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Crossectional Study on the Performance of Screening Questionnaires for Prediction of Moderate to Severe Obstructive Sleep Apnea in Women

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Abstract

Introduction The clinical manifestations of obstructive sleep apnea (OSA) are different between genders. Though there are several screening questionnaires for OSA, their performance in females is not fully understood, as women have been historically underrepresented in research studies.

Objective To assess the performance of screening questionnaires and their capacity to identify a moderate to severe apnea-hypopnea index (AHI) in women.

Materials and Methods The Epworth sleep scale (ESS), Berlin questionnaire, and STOP-BANG questionnaire (SBQ) were correlated with AHI. Also, the sensitivity (S), specificity (Sp), and area under the receiver operating characteristic (AUC-ROC) curve were calculated for each questionnaire and combinations thereof. Multiple regression models were used to identify ≥15 ev/h AHI.

Results Our study included 5,344 patients: 1978 women (37.1%) aged 55.06 ± 14 years with body mass index (BMI): 32.6 ± 8.30 kg/m^2, ESS: 7.69 ± 5.2 points, and high-risk Berlin score: 87.25%. An AHI ≥15 ev/h was found in 30.4% of women. In terms of the capacity to identify an ≥15 ev/h AHI in women, the AUC-ROC of ESS >10 and high-risk Berlin was 0.53 and 0.58, respectively. Three components of SBQ in any combination showed: a S of 65.1% (95% CI: 61.2–68.9), a Sp: 61.5% (95% CI: 58.9–64.1), with the AUC-ROC: 0.67.

Conclusions Questionnaires perform differently in women. Therefore, it is necessary to take a gender-specific approach. The SBQ showed a higher discriminative power and more specificity than the ESS and the Berlin questionnaire. The best performance was obtained with any combination of 3 SBQ components. Age, BMI, neck circumference, and hypertension were the strongest predictors.

Keywords
- sleep apnea syndrome
- respiratory polygraphy
- surveys and questionnaires

Introduction

Obstructive sleep apnea (OSA) is the most frequent sleep respiratory disorder. It is more common in men, with a prevalence between 9 and 38% in the general population.[1] The HypnoLaus study reported that the estimated prevalence of moderate to severe OSA is 49.7% in men and 23.4% in women, based on an apnea hypopnea index (AHI) per hour of sleep of ≥15 events per hour.[2] In Latin America, Tufik et al. conducted a study on the general population of Sao Paulo,

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Brazil, using polysomnography and the same AHI criteria. They found significant OSA in >10% of their female patients.[3]

The differences in the prevalence of OSA among different populations, even between genders, could result from cultural, physiological, anthropometric, and clinical factors. Additionally, women are more likely to refer nonspecific symptoms (e.g., headache, fatigue, anxiety, depression, insomnia, or fragmented sleep) more frequently than men;[4] while they sometimes refrain from reporting snoring and apnea during clinical examinations because of social perceptions.

According to the Sleep Heart Health Study Group,[5] men and women do not answer sleep questionnaires similarly. Therefore, the Epworth sleepiness scale (ESS) is more likely to identify symptomatic men. This means that excessive daytime sleepiness, extreme fatigue, and sleep-related poor quality of life, which are frequently included in questionnaires, could be less specific in women.[6]

The use of questionnaires to detect OSA is customary in sleep units. However, sex-specific information on the performance of these questionnaires is scarce[7,8] because women have been historically underrepresented in multiple aspects of OSA research.[5–9]

The original validation study for the STOP-BANG questionaire (SBQ) (STOP: snoring, tiredness, observed apnea, and high blood pressure. BANG: body mass index, age, neck circumference, and gender)[10] stated that the STOP combination has better diagnostic sensitivity administered in the male gender (S: 40.1%, 95% CI: 33.2–47.3), with body mass index (BMI) $\geq$35 kg/m^2 (S: 20.8%, 95% CI: 15.4–27.2), or neck circumference $\geq$ 40cm (S: 33.5%, 95% CI: 27–40.6). This means that male gender performs better as a predictor, while women have one less component.

Lastly, the Berlin questionnaire has a high sensitivity (>80%) in both populations, even more than SBQ and ESS for moderate to severe OSA and a better predictive value in populations with high cardiovascular risk. It is surprising to note, however, the scant attention paid to a possible gender-based interpretation.[8–13]

Our hypothesis is that standard screening questionnaires to diagnose moderate to severe OSA perform differently in females. Thus, the purpose of this study is to obtain specific information on the performance of SBQ, Berlin questionnaire, and ESS to predict moderate to severe OSA, especially in women, and to identify the questionnaire with the best discriminative power in this specific population.

Materials and Methods

Study Design

This crossectional study was approved by the Ethics Committee and the Institutional Review Board according to the Declaration of Helsinki (1975), as amended (#849).

Sampling

Nonprobability, consecutive sampling was applied. We used the systematic data gathering database of the sleep unit of Hospital Británico, Buenos Aires, Argentina (2011–2018), which is an urban general university hospital with 350 beds that offers polysomnography testing (2,000 tests/year) and home-based respiratory polygraphy (1,000 tests/year) for OSA management.

The sample size for comparison purposes was estimated at 399 observations with a Type I error (α) of 5% and a power of 80%.

Study Population

Inclusion Criteria

The present study included adult patients with suspected OSA who underwent a home-based diagnostic respiratory polygraphy (RP) and completed the SBQ, Berlin, and ESS questionnaires.

Exclusion Criteria

The exclusion criteria for this study were patients with other respiratory or nonrespiratory sleep disorders. Those under use of noninvasive ventilation, CPAPs, or known neuromuscular diseases. Pregnant women. Those with a valid total recording time (TRT) lower than 240 minutes. Those with incomplete questionnaires. And, finally, patients with communication barriers that affect their understanding of the test (deafness, blindness, mental disorders etc.).

Recorded Demographic Variables

Age (years), gender (female/male), body weight (kg), height (centimeters), and BMI (kg/m^2).

►Fig. 1 shows the flowchart of patient selection.

Measurements

Before the RP, all patients completed the Spanish version of the questionnaires.

STOP-BANG Questionnaire

Risk for OSA was measured considering patients' affirmative answers and was classified as: low risk ($\leq$ 2 answers); intermediate risk (3–4 answers); or high risk ($\geq$ 5 answers,

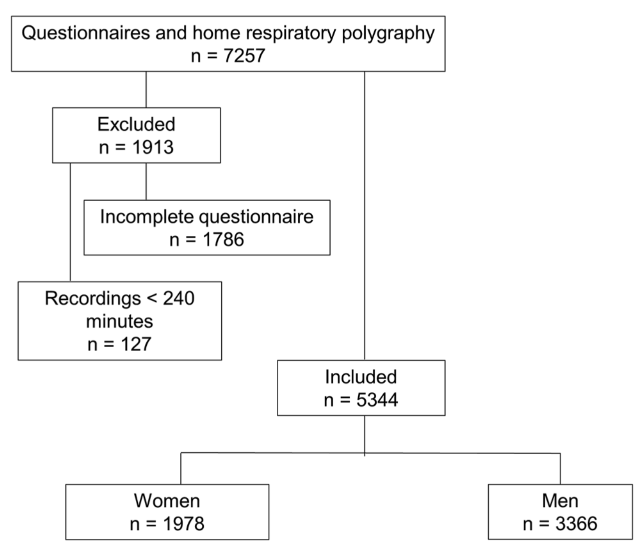

Fig. 1 FlowChart of patient's selection.

2/4 of STOP + male gender, 2/4 answers of STOP + BMI > 35 kg/m^2, or 2/4 answers of STOP + neck circumference > 42 cm for men or > 41 cm for women).[9–15]

Berlin Questionnaire

The risk classification for OSA was based on the responses to three categories of this questionnaire: 1) persistent symptoms of snoring and apnea; 2) persistent symptoms of excessive daytime sleepiness and/or drowsiness when driving; 3) history of hypertension or BMI > 30 kg/m^2. Patients were considered to be at high risk for OSA if two or more categories were present.[16]

Epworth Sleepiness Scale

We assessed sleepiness with a scoring system from 0 to 3 for each of 8 questions about falling asleep during daily situations or activities. A >10 score was considered as excessive daytime sleepiness.[17]

Self-administered Home-based Respiratory Polygraphy

Patients were instructed on the use of a self-administered home-based RP. The ApneaLink Plus and Apnea Link Air (ResMed, San Diego, CA, USA) devices were used to record nasal airflow, snoring, thoracoabdominal respiratory effort (qualitative band), and pulse oximetry (Nonin, XPOD, Plymouth, MN, USA). Signal analysis was performed with the ApneaLink 9.0 software in a sequential manner (automatic analysis with manual editing).

Respiratory events were classified according to international criteria.[18] Apnea was defined as a >90% reduction in airflow for ≥10 seconds, and hypopnea as a ≥50% reduction in airflow for ≥10 seconds, associated with ≥3% oxygen desaturations. The AHI was calculated as the number of apnea and hypopnea events per hour of valid recording time (ev/h), with results of ≥15 ev/h being considered as moderate to severe OSA.

Table 1 Characteristics of study population.

Variables	Women	Men	*p*-value
n	1,978	3,366	
Age (±SD)	55.06 ± 14.04 (95% CI 55–57)	54.37 ± 14.30 (95% CI 54–56)	0.09
BMI kg/m^2 (±SD)	32.60 ± 8.30 (95% CI 30.8–31.5)	31.40 ± 6.10 (95% CI 30–30.5)	0.0001
Obesity (%)	57.48	55.05	0.08
High-risk Berlin score (n:%)	1,726 (87.25)	3,013 (89.51)	0.014
ESS (±SD)	7.69 ± 5.20 (95% CI 7–7)	7.93 ± 5.14 (95% CI 7–7)	0.11
ESS > 10 (%)	28.41	28.60	0.52
S (n:%)	822 (41.55)	2,255 (66.9)	0.0001
T (n:%)	1,472 (74.41)	2,294 (68.75)	0.0001
O (n:%)	675 (34.12)	1,724 (51.21)	0.0001
P (n:%)	955 (48.28)	1,845 (54.81)	0.0001
B (n:%)	674 (34.07)	728 (21.62)	0.0001
A (n:%)	1,021 (51.6)	1,653 (49.10)	0.08
N (n:%)	860 (43.47)	2,222 (66.01)	0.0001
G (n)	1,978	3,366	/
STOP-BANG components (n)	3 (2–5)	5 (4–6)	0.0001
STOP	2 (1–3)	3 (2–3)	0.0001
BANG	1 (1–2)	2 (2–3)	0.0001
AHI ev/h (±SD)	13.7 ± 13.5 (95% CI 9–10.3)	22.3 ± 18.6 (95% CI 16.1–18)	0.0001
ODI ev/h (±SD)	14.5 ± 13.9 (95% CI 10–11)	22.8 ± 18.3 (95% CI 17–18.5)	0.0001
T< 90% (%TRT)	5 (1–21) (95% CI 4–5)	11 (2–29) (95% CI 9–11)	0.0001
AHI > 15 ev/h (n:%)	602 (30.43)	1,835 (54.5)	0.0001

Abbreviations: Abbreviations: STOP-BANG components (S, snoring; T, tiredness; O, observed apnea; P, high blood pressure; B, body mass index; A, age; N, neck circumference; G, gender); 95% CI, 95% confidence interval; AHI, apnea-hypopnea index per hour of record; BMI, body mass index (Kg/m2); ESS, Epworth sleep scale; ODI, oxygen desaturation index O2 3%. Notes: T<90%: time with oxygen saturation below 90% (as a percentage of valid total recording time: TRT). Ev/h: events recorded per hour.standard deviation (SD). The interquartile range is shown between parenthesis (25–75%).

Statistical Analysis

We performed a descriptive statistical analysis showing the mean or median value and their measures of variability (standard deviation [SD], 95% confidence interval [CI], or 25–75%) depending on the distribution of variables. We calculated the area under the receiver operating characteristic (ROC) curve and the sensitivity (S), specificity (Sp), positive likelihood ratio (PLR), and negative likelihood ratio (NLR) of the SBQ, Berlin, and Epworth (test method) as compared with ≥15 ev/h AHI (reference method) in men and women. According to DeLong et al., the best S/Sp relationship was obtained with the AUC-ROC analysis (binomial exact CI).[19] A pairwise comparison was used to analyze the differences between AUC-ROC obtained from different questionnaires.

The relationship between SBQ and a ≥15 ev/h AHI was analyzed with multiple logistic regression expressing the odds ratio (OR) with the corresponding 95% CI for each component, considering the following dichotomic variables: snoring, tiredness, observed apneas, hypertension, BMI ≥ 35 kg/m^2, age > 55 years, neck circumference (≥40 cm in women, or ≥ 42 cm in men). A p-value < 0.05 was considered significant.

The statistical analysis software used was Prism v.8.02 (GraphPad, La Jolla, CA, USA).

Results

We studied 7,257 patients with suspected OSA referred for RP, of which 1,913 were excluded for not meeting inclusion criteria or having incomplete questionnaires. Finally, we analyzed 5,344 patients, out of whom 1,978 (37%) were women (►**Table 1**).

The median age was 55 years in women, with a mean BMI of 32.6 kg/m^2. ►**Table 1** shows the characteristics of the study population.

The prevalence of moderate to severe OSA was 30.4% (602) in women and 54.5% (1,835) in men, $p = 0001$. In women, the mean of SBQ components was 3 points, and for ESS it was 8 points (28% with >10 points), while 87% patients presented high-risk for OSA according to the Berlin questionnaire.

Performance of SBQ to Identify ≥15 ev/h AHI

Any combination of 3 SBQ components showed better sensitivity and specificity for ≥15 ev/h AHI in women (S: 65, 95% CI: 61–69, Sp: 61, 95% CI: 59–64, AUC-ROC: 0.67), as shown in ►**Table 2**. In men, the best performance was obtained with 4 components (S: 67, 95% CI: 67–71, Sp: 55, 95% CI: 53–58, AUC-ROC: 0.66), as shown in ►**Table 3**.

Table 2 Sensitivity and specificity of STOP-BANG in women.

Criteria	Sensitivity	95% CI	Specificity	95% CI	PLR	95% CI	NLR	95% CI	PPV	NPV
≥0	100	99.4–100.0	0	0.0–0.3	1				30.5	
>0	100	99.4–100.0	0.95	0.5–1.6	1.01	0.6–1.7	0		30.7	100
>1	97.34	95.7–98.5	11.27	9.6–13.1	1.1	0.9–1.3	0.24	0.1–0.4	32.4	90.6
>2	84.55	81.4–87.3	35.05	32.5–37.6	1.3	1.2–1.4	0.44	0.4–0.5	36.3	83.8
>3*	65.12	61.2–68.9	61.53	58.9–64.1	1.69	1.6–1.8	0.57	0.5–0.6	42.6	80.1
>4	39.87	35.9–43.9	80.95	78.8–83.0	2.09	1.9–2.3	0.74	0.7–0.8	47.8	75.5
>5	16.28	13.4–19.5	94.11	92.7–95.3	2.76	2.3–3.3	0.89	0.7–1.1	54.7	72
>6	3.16	1.9–4.9	98.98	98.3–99.4	3.1	2.0–4.8	0.98	0.6–1.6	57.6	70
>7	0	0.0–0.6	100	99.7–100.0			1			69.5

Abbreviations: 95% CI, 95% confidence interval; PLR, positive likelihood ratio; NLR, negative likelihood ratio; PPV, positive predictive value; NPV, negative predictive value. **Notes:** *Best cut-off point for sensitivity/specificity of STOP-BANG questionnaire.

Table 3 Sensitivity and specificity of STOP-BANG in men.

Criteria	Sensitivity	95% CI	Specificity	95% CI	PLR	95% CI	NLR	95% CI	PPV	NPV
≥1	100	99.8–100.0	0	0.0–0.2	1				54.5	
>1	99.4	98.9–99.7	1.57	1.0–2.3	1.01	0.7–1.5	0.38	0.2–0.7	54.8	68.6
>2	95.8	94.8–96.7	11.82	10.2–13.5	1.09	0.9–1.2	0.35	0.3–0.4	56.6	70.2
>3	86.38	84.7–87.9	29.92	27.6–32.3	1.23	1.1–1.3	0.46	0.4–0.5	59.6	64.7
>4*	68.99	66.8–71.1	55.58	53.1–58.1	1.55	1.5–1.6	0.56	0.5–0.6	65.1	59.9
>5	43.6	41.3–45.9	79.29	77.2–81.3	2.11	2.0–2.2	0.71	0.6–0.8	71.6	54
>6	20.16	18.3–22.1	93.14	91.8–94.4	2.94	2.7–3.2	0.86	0.7–1.0	77.9	49.3
>7	4.09	3.2–5.1	99.28	98.7–99.6	5.69	4.6–7.1	0.97	0.5–1.7	87.2	46.3
>8	0	0.0–0.2	100	99.8–100.0			1			45.5

Abbreviations: 95% CI, 95% confidence interval; PLR, positive likelihood ratio; NLR, negative likelihood ratio; PPV, positive predictive value; NPV, negative predictive value. **Notes:** *Best cut-off point for sensitivity/specificity of STOP-BANG questionnaire.

Table 4 AUC-ROC, sensitivity, and specificity of SBQ, ESS, and high-risk Berlin variables in women and men.

Questionnaires	Women			Men			
SBQ components	AUC-ROC (±SD)	Sensitivity	Specificity	AUC-ROC (±SD)	Sensitivity	Specificity	*p*-value
S	0.55 ± 0.12	65.2 (61.2–68.9)	44.5 (41.9–47.2)	0.60 ± 0.006	70.7 (68.6–72.8)	37.5 (35.1–40)	0.0001
T	0.58 ± 0.06	74.6 (70.9–78)	25.7 (23.4–28.4)	0.58 ± 0.007	58.5 (56.2–60.7)	57.5 (55–60)	0.78
O	0.52 ± 0.12	40.8 (36.9–44.9)	68.9 (66.4–71.3)	0.59 ± 0.08	58.5 (56.2–60.7)	57.5 (55–60)	0.001
P	0.53 ± 0.05	59.4 (55.4–63.4)	56.6 (54–59.3)	0.61 ± 0.006	61.2 (59–63.5)	52.9 (50.4–55.4)	0.001
B	0.52 ± 0.04	45.0 (41–49)	70.8 (68.3–73.2)	0.57 ± 0.05	29.2 (27.2–31.4)	87.5 (85.8–89.1)	0.001
A	0.53 ± 0.05	63.6 (59.6–67.5)	53.6 (50.9–56.3)	0.59 ± 0.06	53.9 (51.6–56.2)	56.6 (54.1–59.1)	0.001
N	0.51 ± 0.05	57.6 (53.6–61.6)	62.7 (60.1–65.3)	0.64 ± 0.006	75.4 (73.4–77.4)	45.2 (42.7–47.8)	0.001
G	/	/	/	/	/	/	/
Other questionnaires							
ESS > 10 points	0.53 ± 0.04	92.6 (91.7–93.7)	13.1 (11.9–14.4)	0.52 ± 0.06	23.9 (22.2–25.6)	86.1 (84.8–87.4)	0.43
High-risk Berlin score	0.58 ± 0.06	77.0 (75.3–78.7)	39.9 (38.2–41.7)	0.63 ± 0.06	70.6 (68.8–72.5)	55.6 (53.8–57.4)	0.001

Abbreviations: AUC-ROC, area under the ROC curve; O, observed apnea; P, pressure: hypertension; S, snoring; T, tiredness. B, body mass index (BMI) >35 kg/m^2, A, age > 55; N, neck > 40cm in women or > 42cm in men; G, gender: male; ESS, Epworth sleep scale. **Notes:** ± standard deviation (SD). The 95% CI is shown between parentheses.

For the same number of components, Sp was higher, but S was lower in women in the diagnosis of moderate to severe OSA. ►**Table 4** shows the relationship between ≥15 ev/h AHI and the analysis of 7 SBQ components (except gender).

Performance of the Berlin Questionnaire to Identify ≥15 ev/h AHI

This questionnaire did not perform as well as SBQ to identify ≥15 ev/h AHI, but its Sp was higher than that of ESS, with a S: 77 (95% CI: 75–78) and a Sp: 40 (95% CI: 38–42), as shown in ►**Table 4**. Likewise, its discriminative power was higher in men (AUC-ROC 0.63 ± 0.06 vs. 0.58 ± 0.06, $p = 0.001$).

Performance of Epworth Questionnaire to Identify ≥15 ev/h AHI

The ESS presented the poorest performance to identify ≥15 ev/h AHI, with a S: 93 (95% CI: 92–94) and a Sp: 13 (95% CI: 11–14), as shown in ►**Table 4**. Its discriminative power was similar between genders (AUC-ROC 0.52 ± 0.06 vs. 0.53 ± 0.04, $p = 0.43$).

Comparison of Differences in AUC-ROC Obtained from the Questionnaires for ≥15 ev/h AHI in Women

The differences in the AUC-ROC results were statistically significant ($p = 0.0001$) when comparing SBQ with Berlin (15% ± 0.006) and SBQ with ESS (17.5% ± 0.008). On the other hand, the difference between high-risk Berlin and >10 ESS was smaller (2.5% ± 0.007, $p = 0.0004$). ►**Figure 2** compares the AUC-ROC of the different questionnaires to predict moderate to severe OSA in women.

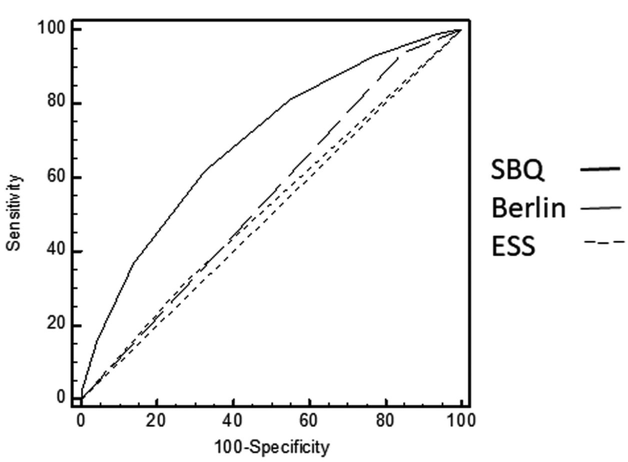

Fig. 2 Comparison of AUC-ROC corresponding to SBQ, Berlin questionnaire, and ESS, to discriminate AHI ≥15 ev/h in women.

Multiple Logistic Regression Analysis

►**Table 2** shows the prediction model for SBQ to diagnose moderate to severe OSA.

As shown in ►**Table 5**, the four variables with the highest discriminatory ability to identify ≥15 ev/h AHI were hypertension with an OR: 1.93 (95% CI: 1.59–2.35; $p = 0.003$); BMI > 35 with an OR: 1.92 (95% CI: 1.53–2.39; $p = 0.001$); neck circumference > 40 cm, with an OR: 1.90 (95% CI: 1.54–2.34; $p = 0.001$); and age > 55 years, with an OR: 2.35 (95% CI: 1.90–2.89; $p = 0001$).

Discussion

In this study, we describe the performance of standard questionnaires to diagnose moderate to severe OSA with focus on the female population.

We found moderate to severe OSA with a prevalence of >30% in women, which is higher than the percentage reported in the literature. The HypnoLaus[2] study reported an estimated prevalence of 23.4%, while a study conducted in South America[3] reported 9.6%. The fact that a nonprobabilistic sampling method was used could account for this, as older women (median age of 55 years) with a higher prevalence of obesity, and cardiovascular risk factors were included.

A result in the SBQ of 3 or more components in any combination showed the best performance to identify ≥15 ev/h AHI, with hypertension, BMI, neck circumference, and age as the variables with the strongest discriminative power.

An interesting finding was that with the same number of components, women showed a higher Sp. Likewise, Mou et al. reported that SBQ has an extremely low Sp in men with the cut-off value of ≥ 3 components. They suggested that alternative scoring systems should be used and identified the need to develop optimal values, especially for BMI in women and neck circumference in men.[20]

Table 5 Multiple regression logistic for SBQ components in women.

Variables	OR	95% CI	*p*-value
Snoring	1.33	1.08–1.64	0.0072
Tiredness	0.94	0.75–1.18	0.6169
Observed apneas	1.47	1.19–1.82	0.0003
Hypertension	1.93	1.59–2.35	0.0001
BMI > 35 kg/m^2	1.92	1.53–2.39	0.0001
Age > 55 years old	2.35	1.90–2.89	0.0001
Neck > 40 cm	1.90	1.54–2.35	0.0001

Abbreviations: BMI, body mass index (kg/m^2); OR/CI 95%, odds ratio/95% confidence interval; SBQ, STOP-BANG questionnaire.

The high S of SBQ makes it useful as a screening tool for OSA. However, this questionnaire has a poor Sp (43% for AHI ≥15 ev/h in both genders according to the original description)[10] and false positives. This could lead to unnecessary sleep unit referrals and longer waiting lists. In our series, there was a higher Sp in women (61.53%, 95% CI: 58.9–64.1) and a higher negative predictive value for 3 components in any combination as a predictor of OSA.[21]

In a study conducted in 350 patients with cardiovascular risk evaluated with polysomnography, Pataka et al. described a similar S/Sp ratio for SBQ in women, showing different performance between sexes. They suggested that a gender-adjustment should be applied for interpretation purposes.[13] Besides, male sex is an intrinsic component of SBQ, which assigns a higher final score to men without accounting for other sex-related aspects or clinical signs.[22,23]

Taking this into consideration, to define a prioritization strategy when referring women to sleep tests, we could use four variables: age, BMI, neck circumference, and a history of hypertension.[24,25]

According to our findings, ESS was not very useful to screen women for OSA due to the low frequency of daytime sleepiness (<30%). Drowsiness, although reported by a significant number of patients, presented a low Sp and may be caused by other prevalent causes like stress and depression[4–22]. Finally, the Berlin questionnaire showed a lower discriminative power, as compared with SQB (3 components) in women (AUC-ROC: 0.58 vs. 0.0.67), and less Sp, which results in lower clinical usefulness.

Our study has multiple limitations. First, this is a single-center retrospective study with the limitations inherent to its nature. Second, patient selection may have been subject to bias since the population was referred due to a clinical suspicion of OSA and is not representative of the general population. Third, we used as a reference the AHI obtained from outpatient tests, whose underestimation rate is 15 to 20%.[18–26] Fourth, our approach relied on a self-recorded history of hypertension (SBQ) without objective records. Fifth, we did not have a validation group. Finally, we are not considering menopausal status, which could also play a role in the prevalence of OSA.

Conclusions

The questionnaires used to screen for moderate to severe OSA perform differently in women. Therefore, a gender-based approach is necessary. In women, the SBQ's discriminative power was larger than that of the ESS and Berlin tests, and it showed more Sp. Three of the SBQ components in any combination showed the best performance to identify OSA, with higher age, BMI, neck circumference, and hypertension as the most powerful predictors.

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Conflict of Interests
The authors have no conflict of interests to declare.

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