Application of Neck Circumference in Four-Variable Screening Tool for Early Prediction of Obstructive Sleep Apnea in Acute Ischemic Stroke Patients

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Background: The purpose of this study was to validate and pilot the use of the four-variable screening tool (4V) and modified 4V tools to identify acute ischemic stroke and transient ischemic attack (TIA) patients at high risk of obstructive sleep apnea (OSA). *Methods:* Two modified scales, 4V-1 (ie, using neck circumference instead body mass index, regardless of gender) and 4V-2 (ie, as above but scored differently according to gender) were designed. These tools were used in a consecutive cohort of 124 acute ischemic stroke/TIA patients, together with the 4V-1, 4V-2, 4V, as well as the STOP-BANG, the Berlin questionnaire, and the Epworth Sleepiness Scale (ESS). Objective level 2 or level 3 polysomnography was used to confirm OSA and its severity. Both questionnaires and polysomnography were completed within 1 week from symptom onset. *Results:* Area under the curve (AUC) of 4V was 0.807 ($P < .0001$) while AUC of STOP-BANG, Berlin Questionnaire and ESS were .701 ($P < .0001$), .704 ($P < .0001$) and .576 ($P = .1556$), respectively. AUC of 4V was greater than of STOP-BANG ($z = 2.200$, $P = .0220$), Berlin ($z = 2.024$, $P = .0430$) and ESS ($z = 3.363$, $P = .0003$). AUC of modified 4V-1 and modified 4V-2 were .824 ($P < .001$) and .835 ($P < .001$), respectively. Performance of modified 4V-2 was higher versus modified 4V-1 ($z = 2.111$, $P = .0348$) and higher but not significantly so to regular 4V ($z = 1.784$, $P = .0744$). *Conclusions:* Neck circumference scored by gender is a useful substitution to body mass index in the 4V when screening OSA at early stages of ischemic stroke/TIA patients.

Key Words: Obstructive sleep apnea—acute ischemic stroke—transient ischemic attack—four-variable screening tool

Introduction

Obstructive sleep apnea (OSA) is common in ischemic stroke and transient ischemic attack (TIA) patients, affecting 60%-80% after a cerebrovascular event.[1,2] OSA is not only a well-established independent risk factor for stroke, but is also associated with a poorer functional outcome, a worsen quality of life and, most importantly an increased risk of recurrent stroke and subsequent mortality.[3,4] In spite of this however, as many as 70%-80% of ischemic stroke and TIA patients with OSA are neither diagnosed nor treated.[1] Not surprisingly, ischemic stroke and TIA prevention guidelines, including the American Heart Association/American Stroke Association guidelines for the prevention of stroke,[1] the Canadian Stroke Best Practice Recommendations,[5] the American Academy of Sleep Medicine (AASM) clinical practice guidelines,[6] as well as the Chinese guidelines for secondary prevention of ischemic stroke and TIA,[7] recommend screening and treating OSA in those patients.

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Although there is little data about the long-term effects of OSA therapy in patients with ischemic stroke or TIA, several studies suggests that early treatment improves stroke-specific outcomes including stroke severity, functional status, and recurrence of vascular events.[8-10] Most notably, a randomized trial evaluated use of early continuous positive airway pressure (CPAP) among 70 patients with acute TIA and found that vascular event rate decreased as CPAP use increased (8% among patients with no CPAP use, 6% among patients with some CPAP use, and 0% among patients with good CPAP use).[1,11] Based on these results, it is likely that OSA is important to recognize and treat in patients with acute ischemic stroke or TIA.

Although the gold standard for diagnosing OSA is polysomnography (PSG), it is often difficult to systematically conduct PSGs in this population due to limited access, cost, and technical difficulties secondary to motor deficits. A reasonable alternative may thus be that to only use PSG in high-risk patients first screened by questionnaire. Unfortunately however, clinical manifestations of OSA in acute ischemic stroke or TIA patients have been shown to be atypical,[8,12,13] making usual OSA screening tools such as Epworth Sleepiness Scale or Berlin Questionnaire unreliable[13,14] be not reliable. For this reason, a four-variable screening tool was recently designed and validated, showing only moderate predictability for OSA when used within 180 days of a stroke/TIA.[15] In our clinical practice, we noticed that body mass index (BMI), one of the variables of the four-variable screening tool, was often difficult to accurately measure in the acute stroke patients due to mobility issues. In contrast, neck circumference, another risk factor of OSA that correlates with BMI[16-18] can easily be obtained. We therefore modified the 4-variable screen tool, by substituting BMI with neck circumference, and evaluated if the modified four-variable screening tool could predict OSA in patients with acute stroke/TIA patients.

Methods

Ethical Approval

The study was approved by the Ethics Committee of Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, China. Written informed consent was obtained from all patients.

Subjects

Patients diagnosed with ischemic stroke or TIA were admitted to the Department of Neurology, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, China, from June 2016 to May 2017. A diagnosis of ischemic stroke was made according to clinical criteria, and tissue-based definition (negative MR diffusion-weighted imaging) was used for TIA. Head computerized tomography scans were used for every subject to exclude hemorrhagic stroke. Patients were excluded if they had: (1) moderate/severe pulmonary disease or congestive heart failure that could compromise accuracy of a level 3 PSG, (2) any medical device that would interfere with placement of the device, or (3) decreased consciousness (ie, the 1a score of NIH stroke scale [NIHSS] > 0), severe stroke (ie, NIHSS > 25), or cognitive impairment/aphasia which made questionnaires impossible.

Sleep Apnea Screening Questionnaires

Patients completed the 4V (plus modified 4V), STOP-BANG, Berlin questionnaire, and Epworth sleepiness scale within 1 week of symptom onset of their ischemic stroke/TIA.

Four-Variable Screening Tool

The 4V has been validated for the identification and assessment of moderate to severe sleep-disordered breathing. Four variables (sex, BMI, blood pressure, and snoring) are used to generate a score ranging from 2 to 18. Because BMI is difficult to assess in patients with limited mobility, it was estimated by the patients. In present study, BMIs of 84 stroke patients were calculated by self-reported weight and height.

Several studies have shown that neck circumference correlates strongly with BMI and is a useful marker for obesity. We therefore modified the 4V by replacing BMI by neck circumference. Neck circumference was measured using a flexible ruler tape on the midpoint of the neck at the level of the thyroid cartilage, with a participant's body lying, eyes facing forward, and normal breathing. This produced 2 types of modified 4V (ie, modified 4V-1 and modified 4V-2) depending if gender was considered as a covariate. The scoring methodology for 4V, modified 4V-1, and modified 4V-2 that uses BMI or neck circumference is summarized in Table 1.

STOP-BANG Questionnaire

Previous literature has validated the STOP-BANG questionnaire in identifying sleep-disordered breathing. The STOP-BANG questionnaire includes first 4 "yes/no" questions: (1) do you snore? (2) do you feel tired, fatigue, or sleepy during the day? (3) Has anyone observed you stop breathing in your sleep? (4) Do you have high blood pressure? For the first 4 "yes/no" questions, a response of "yes" is given one point. An additional one point is awarded for each of the following conditions: BMI of more than 35 kg/m^2, age of 50 years or greater, neck circumference greater than 40 cm, and a final point for patients who are male. STOP-BANG questionnaire generates a score ranging from 0 to 8.

Table 1. *The scores of 4V, modified 4V-1, and modified 4V-2 from BMI or neck circumference*

Score	4V (BMI, kg/m^2)	Modified 4V-1 (neck circumference, cm)	Modified 4V-2 (neck circumference, cm)	
			Male	Female
1	<21	<35	<36	<34
2	21-22.9	35-35.9	36-36.9	34-34.9
3	23-24.9	36-36.9	37-37.9	35-35.9
4	25-26.9	37-37.9	38-38.9	36-36.9
5	27-29.9	38-38.9	39-39.9	37-37.9
6	≥30	≥39	≥40	≥38

Abbreviations: 4V, the four-variable screening tool; BMI, body mass index

Berlin Questionnaire

The Berlin questionnaire was scored according to the original algorithm proposed by Netzer et al,[19] which classified patients either as at high or low risk of OSA. The Berlin questionnaire generates a score ranging from 0 to 3.

Epworth Sleepiness Scale

The Epworth Sleepiness Scale (ESS) was designed to evaluate overall daytime sleepiness. The questionnaire asks respondents to rate how likely they are to fall asleep in 8 different situations. Each circumstance represents a moment of relative inactivity, from lying down for a nap in the afternoon to sitting in a car stopped in traffic. The scale has been validated with a population of adults with ages ranging from 18 to 78 years. Total scores range from 0 to 24.

Objective Sleep Apnea Detection

After completion of all questionnaires, a level 2 PSG (PSG-1100, Nihon Kohden, 1-31-4 Nishiochiai, Shinjuku-ku, Tokyo 161-8560, Japan) or level 3 PSG (Alice PDx, Philips Respironics, Pittsburgh, Pennsylvania, USA) was performed in the hospital inpatient room. Level 3 PSG was performed in the majority of our patients (102 of 124, 82.2%). Both PSG machine setups recorded chest and abdominal respiratory movements, nasal pressure and oral thermistor, oxygen saturation, heart rate, and body position. For level 2 PSG, sleep duration was measured according to *AASM Manual for the Scoring of Sleep and Associated Events*. For level 3 PSG, we used an actigraphy at the same time to measure the sleep duration. Sleep onset was estimated by noting the sustained cessation of movement of the wrist (nonparalytic side) on the actigraphy tracing, and rousing was noted by the appearance of wrist movements on the tracing. Overnight sleep data were analyzed manually by a sleep technologist who was blinded to the other study data. Apnea and hypopnea criteria used were per by the AASM recommended (Medicare) criteria. Apneas were defined as a drop in the peak signal excursion by greater than or equal to 90% of the pre-event baseline that lasted for greater than or equal to 10 seconds. Hypopneas were defined as a reduction in the peak signal excursion of greater than or equal to 30% for greater than or equal to 10 seconds with a corresponding oxygen desaturation event of greater than or equal to 4%. The apnea-hypopnea index (AHI) was calculated from the total apneic and hypopneic events detected per hour of the recorded night data. Our definition for OSA was an AHI greater than or equal to 10, a cut-off for which the level 3 PSG has been demonstrated to be highly sensitive and specific for the detection of OSA.

Statistical Analysis

Statistical analysis was performed using SPSS version 23.0 software (SPSS Inc.) and MedCalc Version 17.9.5 software. Mean and standard deviation were calculated for normally distributed continuous variables and compared using unpaired *t* tests. Median and interquartile ranges were calculated for nonnormal and ordinal data and compared values using Mann-Whitney *U* tests. Frequency counts were computed for categorical variables and compared using chi-squared tests. Receiver operating characteristic (ROC) curves were computed for each OSA screening tool for our definitions of OSA. Area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were computed at each cut-off score. Youden indexes (max [sensitivity + specificity − 1]) were created by MedCalc. We also compared AUCs among the different screening questionnaires, using Egger's method (algorithm described by DeLong et al).[20] For this analysis, statistical significance was defined as $P < .05$.

Results

Baseline Demographics

A total of 124 patients, 80 (64.5%) of whom were male, were recruited for the present study, and completed overnight level 2 or level 3 PSG examination within 1 week of their cerebrovascular events. Clinical and laboratory characteristics of study participants are summarized in Table 2. Mean (±SD) age, BMI, and neck circumference of the recruited patients were 62.6 ± 12.6 years, 25.1 ± 3.6 kg/m^2, and 37.6 ± 2.6 cm, respectively. Among recruited patients, 109 patients (87.9%) had an ischemic stroke, while only 15 (12.1%) had a TIA. Using our definition of OSA (AHI ≥ 10),

Table 2. *Clinical and some laboratory characteristics of study participants*

	Total or mean	OSA	Non-OSA	*P*
Cases (*n*)	124	85	39	
Male (%)	80 (64.5%)	58 (68.2%)	22 (56.4)	.201
Age, years (SD)	62.6 (12.6)	63.7 (13.2)	60.6 (11.2)	.198
AHI, median (range), IQR	19.6 (.9-68.9), 26.6	6.1 (.9-9.6), 5.2	25.5(10.8-68.9), 21.8	**<.001**
BMI	25.1 (3.6)	26.2 (3.3)	22.7 (3.0)	**<.001**
Neck circumference (cm)	37.6 (2.6)	38.5 (2.3)	35.6 (2.1)	**<.001**
Smoking	41 (33.1%)	30 (35.3)	11 (28.2)	.436
Alcohol consumption	22 (17.7)	14 (16.5)	8 (20.5)	.584
Hypertension	101 (81.5%)	78(91.8%)	23(59.0%)	**<.001**
Diabetes mellitus	47 (37.9%)	36 (42.4)	11 (28.2)	.132
Atrial fibrillation	11 (8.9%)	10 (11.8%)	1 (2.6%)	.183
Coronary heart disease	8 (6.5%)	7 (8.2%)	1 (2.6%)	.424
History of stroke	21 (16.9%)	13 (15.3%)	8 (20.5%)	.472
Wake-up stroke	33 (26.6%)	27 (31.8%)	6 (15.4%)	**.055**
Progressive stroke	9 (7.3%)	8 (9.4%)	1 (2.6%)	.321
TIA	15 (12.1)	8 (9.4%)	7 (17.9)	.290
Ischemic stroke	109 (87.9%)	77 (90.6%)	32 (82.1%)	.290
Cortical	42 (33.9%)	29 (34.1%)	13 (33.3%)	.932
Subcortical	69 (55.6%)	43 (50.6%)	26 (66.7%)	.094
Brainstem	12 (9.7%)	10 (11.8%)	2 (5.1%)	.405
Cerebellar	13 (10.5%)	10 (11.8%)	3 (7.7%)	.710
NIHSS	2.6 (3.0)	2.7 (2.9)	2.2 (3.4)	.397
Homocysteine	13.4 mmol/L (8.4)	13.8 mmol/L (8.3)	12.7 mmol/L (8.7)	.510
CRP median (range), IQR	2.0 mg/L (.2-68.5), 4.7	2.1 mg/L (.3-68.5), 9.8	1.4 mg/L (.2-16.5), 2.8	**.018**
Hemoglobin A1c	6.4% (1.4)	6.6% (1.5)	5.9% (1.1)	**.020**

Abbreviations: AHI, apnea-hypopnea index; BMI, body mass index; CRP, C-reactive protein; NIHSS, National Institute of Health stroke scale; TIA: transient ischemic attack.

The BOLD values at the "*P*" column: significantly different between OSA and non-OSA.

85 patients (68.5%) were diagnosed as OSA. OSA prevalence between ischemic patients (77 cases, 70.6%) and TIA patients (8 cases, 53.3%) were not significantly different ($X^2 = 1.117$, $P = .290$). When compared to the patients without OSA, patients with OSA had higher BMI ($t = 5.722$, $P < .001$), higher neck circumference ($t = 6.589$, $P < .001$), and were more likely to have a history of hypertension ($X^2 = 19.026$, $P < .001$). Wake-up stroke (ie, ischemic events happening during sleep) had a prevalence of 31.8% (27 cases) in patients with OSA versus 15.4% (6 cases) without OSA, a difference that approached significance ($X^2 = 3.673$, $P = .055$). Although diabetes mellitus in patients with OSA (36 cases, 42.4%) was not higher than in patients without OSA (11 cases, 28.2%; $X^2 = 2.274$, $P = .132$), hemoglobin A1c level of patients with OSA (6.6 ± 1.5%) was higher than in patients without OSA (5.9 ± 1.1%; $t = 2.352$, $P = .020$). Moreover, CRP level in patients with OSA (median 2.1) was also significantly higher versus patients without OSA (median 1.4) ($z = 2.372$, $P = .018$). Cerebrovascular diseases risk factors, such as smoking, alcohol consumption, atrial fibrillation, coronary heart disease, and a history of stroke and blood homocysteine level showed no significant differences in patients with and without OSA. Stroke locations and severities (NIHSS scores) are also displayed in Table 2. Other demographic data, such as age and gender, were similar in patients with and without OSA.

Comparison Among the Common Screening Tools

Figure 1 displays ROC curves for predicting OSA of common screening tools, while Table 3 provides the corresponding AUCs, Youden indexes, as well as the cutoffs, sensitivities, specificities, PPVs, and NPVs at the Youden

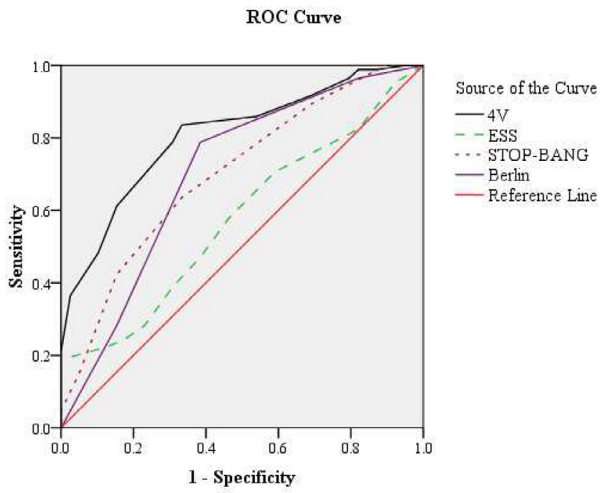

Figure 1. *Receiver operating characteristic curve for common OSA screening tools. Abbreviations: 4V: the four-variable screening tool; ESS, the Epworth Sleepiness Scale.*

Table 3. *Comparison among the common OSA screening tools*

		4V	STOP-BANG	Berlin	ESS
AUC (95%CI)		.807 (.726-.872)	.701 (.612-.780)	.704 (.615-.782)	.576 (.484-.664)
vs Reference line	*P*	**<.0001***	**<.0001***	**<.0001***	.1556
	z	7.723	4.087	3.930	1.420
vs 4V	*P*		**.0220#**	**.0430#**	**.0003#**
	z		2.290	2.024	3.636
Youden index		.5020	.3020	.4036	.1882
Cut-off		>8	>3	>1	>9
Sensitivity, %		83.5	63.5	78.8	18.8
Specificity, %		66.7	66.7	61.5	100.0
PPV, %		84.5	80.6	81.7	100
NPV, %		65.0	45.6	57.1	36.1

Abbreviations: 4V, the four-variable screening tool; AUC, area under receiver operating characteristic curve; ESS, the Epworth Sleepiness Scale; NPV, negative predictive value; PPV, positive predictive value.
*$P < 0.05$, compared with reference line.
#$P < 0.05$, compared with 4V.

indexes. Among screening tools, 4V has the greatest AUC (.807, $z = 7.723$, $P < .0001$, vs reference line). AUCs of STOP-BANG and Berlin questionnaire were .701 ($z = 4.087$, $P < .0001$) and .704 ($z = 3.930$, $P < .0001$), respectively, which are greater than reference line. AUC of ESS was only .576 ($z = 1.420$, $P = .1556$) and had no predictability. The AUC of 4V was greater than that of the STOP-BANG ($z = 2.290$, $P = .0220$), the Berlin questionnaire ($z = 2.024$, $P = .0430$) and the ESS ($z = 3.636$, $P = .0003$). As a result, the 4V questionnaire had the greatest sensitivity, specificity, PPV, and NPV when using cutoffs of Youden indexes (ESS excluded).

Comparison Among the 4 V, Modified 4V-1, and Modified 4V-2

Figure 2 displays ROC curves for 4V, modified 4V-1, and modified 4V-2, while Table 4 provides corresponding AUCs, Youden indexes, as well as the cutoffs, sensitivities, specificities, PPVs, and NPVs. The AUCs of 4V (.807, $z = 7.723$, $P < .0001$), modified 4V-1 (.824, $z = 8.588$, $P < .0001$), and modified 4V-2 (.835, $z = 9.147$, $P < .0001$) were all larger than the reference line, indicating significant predictability. The AUCs of the 4V and modified 4V-1 did not differ significantly ($z = 1.067$, $P = .2861$). The AUC of the modified 4V-2 was significantly higher versus that of the 4V-1 ($z = 2.111$, $P = .0348$) and close to significantly higher versus reference 4V AUC($z = 1.784$, $P = .0744$), Based on these results, and known OSA prevalence in acute stroke/TIA patients, cutoffs for these tools can be selected according to Youden indexes and optimal criterion (taking into account disease prevalence and cost of false and true positive and negative decisions): 4V greater than 8 according to Youden index and optimal criterion, modified 4V-1 greater than 9 (based on Youden index) or greater than 7 (based on optimal criterion), and modified 4V-2 greater than 10 (based on Youden index) and greater than 7 (based on optimal criterion). Sensitivities, specificities, PPVs, and NPVs at these different cutoffs are summarized in Table 4.

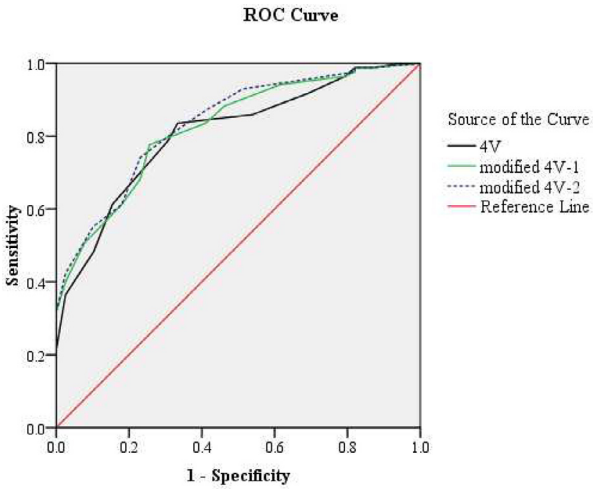

Figure 2. *Receiver operating characteristic curve for the 4V, modified 4V-1, and modified 4V-2. Abbreviation: 4V, the four-variable screening tool.*

Discussion

In the present study, we used consecutive participants from a single center to investigate whether various questionnaire screening tools could predict the presence of OSA in acute ischemic stroke/TIA. To do so, we first compared commonly used OSA screening tools in acute ischemic stroke/TIA patients. We then next created 2 types of modified 4V (modified 4V-1 and modified 4V-2) replacing the BMI in 4V by neck circumference. Gender was taken into consideration for scoring in modified 4V-2, but not in modified 4V-1. In addition, our study confirmed the high rate of OSA in poststroke or TIA patients, occurring in 60%-80% of patients versus 20%-26% of the general population has OSA.[21,22] To our knowledge, our study is the first to evaluate and compare various OSA screening tools in ischemic stroke/TIA patients while still in acute phase, as early as 1 week following cerebrovascular events.

Table 4. *Comparison among the 4V, modified 4V-1, and modified 4V-2*

		4V	Modified 4V-1	Modified 4V-2
AUC (95%CI)		.807 (.726-.872)	.824 (.745-.887)	.835 (.758-.896)
vs Reference line, *P* (*z*)		**<.0001 (7.723)***	**<.0001 (8.588)***	**<.0001 (9.149)***
vs 4V, *P* (*z*)			.2861 (1.067)	.0744 (1.784)
vs Modified 4V-1, *P* (*z*)				**.0348 (2.111)#**
Youden index (Cut-off)		.5020 (>8)	.5201 (>9)	.5104 (>10)
Cut-off > 7	Sensitivity, % (95% CI)	85.9 (76.6-92.5)	88.2 (79.4-94.2)	92.9 (85.3-97.4)
	Specificity, % (95% CI)	46.2 (30.1-62.8)	53.9 (37.2-69.9)	48.7 (32.4-65.2)
	PPV, % (95% CI)	77.7 (72.0-82.5)	80.6 (74.6-85.5)	79.8 (74.3-84.4)
	NPV, % (95% CI)	60.0 (44.5-73.7)	67.7 (52.3-80.1)	76.0 (57.9-88.0)
Cut-off > 8	Sensitivity, % (95% CI)	83.5 (73.9-90.7)	83.5 (73.9-90.7)	87.1 (78.0-93.4)
	Specificity, % (95% CI)	66.7 (49.8-80.9)	59.0 (42.1-74.4)	59.0 (42.1-74.4)
	PPV, % (95% CI)	84.5 (77.6-89.6)	81.6 (75.1-86.7)	82.2 (75.9-87.2)
	NPV, % (95% CI)	65.0 (52.3-75.9)	62.2 (48.8-73.9)	67.6 (53.2-79.4)
Cut-off > 9	Sensitivity, % (95% CI)	78.8 (68.6-86.9)	77.7 (67.3-86.0)	80.0 (69.9-87.9)
	Specificity, % (95% CI)	69.2 (52.4-83.0)	74.4 (57.9-87.0)	69.2 (52.4-83.0)
	PPV, % (95% CI)	84.8 (77.5-90.1)	86.8 (79.3-91.9)	85.0 (77.8-90.2)
	NPV, % (95% CI)	60.0 (48.6-70.4)	60.4 (49.6-70.3)	61.4 (49.7-71.8)
Cut-off > 10	Sensitivity, % (95% CI)	72.9 (62.2-82.0)	68.2 (57.2-77.9)	74.1 (63.5-83.0)
	Specificity, % (95% CI)	74.4 (57.9-87.0)	76.9 (60.7-88.9)	76.9 (60.7-88.9)
	PPV, % (95% CI)	86.1 (78.2-91.5)	86.6 (78.1-92.1)	87.5 (79.6-92.6)
	NPV, % (95% CI)	55.8 (45.9-65.2)	52.6 (43.8-61.3)	57.7 (47.8-67.0)
Cut-off > 11	Sensitivity, % (95% CI)	61.2 (50.0-71.6)	61.2 (50.0-71.6)	61.2 (50.0-71.6)
	Specificity, % (95% CI)	84.6 (69.5-94.1)	82.1 (66.5-92.5)	82.1 (66.5-92.5)
	PPV, % (95% CI)	89.7 (80.3-94.9)	88.1 (78.8-93.7)	88.1 (78.8-93.7)
	NPV, % (95% CI)	50.0 (42.6-57.4)	49.2 (41.7-56.8)	49.2 (41.7-56.8)

Abbreviations: 4V, the four-variable screening tool; AUC, area under receiver operating characteristic curve; NPV, negative predictive value; PPV, positive predictive value.

*$P < 0.05$, compared with reference line.

#$P < 0.05$, compared with 4V-1.

Among commonly used tools, 4V, STOP-BANG and Berlin questionnaire all had significantly higher AUCs in comparison to reference line. In contrast, the ESS did not predict OSA better than chance. Considering that only AUC above .8 can be considered "good" predictors, only the AUC of 4V, which reached .807, performed satisfactorily. With values of .701 and .704, respectively, performances of the STOP-BANG and Berlin questionnaires can only be rated as "fair" (.7-.8).

The low performance of the EES is only partially surprising. This EES scale is widely used in the field of sleep medicine as a subjective measure of a patient's sleepiness, a common behavioral morbidity associated with OSA in the general population with up to 87% of OSA patients with AHI greater than 10 reporting excessive sleepiness. Recent studies have however found that in some particular population, for example patients with chronic obstructive pulmonary disease or cerebrovascular disease, ESS only correlated weakly with OSA severity.[8,23-25] As an example, Parra et al[8] reported that in 126 ischemic stroke (within 3-6 days after the stroke) patients with moderate-severe OSA (AHI: 38.4 ± 13.7), mean ESS was 7.8, a normal value. Other researcher also demonstrated the majority of stroke patients with OSA do not present with excessive daytime sleepiness, and are statistically less likely to have a high ESS (10% vs 38%; $P < .001$) versus OSA cases of the general population.[12,26] Most recently, ESS has proven to only weakly predict the presence of OSA in ischemic stroke/TIA patients, with one study using a "SLEEP INventory" tool that performed better than the ESS.[21] Based on the literature and our results, it seems clear that the ESS is a poor predictor of OSA in acute ischemic stroke/TIA patients.

In contrast to the ESS that only probes sleepiness, the Berlin questionnaire was designed to specifically identify individuals at high risk for sleep apnea. This short survey focuses on 3 categories of apnea signs, symptoms, and consequences: snoring, daytime sleepiness, and high blood pressure.[27,28] The Berlin questionnaire accurately predicts the presence of PSG-defined OSA in primary care (sensitivity 86.0%, specificity 77.0%, and PPV 89.0%) [19,21] or cardiology clinics (sensitivity 86.0%, specificity 89.0%, and PPV 97.0%).[21] When applied to our stroke population (mixed ischemic and hemorrhagic) however, the Berlin questionnaire correlated less well with PSG-defined OSA (sensitivity 68.0%, specificity 59.0%, and PPV 59.0%)[14] than in these other populations. Boulos et al[15] similarly reported that the Berlin questionnaire did not predict the presence of OSA in patients with stroke (mixed ischemic and hemorrhagic) or TIA. Other studies have also found that the Berlin Questionnaire administered to stroke

patients had a generally low predictive utility for OSA.[29-31] In our acute ischemic stroke/TIA patients, the Berlin questionnaire displayed moderate sensitivity (78.8%) and relatively low NPV (57.1%), which made it of limited value to prescreen for the need for a formal PSG sleep study.

The STOP-BANG was designed to screen for symptoms of OSA in surgical patients as well as in the general population. Among preoperative obese patients, a STOP-BANG score of 4 identified severe OSA on PSG with both high sensitivity (87.5%) and NPV (90.5%), with a higher score being associated with increased specificity.[31,32] In the general population, the STOP-BANG has only a moderate sensitivity (66.2%) and specificity (74.7%), but has high NPV (85%) and low PPV (50.6%) for subjects with moderate to severe OSA.[32,33] When applied to patients with cerebrovascular disease, Sico et al[19,21] found lower sensitivity (35.3%) and NPV (41.7%) with very low AUC (.55). Boulos et al[15] similarly used the STOP-BAG (which does not include neck circumference), showing predictability but with a moderately predictive value at cutoffs that maximized sensitivity. In our cohort of acute stroke/TIA patients, the STOP-BANG only yielded moderate sensitivity (63.5%) and specificity (66.7%), a relatively high PPV (80.6%), but a low NPV (45.6%), which meant it was of limited value to predict the need for a PSG study.

The development of more specialized screening tools in acute ischemic stroke/TIA patients is mandated by the high prevalence and potential benefit of early treatment of OSA in this population and the poor performance of commonly OSA screening tools. In the present study, we found that 4V had a "good" level of AUC (.807), values which are significantly higher ($P < .05$) than AUCs of the Berlin questionnaire (.704) and of the STOP-BANG (.701). In addition, the 4V had a high sensitivity (83.5%) and PPV (84.5%), relatively low specificity (66.7%) and NPV (65.0%) using a cut-off point of 8. The 4V was designed by Takegami et al[34] and validated in Japanese patients for screening OSA, with an AUC of .90, sensitivity of .93, and specificity of .66, using a cut-off point of 11. Surprisingly, the predictive performance of 4V in our acute ischemic stroke/TIA patients was not as good as reported by Takegami et al,[34] probably partly because of differences in clinical features across poststroke OSA patients. Further, our data indicate that suitable cutoffs for the 4V may vary across patient populations.

As all 4 variables in the 4V are also included in the STOP-BANG, why did the 4V produce a higher predictive performance than the STOP-BANG? The 4V was initially applicated in Japanese population, which is more similar ethnically to Chinses population, whereas other tools (STOP-BANG, for example) typically developed for Caucasians. Blood pressure (a value from 1 to 4) and BMI (a value from 1 to 6) scoring points are more elaborate in the 4V than in the STOP-BANG. In the STOP-BANG, both blood pressure (based on a history of hypertension) and BMI (>35 kg/m^2) produce a score of 1 (otherwise the score is 0), which is likely too basic to predict OSA. To illustrate this point, the highest BMI in our acute ischemic stroke/TIA patient population was 32.4 kg/m^2, which made this variable essentially worthless in this population. Other lines of evidence indicate that multiple and differential cutoffs of BMI and neck circumference in the STOP-BANG should be used in Asian populations. Pavarangkul et al[35] reported for example that more appropriate cut-off points of BMI and neck circumference for Thai STOP-BANG questionnaires were 25 kg/m^2 and 36 cm, respectively. On the other hand, some publication suggests that the STOP-BANG has a higher sensitivity than the 4V in screening OSA in Caucasian population.[36] In addition, some other variables in the STOP-BANG which are not included in the 4V, such as age, have only limited value in cerebrovascular disease patients. A value of 1 would be used in the STOP-BANG when a patient is older than 50 years, which really does not apply to most stroke patients who are older than 50 years. Taken together, we speculate that the 4V is more suitable for the screening of OSA in Chinese population than the STOP-BANG.

In spite of this, the 4V is far from being ideal as a screening tool for OSA in acute ischemic stroke/TIA patients, because BMI is difficult to measure in this population. Indeed, body weight and height had to be estimated (not measured) in 65 of our 124 patients, Further, the 4V AUC in our acute ischemic stroke/TIA patient population rated only as "fair," and not "excellent" as described by Takegami et al.[34] To address this issue, we used neck circumference rather than BMI, which can easily be measured in an immobile patient, resulting in the creation of the modified 4V-1 and 4V-2 (gender-specific cutoffs). In the present study, the AUCs of the modified 4V-1 and the modified 4V-2 scale we created were .824 and .835, significantly higher than the AUC of reference line and with better performance as the 4V, although it is difficult to know how much the low performance of the 4V was due to imprecise measurements of BMI in our study. Using a cut-off point of 7 (calculated by MedCalc using optimal criterion), the modified 4V-2 produced a high sensitivity of 92.9% and a moderate NPV of 76.0%, and showed the best predictive performance of all the tools used in this study.

In conclusion, by replacing BMI by neck circumference, we amended a previously published tool, the 4V, creating the modified 4V-1 and modified 4V-2. According our data, modified 4V-1 and modified 4V-2 had at least similar prediction ability with the original 4V for OSA in a population of Chinese stroke/TIA patients. When accurate BMI is not available, the modified 4V-1 and modified 4V-2 can be useful for the OSA screening.

Conflicts of Interest

None.

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