and OSA were statistically less likely to have a high ESS (10% versus 38%; $P < .001$) and to be obese (26% versus 70%; $P < .001$). The authors noted that sleepiness is an uncommon feature of OSA, and that obesity seemed less likely to contribute to the development of OSA among patients with cerebrovascular disease.[21] Interestingly, our

study demonstrated that the relationship between ESS values and the log odds of sleep apnea is not linear, but quadratic, with higher ESS scores associated with a decreased likelihood of OSA in the stroke population. Conceivably, patients with stroke who are excessively sleepy may be so for reasons other than OSA (e.g., direct impact of stroke, use of antihypertensive medications). Explanations for this difference between our findings and those of Arzt et al may be because we used an exclusively post-ischemic stroke or TIA population, rather than a combination of ischemic and hemorrhagic stroke patients. Also, we found that the relationship between ESS and OSA is more complex than perhaps previously appreciated; similar to other studies, when we used the ESS as a binary variable, it was not predictive of OSA (data not shown).[5]

In applying these data to the patient with ischemic stroke or TIA, the PPV and NPVs of the OSA screening instruments should be considered. Given that the prevalence of OSA among patients with stroke and TIA exceeds 50%, it is reasonable for clinicians to presume that their patient with cerebrovascular disease has OSA. In this situation, the NPV, or the probability that an individual does not have OSA based on a negative screening result, becomes important in assessing the clinical usefulness of the screening instrument. Based on the current results, the SLEEP INventory, having the greatest NPV in the cerebrovascular disease population compared with other models, could be used clinically to aid determinations regarding which patients might not need referral.

The strengths of our study include our large sample size, having separate development and validation cohorts in which to generate and validate our clinical prediction model, and having complete PSG study data on all patients in the development cohort. The development set included chronic post-stroke or TIA patients, whereas the validation cohort included patients with acute ischemic stroke. Combined, these 2 cohorts encompass post-stroke or TIA patients across the continuum of their care in non-Veterans and Veterans health-care settings, thereby increasing the generalizability of our model. Additionally, we examined the utility of OSA prediction models exclusively among patients with an ischemic stroke or TIA, rather than a mixed population of patients with ischemic and hemorrhagic stroke.[6,8,10] Finally, the SACS has not been previously examined among patients with cerebrovascular disease.

Several limitations should be noted. First, we defined OSA as an AHI 5 events per hour documented on PSG (based on American Academy of Sleep Medicine guidelines)[14,15,28]; other studies have examined alternative AHI values (e.g., AHI 10) to identify OSA presence.[7,10] Of note, the SLEEP INventory performed equally in regard to predicting AHI 5 and 30 in the current analysis. Second, when both the BQ and the SACS were developed, the authors found hypertension to be predictive of OSA,[8,15] whereas our development cohort consisted entirely of patients with hypertension (and we were therefore unable to model hypertension in our current work). Third, these data came from 2 randomized trials, and are subject to issues of generalizability related to study design.[29,30] Fourth, there is a paucity of validated screening tools for patients older than the age of 75; future work should seek to validate our findings within a cohort of exclusively older patients. Finally, we recognize that our model may be more complex to implement in a clinic setting compared with the BQ, ESS, STOP-BANG, or SACS. Feasible options to help providers

make determinations about prioritizing PSG by incorporating the SLEEP INventory into the workflow of a busy clinic to referrals include integrating it into an existing EHR, developing a separate online SLEEP INventory calculator, and having this screening instrument as part of a nursing intake for stroke patients at follow-up.

Conclusions

This study confirmed the high prevalence of previously undiagnosed OSA and reported the limited utility of the BQ, ESS, STOP-BANG, and SACS as OSA screening instruments for patients with an ischemic stroke or TIA. Given the high prevalence and potential treatment implications in discerning whether a patient with a cerebrovascular event has OSA, if clinicians presume that their patient has OSA, the SLEEP INventory (with its NPV) may help make determinations regarding which patients are least in need of sleep center referral. However, this approach would still misclassify approximately 25% of all patients with a cerebrovascular event as not having OSA, suggesting that in a population where OSA is exceedingly prevalent and difficult to screen for, there likely is an important role for formal sleep testing (e.g., PSG).

Acknowledgments

References

1. Yaggi H, Concato J, Kernan W, et al. Obstructive sleep apnea as a risk factor for stroke and death. NEJM. 2005; 353:2034–2041. [PubMed: 16282178]

2. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/ American Stroke Association. Stroke. 2014; 45:2160–2236. [PubMed: 24788967]

3. Marin JM, Carrizo SJ, Vicente E, et al. Long-term cardiovascular outcomes in men with obstructive sleep apnoeahypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet. 2005; 365:1046–1053. [PubMed: 15781100]

4. Kanagala R, Murali N, Friedman P, et al. Obstructive sleep apnea and the recurrence of atrial fibrillation. Circulation. 2003; 107:2589–2594. [PubMed: 12743002]

5. Arzt M, Young T, Peppard PE, et al. Dissociation of obstructive sleep apnea from hypersomnolence and obesity in patients with stroke. Stroke. 2010; 41:e129–e134. [PubMed: 20075361]

6. Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep. 1991; 14:540–545. [PubMed: 1798888]

7. Srijithesh PR, Shukla G, Srivastav A, et al. Validity of the Berlin Questionnaire in identifying obstructive sleep apnea syndrome when administered to the informants of stroke patients. J Clin Neurosci. 2011; 18:340–343. [PubMed: 21237648]

8. Netzer NC, Stoohs RA, Netzer CM, et al. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. Ann Intern Med. 1999; 131:485–491. [PubMed: 10507956]

9. Severine JE, Thanavaro J, Lorenz R, et al. Screening for obstructive sleep apnea in hospitalized transient ischemic attack stroke patients using the STOP-Bang Questionnaire. J Nurse Pract. 2016; 12:19–26.

10. Boulos MI, Wan A, Im J, et al. Identifying obstructive sleep apnea after stroke/TIA: evaluating four simple screening tools. Sleep Med. 2016; 21:133–139. [PubMed: 27448484]

11. Bravata DM, Concato J, Fried T, et al. Auto-titrating continuous positive airway pressure for patients with acute transient ischemic attack: a randomized feasibility trial. Stroke. 2010; 41:1464–1470. [PubMed: 20508184]

12. Bravata D, Ferguson J, Miech E, et al. Diagnosis and treatment of sleep apnea in patients' homes: the rationale and methods of the "GoToSleep" randomized-controlled trial. J Clin Sleep Med. 2012; 8:27–35. [PubMed: 22334806]

13. Loube DI, Gay PC, Strohl KP, et al. Indications for positive airway pressure treatment of adult obstructive sleep apnea patients: a consensus statement. Chest. 1999; 115:863–866. [PubMed: 10084504]

14. Meoli AL, Casey KR, Clark RW, et al. Hypopnea in sleep-disordered breathing in adults. Sleep. 2001; 24:469–470. [PubMed: 11403531]

15. Flemons WW, Whitelaw WA, Brant R, et al. Likelihood ratios for a sleep apnea clinical prediction rule. Am J Respir Crit Care Med. 1994; 150:1279–1285. [PubMed: 7952553]

16. Epstein LJ, Kristo D, Strollo PJ Jr, et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. J Clin Sleep Med. 2009; 5:263–276. [PubMed: 19960649]

17. Stahl SM, Yaggi HK, Taylor S, et al. Infarct location and sleep apnea: evaluating the potential association in acute ischemic stroke. Sleep Med. 2015; 16:1198–1203. [PubMed: 26429745]

18. LaValley MP. Logistic regression. Circulation. 2008; 117:2395–2399. [PubMed: 18458181]

19. Rubins JB, Kunisaki KM. Contemporary issues in the diagnosis and treatment of obstructive sleep apnea. Postgrad Med. 2008; 120:46–52.

20. Park JG, Ramar K, Olson EJ. Updates on definition, consequences, and management of obstructive sleep apnea. Mayo Clin Proc. 2011; 86:549–555. [PubMed: 21628617]

21. Bassetti C, Aldrich MS, Chervin RD, et al. Sleep apnea in patients with transient ischemic attack and stroke: a prospective study of 59 patients. Neurology. 1996; 47:1167–1173. [PubMed: 8909424]

22. Young T, Peppard P, Gottlieb D. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med. 2002; 165:1217–1239. [PubMed: 11991871]

23. Peppard PE, Young T, Barnet JH, et al. Increased prevalence of sleep-disordered breathing in adults. Am J Epidemiol. 2013; 177:1006–1014. [PubMed: 23589584]

24. Hla KM, Skatrud JB, Finn L, et al. The effect of correction of sleep-disordered breathing on BP in untreated hypertension. Chest. 2002; 122:1125–1132. [PubMed: 12377832]

25. Mohsenin V. Sleep-related breathing disorders and risk of stroke. Stroke. 2001; 32:1271–1278. [PubMed: 11387486]

26. Chung F, Yang Y, Liao P. Predictive performance of the STOP-Bang score for identifying obstructive sleep apnea in obese patients. Obes Surg. 2013; 23:2050–2057. [PubMed: 23771818]

27. Rowley JA, Aboussouan LS, Badr MS. The use of clinical prediction formulas in the evaluation of obstructive sleep apnea. Sleep. 2000; 23:929–938. [PubMed: 11083602]

28. Berry RB, Budhiraja R, Gottlieb DJ, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. J Clin Sleep Med. 2012; 8:597–619. [PubMed: 23066376]

29. Levin KA. Study design VII. Randomised controlled trials. Evid Based Dent. 2007; 8:22–23. [PubMed: 17380181]

30. Concato J, Horwitz RI. Beyond randomised versus observational studies. Lancet. 2004; 363:1660–1661. [PubMed: 15158623]
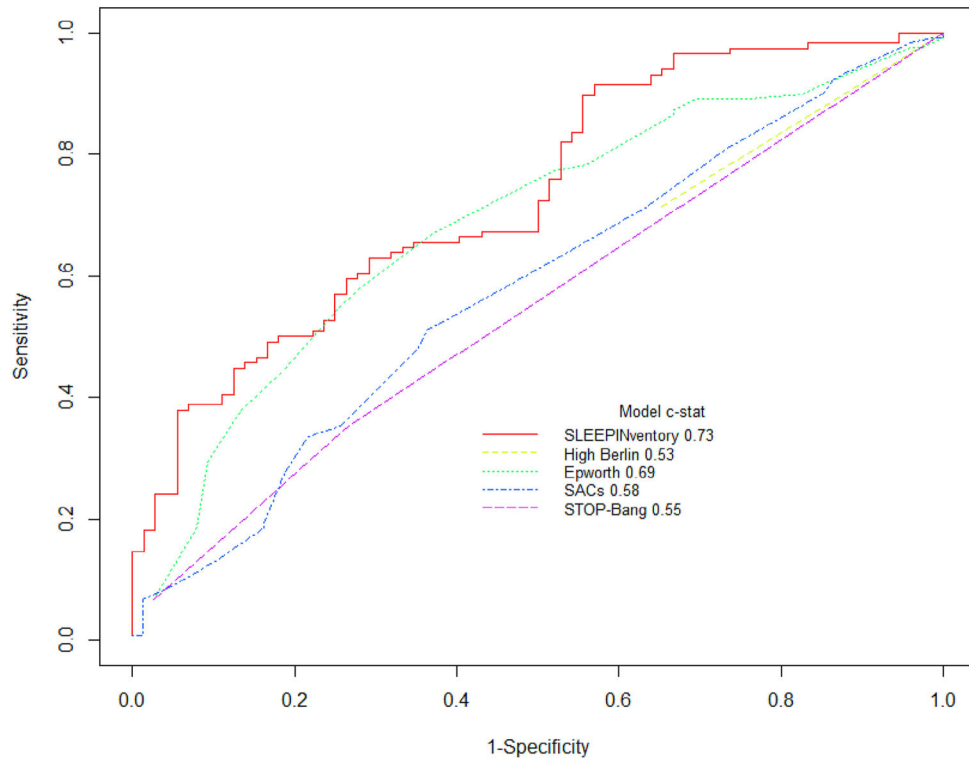
Figure 1.
Receiving operator curves for SLEEP INventory and other predictors of obstructive sleep apnea

Table 1

Characteristics of patients in the development and validation cohorts

Characteristics	Development set			Validation set		
	OSA present	OSA absent	*P*-value	OSA present	OSA absent	*P*-value
	n = 119	n = 75		n = 84	n = 25	
Demographic						
Age (y)						
Mean ± SD	70.8 ± 9.9	68.7 ± 10.6	.18	60.7 ± 11.5	55.5 ± 14.0	.13
Median (min, max)	71 (48, 91)	68 (45, 88)		60 (32, 94)	59 (30, 80)	
Race						
White	100 (84.0%)	59 (78.7%)	.56	52 (61.9%)	19 (76.0%)	.24
Black	18 (15.1%)	15 (20.0%)		30 (35.7%)	6 (24.0%)	
Other	1 (.8%)	1 (1.3%)		2 (2.4%)	0 (.0%)	
Gender						
Male	117 (98.3%)	71 (94.7%)	.21	56 (66.7%)	14 (56.0%)	.33
Anthropometric						
Height (m)						
Mean ± SD	1.7 ± .1	1.8 ± .1	.48	1.7 ± .1	1.7 ± .1	.28
Median (min, max)	1.8 (1.6, 1.9)	1.8 (1.5, 1.9)		1.7 (1.3, 1.9)	1.7 (1.6, 1.9)	
Weight (kg)						
Mean ± SD	87.7 ± 14.8	84.8 ± 16.4	.21	88.9 ± 20.6	84.7 ± 19.7	.28
Median (min, max)	86 (57, 129)	83 (50, 128)		88.8 (54.4, 136)	82.1 (59, 145)	
BMI						
Mean ± SD	44.3 ± 11.9	42.9 ± 12.6	.39	30.4 ± 7.0	29.9 ± 8.7	.41
Median (min, max)	46.9 (18.0, 69.7)	42.9 (16.0, 71.1)		29.1 (16.4, 51.5)	28.0 (20.8, 58.8)	
Large neck circumference						
Yes	30 (25.2%)	15 (20.3%)	.43	23 (27.7%)	0 (.0%)	.003
No	89 (74.8%)	59 (79.7%)		60 (71.4%)	25 (100%)	
Waist circumference (cm)						
Mean ± SD	107.1 ± 12.7	104 ± 12.9	.15	107.7 ± 14.6	101.6 ± 14.2	.02
Median (min, max)	107 (78, 142)	103 (71, 130)		110 (76.5, 145)	99 (81.5, 135.3)	

	Development set			Validation set		
	OSA present	OSA absent	*P*-value	OSA present	OSA absent	*P*-value
Medical history						
Ischemic stroke	71 (59.7%)	36 (48.0%)	–	13 (15.5%)	6 (24.0%)	–
TIA	32 (26.9%)	25 (33.3%)	–	6 (7.1%)	1 (4.0%)	–
Ischemic stroke or TIA	16 (13.5%)	14 (18.7%)	.27	4 (4.8%)	0 (.0%)	.68
Hypertension	119 (100%)	75 (100%)	–	51 (60.7%)	14 (56.0%)	.67
Hyperlipidemia	103 (86.6%)	55 (73.3%)	.02	47 (56.6%)	12 (48.0%)	.45
Diabetes	52 (43.7%)	25 (33.3%)	.15	22 (26.2%)	8 (32.0%)	.57
with end organ complications	21 (17.6%)	9 (12.0%)	.29	9 (10.7%)	2 (8.0%)	.42
Atrial fibrillation	19 (16.0%)	11 (14.7%)	.81	8 (9.5%)	1 (4.0%)	.68
Congestive heart failure	14 (11.8%)	6 (8.0%)	.40	5 (6.0%)	2 (8.0%)	.65
Myocardial infarction	28 (23.5%)	20 (26.7%)	.62	17 (20.2%)	2 (8.0%)	.23
Dementia	10 (8.4%)	5 (6.7%)	.66	1 (1.2%)	0 (.0%)	–
Polysubstance use						
Smoking or smoked	85 (71.4%)	62 (82.7%)	.08	54 (64.3%)	16 (64.0%)	.98
Cocaine use or used	11 (9.2%)	11 (14.7%)	.25	15 (17.9%)	4 (16.0%)	.99
Charlson Comorbidity score						
Mean ± SD	2.4 ± 2.1	2.6 ± 2.4	.67	2.0 ± 2.1	2.0 ± 2.0	.90
Median (min, max)	2 (0, 11)	2 (0, 12)		2.0 (0, 9)	1.0 (0, 6)	
Modified Rankin						
Mean ± SD	1.1 ± 1.3	1.2 ± 1.2	.49	1.6. ± 1.3	1.5 ± 1.2	.69
Median (min, max)	1 (0, 4)	1 (0, 4)		1 (0, 4)	1 (0, 4)	
PHQ-8						
Mean ± SD	6.0 ± 5.3	7.5 ± 5.8	.05	5.0 ± 4.3	6.4 ± 4.6	.14
Median (min, max)	5 (0, 21)	6 (0, 23)		3 (0, 18)	6 (0, 18)	
Neurological symptoms						
NIHSS score						
Mean ± SD	1.8 ± 2.7	1.8 ± 2.1	.36	1.9 ± 2.2	2.3 ± 2.2	.30
Median (min, max)	1 (0, 13)	1 (0, 9)		1 (0, 12)	2 (0, 8)	
Sleep inventories						
ESS						

	Development set			Validation set		
	OSA present	OSA absent	P-value	OSA present	OSA absent	P-value
Mean ± SD	7.6 ± 4.4	7.1 ± 5.8	.15	7.0 ± 4.3	6.3 ± 5.2	.39
Median (min, max)	7 (0, 22)	5 (0, 20)		7 (0, 21)	6 (0, 18)	
High risk	40 (33.6%)	23 (30.7%)	.67	17 (20.2%)	6 (24.0%)	.73
BQ						
High risk	85 (71.4%)	49 (65.3%)	.37	56 (66.7%)	14 (56.0%)	.46
SACS						
Mean ± SD	19.7 ± 15.9	16.2 ± 12.5	.07	14.1 ± 19.1	5.1 ± 4.6	.002
Median (min, max)	16 (1, 110)	13 (3, 80)		8 (0, 110)	4 (0, 22)	
SACS 15	62 (52.1%)	28 (37.3%)	.04	25 (29.8%)	1 (4.0%)	.008
STOP-BANG						
Mean ± SD	3.9 ± 1.0	3.8 ± .8	.63	3.9 ± 1.5	3.0 ± 1.2	.006
Median (min, max)	4 (2, 6)	4 (1, 6)		4 (1, 8)	3 (1, 6)	

BMI, body mass index; BQ, Berlin Questionnaire; ESS, Epworth Sleepiness Scale; NIHSS, National Institutes of Health Stroke Scale; OSA, obstructive sleep apnea; PHQ, Patient Health Questionnaire; SACS, Sleep Apnea Clinical Score; SD, standard deviation; TIA, transient ischemic attack.

Table 2

SLEEP INventory development: predictors of sleep apnea in patients with stroke or TIA

	OR (95% CI)	
	Development	**Validation**
Covariates	**(n = 188)**	**(n = 106)**
Female	.10 (.01, 1.04)	.90 (.31, 2.61)
Weight	1.02 (1.00, 1.05)	1.00 (.97, 1.03)
Weight squared	1.000 (.999, 1.001)	1.000 (.999, 1.001)
Large neck	1.10 (.41, 3.00)	_*
Congestive heart failure	1.16 (.40, 3.37)	.59 (.05, 6.53)
Diabetes	1.71 (.85, 3.43)	.69 (.22, 2.17)
NIH Stroke Scale	.57 (.34, .96)	.74 (.43, 1.25)
NIHSS squared	1.09 (1.00, 1.20)	1.03 (.97 1.09)
Epworth	1.47 (1.17, 1.85)	1.23 (.90, 1.67)
Epworth squared	.98 (.97, .99)	.99 (.98, 1.01)
C-statistic	.732	.731
Predicted probability		
Cutoff for classification	.465	.465
Sensitivity	106/116 (91.4%)	82/82 (100%)
False-negative rate	10/116 (8.6%)	0/82 (.0%)
Specificity	32/73 (43.8%)	3/24 (12.5%)
False-positive rate	41/73 (56.2%)	21/24 (87.5%)
Classified correctly	138/189 (73.2%)	85/106 (80.2%)
Misclassified	51/189 (27.0%)	21/106 (19.1%)

CI, confidence interval; OR, odds ratio; SD, standard deviation; TIA, transient ischemic attack.

*
Not able to estimate because no patients without sleep apnea had a large neck.

Regression diagnostics showed 5 subjects in the development sample to be overly influential, so they were not included in the final predictive model. One subject in the development sample had missing values for explanatory variables and was omitted from modeling. Three subjects in the validation sample had missing values for explanatory variables and were not included in modeling.

Table 3

SLEEP INventory and additional models of multivariable predictors of sleep apnea in patients with stroke or TIA

	BQ		ESS		STOP-BANG		SACS		SLEEP INventory	
	D	V	D	V	D	V	D	V	D	V
Sensitivity	85/119	81/81	69/119	75/82	42/119	69/84	57/119	76/83	106/116	82/82
(%)	(71.4)	(100.0)	(58.0)	(91.5)	(35.3)	(82.1)	(47.9)	(91.6)	(91.4)	(100.0)
False negative rate	34/119	0/81	50/119	7/82	77/119	15/84	62/119	7/83	10/116	0/82
(%)	(28.6)	(.0)	(42.0)	(8.54)	(64.7)	(17.9)	(52.1)	(8.4)	(8.6)	(.0)
Specificity	26/75	0/23	54/75	6/25	55/75	10/25	49/75	1/23	32/73	3/24
(%)	(34.7)	(.0)	(72.0)	(24.0)	(73.3)	(40.0)	(65.3)	(4.35)	(43.8)	(12.5)
False positive rate	49/75	23/23	21/75	19/25	20/75	15/25	26/75	22/23	41/73	21/24
(%)	(65.3)	(100.0)	(28.0)	(76.0)	(26.7%)	(60.0)	(34.7)	(95.7)	(56.2)	(87.5)
NPV (%)	43.3	–	51.9	46.2	41.7	40.0	44.1	12.5	76.2	100.0
PPV (%)	63.4	77.9	76.7	79.8	67.7	82.1	68.7	77.6	72.1	79.6
Classified correctly	111/194	81/104	123/194	81/107	109/194	83/108	106/194	77/106	138/189	85/106
(%)	(57.2)	(77.9)	(63.4)	(75.7)	(56.2)	(76.9)	(54.6)	(72.6)	(73.2)	(80.2)
Misclassified	83/194	23/104	71/194	26/107	85/194	25/108	88/194	29/106	51/189	21/106
(%)	(42.8)	(22.1)	(36.6)	(24.3)	(43.8)	(23.2)	(45.4)	(27.4)	(27.0)	(19.1)
Cutoff for classification	.634	.634	.684	.684	.654	.654	.609	.609	.465	.465
C-statistic	.530	.541	.685	.582	.547	.631	.577	.715	.732	.731

BQ, Berlin Questionnaire; D, development; ESS, Epworth Sleepiness Scale; NPV, negative predictive value; PPV, positive predictive value; SACS, Sleep Apnea Clinical Score; SLEEP IN, Sex, Left heart failure, Epworth sleepiness score, Enlarged neck, weight (in pounds), Insulin resistance or diabetes, and National Institutes of Health Stroke Scale; STOP-BANG, Snoring, Tiredness, Observed Apnea, high blood Pressure-Body mass index, Age, Neck circumference, and Gender; TIA, transient ischemic attack; V, validation.