Original Article

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Obstructive sleep apnea and stroke severity: Impact of clinical risk factors

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Abstract:

BACKGROUND: Specific clinical and demographic risk factors may be associated with improving or worsening neurologic outcomes within a population of acute ischemic stroke (AIS) patients with a history of obstructive sleep apnea (OSA). The objective of this study was to determine the changes in neurologic outcome during a 14-day recovery as it relates to initial stroke severity in AIS patients with OSA.

METHODS: This retrospective study analyzed baseline clinical risk factors and demographic data collected in a regional stroke center from January 2010 to June 2016. Our primary endpoint measure was the National Institutes of Health Stroke Scale (NIHSS) score and our secondary endpoint measures included the clinical factors associated with improving (NIHSS score ≤7) or worsening (NIHSS score >7) neurological outcome. The relative contribution of each variable to stroke severity and related outcome was determined using a logistic regression. The regression models were checked for the overall correct classification percentage using a Hosmer–Lemeshow test, and the sensitivity of our models was determined by the area under the receiver operating characteristic curve.

RESULTS: A total of 5469 AIS patients were identified. Of this, 96.89% did not present with OSA while 3.11% of AIS patients presented with OSA. Adjusted multivariate analysis demonstrated that in the AIS population with OSA, atrial fibrillation (AF) (odds ratio [OR] = 3.36, 95% confidence interval [CI], 1.289–8.762, *P* = 0.013) and changes in ambulatory status (OR = 2.813, 95% CI, 1.123–7.041, *P* = 0.027) showed an association with NIHSS score >7 while being Caucasian (OR = 0.214, 95% CI, 0.06–0.767, *P* = 0.018) was associated with NIHSS score ≤7.

CONCLUSION: In AIS patients with OSA, AF and changes in ambulatory status were associated with worsening neurological outcome while Caucasian patients were associated with improving neurological outcome. Our findings may have significant implications for patient stratification when determining treatment protocols with respect to neurologic outcomes in AIS patients with OSA.

Keywords:

Acute ischemic stroke, National Institutes of Health Stroke Scale score, obstructive sleep apnea, stroke severity

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Introduction

Obstructive sleep apnea (OSA) is a treatable form of abnormal breathing in which the upper airway closes repeatedly during sleep.[1] This syndrome is known to be associated with vascular risk factors and represents an important risk factor for ischemic stroke.[2] While several studies[2-4] have shown the prevalence of OSA among acute ischemic stroke (AIS) patients, whether the observed severity in AIS patients with a history of OSA is linked to specific clinical risk factors is not fully understood. There are numerous potential clinical risk factors for stroke in the OSA population including obesity, hypertension (HTN), atherosclerosis, endothelial dysfunction, and cardiac arrhythmias.[5,6] These factors

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are also known to contribute to poor neurologic recovery in AIS patients.[7] Therefore, identification of specific risk factors associated with AIS patients with OSA could represent an important strategy for the management of AIS patients with OSA.[8]

The National Institutes of Health Stroke Scale (NIHSS) score is one of the most widely used tools in stroke neurology[9] to assess neurological deficits after an anterior stroke.[10] The threshold for NIHSS values less than or greater than 7 has been used in the stratification of stroke severity in AIS.[11,12] For example, a NIHSS score >7 within a 48-h period is a significant clinical indicator of neurologic worsening and poor prognosis at discharge,[12] while a score of ≤7 is linked to improved neurological outcome.[13] This finding reveals that the course of neurologic outcome following AIS depends on the initial stroke severity, and that a dichotomy in neurologic outcome exists based on the initial NIHSS score when stratified by ≤7 and >7.[12] This implies that in a standard statistical approach of modeling, baseline NIHSS score can help predict neurologic outcomes in AIS patients with OSA using their clinical risk factors.[12]

Despite presenting with more cardiovascular conditions, AIS patients with OSA have been shown to present with less neurological injury at the time of hospital admission when compared to patients without OSA.[14] A recent study[15] also indicates poor functional outcome in AIS patients with OSA. However, in these studies,[14,15] AIS-OSA patients were not stratified based on initial stroke severities using initial NIHSS scores. It is possible that AIS-OSA patients with varying severities present with a nonlinear profile of recovery after 14 days, and the early course of improvement may be greater at the lower end of the deficit NIHSS than at the higher end. If this is the case, then more AIS-OSA patients will show improvement if they present with lower NIHSS scores during admission. Another possibility is that there may also be a population of AIS-OSA patients with worsening presentation based on the initial severity of their stroke, resulting in poor neurologic outcome. In this context, specific baseline clinical factors may influence stroke severity differentially to affect neurologic outcome in AIS populations with and without OSA. Therefore, the objective of the current study is to identify clinical and demographic factors that contribute to worsening or improving neurologic outcome in AIS patients with OSA. Because neurological outcome following an acute stroke is dependent on the initial stroke severity, baseline NIHSS scores were analyzed to predict progression and improvement in neurologic outcomes. Understanding the potential effect of demographic and risk factors on the course of neurologic worsening and improvement may help in the development of management strategies for AIS patients with OSA.

Methods

Study population

This institutional review board (IRB)-approved, retrospective study analyzed data from 5,469 AIS patients who were admitted and treated at Prisma Health (previously Greenville Health System) located in Greenville, South Carolina, USA, from January 2010 to June 2016. Of the 5,469 AIS patients, 5,299 patients did not present with OSA while 170 patients presented with OSA. The IRB of PRISMA Health Institutional Committee for Ethics approved this study. Patients included in this study presented within 24 h of onset of AIS symptoms, based on relevant lesions demonstrating ischemia or injury on brain magnetic resonance imaging or computed tomography, such as decreased gray/white matter distinction, parenchymal hypodensity, sulcal swelling, or cerebral artery hyperdensity. The stroke registry, previously described in other studies,[16-25] provided data on patient demographics, laboratory values, clinical presentation, and medical history. The demographic variables studied include age, race, gender, ethnicity, body mass index (BMI), and medication history on admission. The clinical characteristics that were collected include atrial fibrillation (AF)/atrial flutter, coronary artery disease (CAD), carotid artery stenosis, depression, dyslipidemia, diabetes mellitus, drug or alcohol abuse, congestive heart failure, family history of stroke, hormonal replacement therapy, migraine, obesity, HTN, previous stroke or transient ischemic attack, peripheral vascular disease (PVD), sickle cell disease, chronic renal disease, OSA, and history of smoking. Ambulation data were obtained upon admission, during admission, and following discharge. Patients' ambulatory data were recorded from a range of 0–3: undocumented (0), patient not able to ambulate (1), patient able to ambulate with assistance (2), and patient able to ambulate independently (3). The ambulation score at discharge was compared to the ambulation score on admission which quantitatively showed if there was an improvement in ambulation. This method of scoring has been described in a previous study.[26]

Statistical analysis

A univariate statistical analysis of the risk factors and differences of AIS patients with or without OSA was performed. This analysis used the Pearson Chi-square test to analyze discrete variables and the Student's *t*-test to analyze all continuous variables. The data on demographic and clinical risk factors in patients with a NIHSS ≤7 or a NIHSS >7 dependent on their OSA diagnosis were analyzed through a univariate analysis done similarly to the first analysis. Next, a binary logistic multivariate analysis was constructed by including the established predictors with a probability value <0.3 from the univariate analysis building to identify independent

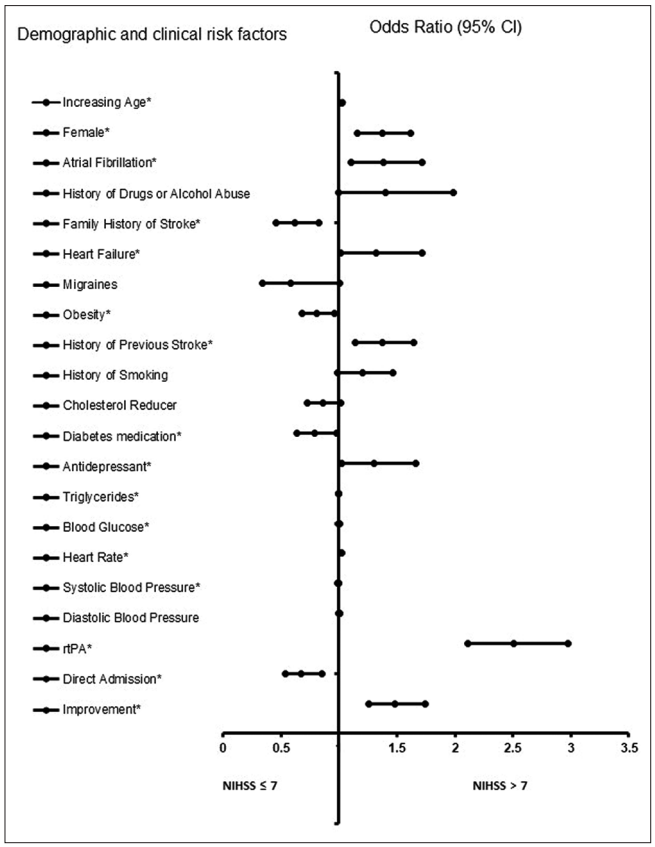

Figure 1: Forest plot representation of Table 3. Confidence interval band below 1 denotes factors that are associated with a National Institutes of Health Stroke Scale score ≤7 while confidence interval band above 1 denotes factors that are associated with a National Institutes of Health Stroke Scale score >7. *Statistical significance ($P < 0.05$) with a 95% confidence interval.

predictors of higher NIHSS scores in the two groups based on sleep apnea status. A *post hoc* adjusted analysis (logistic regression) of baseline risk factors associated with lower or higher NIHSS was analyzed using the likelihood ratio backward selection method. The decision to use a backward selection model allowed all of the clinical and demographic risk factors that were approaching significance to be initially included in the model and then systematically removed if they did not add to the significance of the overall model. Another reason this was done is due to the retrospective nature of the data.

In the binary regression model, the stroke severity based on NIHSS score stratification was the dependent variable. The demographic and clinical risk factors for the groups stratified by the presence or absence of OSA were the primary independent variables in this patient population. The odds for presenting with a more severe stroke (NIHSS >7) or a stroke of moderate severity (NIHSS ≤7) were analyzed separately for the group with sleep apnea and the group without sleep apnea upon presentation of symptoms. Odds ratios (ORs) and 95% confidence intervals (CIs) of outcome measures were obtained from this model with the significance set at a 0.05 probability level. The ORs were then used to predict which independent variables positively influenced a patient with or without sleep apnea to have a more severe stroke, as defined by a NIHSS >7. After the model was built, the specificity, sensitivity, and accuracy of the regression model was studied using the area under the receiver operating characteristic curve (ROC) and overall correct classification percentage. Multicollinearity and interactions between independent variables were identified by using Hosmer–Lemeshow test. All statistical analyses were done using the Statistical Package for Social Sciences (SPSS) version 26.0 for Windows (SPSS, Chicago, IL, USA).

Results

A total of 5,469 AIS patients were identified. In this population, 5,299 patients did not have OSA and 170 patients did have OSA [Table 1]. In comparison to patients without OSA, patients with OSA were more likely to be Caucasian, with a higher mean BMI, but were less likely to be female. The patients with OSA presented with higher rates of CAD, depression, diabetes, dyslipidemia, heart failure, HTN, migraines, obesity, PVD, and chronic renal disease. In addition, patients with OSA presented with a lower rate of history of smoking and were more likely to be taking a HTN medication, cholesterol reducer, diabetes, and antidepressant medications. They were also more likely to present with higher triglyceride levels, lipid levels, and blood glucose levels but lower high-density lipoprotein (HDL) levels. NIHSS scores on admission were not significantly different for patients with and without OSA.

The clinical and demographic characteristics associated with stroke severity for patients separated by sleep apnea diagnosis are presented in Table 2. Ischemic stroke patients without OSA, with NIHSS >7 presented with higher rates of AF, heart failure. They were less likely to present with a family history of previous stroke, but presented with lower rates of diabetes, migraines, obesity, and a history of smoking. They were less likely to be taking a diabetes medication and presented with lower total cholesterol levels, triglyceride, and low-density lipoprotein levels. Ischemic stroke patients with OSA presented with higher levels of HDL, blood glucose levels, international normalized ratio levels, higher heart rates; however, they presented with lower systolic blood pressure (BP). They displayed improvement or changes in ambulation and were more likely to be treated with recombinant tissue plasminogen activator (rtPA) but were less likely to be directly admitted to the neurology unit. Patients with OSA and a NIHSS >7 were more likely to present with higher rates of AF and treated with HTN

Table 1: Baseline characteristics of ischemic stroke patients divided by diagnosis of sleep apnea

Characteristic	No sleep apnea, *n* (%)	Sleep apnea, *n* (%)	*P*
Number of patients	5299	170	
Age group			
<50	644 (12.2)	14 (8.2)	0.003*,a
50-59	956 (18.0)	40 (23.5)	
60-69	1256 (23.7)	43 (25.3)	
70-79	1181 (22.3)	50 (29.4)	
≥80	1262 (23.8)	23 (13.5)	
Mean±SD	67.28±14.81	66.33±12.3	0.326
Race			
White	4143 (78.2)	145 (85.3)	0.018*,a
Black	977 (18.4)	25 (14.7)	
Other	179 (3.4)	0	
Gender			
Female	2738 (51.7)	69 (40.6)	0.004*,a
Male	2561 (48.3)	101 (59.4)	
Hispanic ethnicity	85 (1.6)	0	0.096
BMI (mean±SD)	28.15±6.85	34.23±8.39	<0.001*,b
Medical history			
Atrial fib	886 (16.7)	38 (22.4)	0.054
CAD	1590 (30.0)	71 (41.8)	0.001*,a
Carotid artery stenosis	321 (6.1)	13 (7.6)	0.394
Depression	637 (12.0)	84 (49.4)	<0.001*,a
Diabetes	1836 (34.6)	99 (58.2)	<0.001*,a
Drugs or alcohol	327 (6.2)	10 (5.9)	0.878
Dyslipidemia	2634 (49.7)	121 (71.2)	<0.001*,a
Stroke family history	473 (8.9)	21 (12.4)	0.125
Heart failure	556 (10.5)	34 (20.0)	<0.001*,a
Hormonal replacement therapy	75 (1.4)	4 (2.4)	0.313
HTN	4152 (78.4)	154 (90.6)	<0.001*,a
Migraine	124 (2.3)	10 (5.9)	0.003*,a
Obesity	2159 (40.7)	152 (89.4)	<0.001*,a
Previous stroke	1374 (25.9)	50 (29.4)	0.308
Previous TIA (>24 h)	462 (8.7)	15 (8.8)	0.962
Prosthetic heart valve	62 (1.2)	0	0.156
Peripheral vascular disease	378 (7.1)	22 (12.9)	0.004*,a
Chronic renal disease	418 (7.9)	29 (17.1)	<0.001*,a
Sickle cell disease	4 (0.1)	0	0.720
Smoker	1461 (27.6)	25 (14.7)	<0.001*,a
Medication history			
HTN medication	3656 (69.0)	138 (81.2)	0.001*,a
Cholesterol reducer	2330 (44.0)	98 (57.6)	<0.001*,a
Diabetes medication	1413 (26.7)	82 (48.2)	<0.001*,a
Antidepressant	631 (11.9)	80 (47.1)	<0.001*,a
Initial NIHSS score			
0-9	3177 (71.7)	112 (72.7)	0.952
10-14	489 (11.0)	18 (11.7)	
15-20	486 (11.0)	15 (9.7)	
21-25	281 (6.3)	9 (5.8)	
Mean±SD	8.32±8.27	7.3±7.54	0.127
Laboratory values, mean±SD			
Total cholesterol	171.95±51.92	168.67±48.6	0.441
Triglycerides	139.09±105.7	156.11±86.33	0.049*,b
HDL	41.92±13.88	37.63±11.85	<0.001*,b
LDL	104.68±41.33	102.75±39.99	0.568
Lipids	6.52±2.57	6.97±2.06	0.032*,b

Contd...

Table 1: Contd...

Characteristic	No sleep apnea, *n* (%)	Sleep apnea, *n* (%)	*P*
Blood glucose	146.78±80.59	163.48±92.82	0.022*,b
Serum creatinine	1.29±1.18	1.34±0.91	0.601
INR	1.14±0.5	1.16±0.37	0.722
Vital signs, mean±SD			
Heart rate	82.02±18.59	81.47±16.4	0.703
BP systolic	151.9±29.27	149.45±30.65	0.283
BP diastolic	82.48±19.04	81.35±21.53	0.451
Ambulation status prior to event			
Ambulate independently	4735 (89.4)	152 (89.4)	0.852
Ambulate with assistance	199 (3.8)	4 (2.4)	
Unable to ambulate	205 (3.9)	8 (4.7)	
Not documented	159 (3.0)	6 (3.5)	
Ambulation status on admission			
Ambulate independently	1279 (24.1)	52 (30.6)	0.013*,a
Ambulate with assistance	1571 (29.6)	55 (32.4)	
Unable to ambulate	1676 (31.6)	52 (30.6)	
Not documented	773 (14.6)	11 (6.5)	
Ambulation status on discharge			
Ambulate independently	2096 (39.6)	78 (45.9)	0.385
Ambulate with assistance	1771 (33.4)	49 (28.8)	
Unable to ambulate	1039 (19.6)	30 (17.6)	
Not documented	393 (7.4)	13 (7.6)	
rtPA received	1282 (24.2)	45 (26.5)	0.495
First care received			
Emergency department	4158 (79.2)	139 (82.7)	0.259
Direct admission	1095 (20.8)	29 (17.3)	
Improved ambulation	1773 (36.0)	52 (32.9)	0.429
NIHSS>7	1811 (38.7)	56 (35.4)	0.404
Diastolic BP ≥80 mmHg	2805 (53.0)	83 (48.8)	0.281

Results for continuous variables are presented as mean±SD, while discrete data are presented as percentage frequency. [a]Pearson's Chi-square test, [b]Student's *t*-test, **P*<0.05. NIHSS: National Institutes of Health Stroke Scale, SD: Standard deviation, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, INR: International normalized ratio, HTN: Hypertension, TIA: Transient ischemic attack, CAD: Coronary artery disease, BP: Blood pressure, rtPA: recombinant tissue plasminogen activator

medications. These patients presented with higher heart rates, changes, or an improved ambulatory status and lower triglyceride levels.

In the adjusted analysis for the patient cohort without OSA, increasing age, being female, AF, heart failure, history of previous stroke, antidepressant use, higher blood glucose level, higher heart rate, rtPA administration, and changes in ambulatory status were associated with worsening neurologic outcomes, while family history of stroke, obesity, diabetic medication, higher triglyceride levels, higher systolic BP readings, and direct admission were associated with an improvement in neurologic outcomes [Table 3 and Figure 1]. The model demonstrated moderately strong discriminating capability see Figure 2, and the area under the curve (AUROC) was 0.704 (95% CI, 0.687–0.721, $P < 0.001$).

In the adjusted analysis for AIS with OSA [Table 4 and Figure 3], AF and changes of an improvement in ambulation were associated with worsening neurologic outcomes, while Caucasians were more likely to be associated with improving neurologic outcomes. As presented in Figure 4, the logistic regression demonstrated strong predictive power. The AUROC is 0.761 (95% CI, 0.679–0.843, $P < 0.001$).

Discussion

OSA has been linked with vascular diseases, including stroke, but it is unclear whether specific demographic or clinical factors may differentially influence neurologic outcomes in AIS populations with OSA. There are conflicting studies pointing to OSA having both a protective effect and an increased risk for AIS indicating the need to understand the baseline clinical risk factors in AIS patients with a history of OSA. Baseline NIHSS score is a strong predictor of outcomes and represents a major evaluation tool to determine stroke severity and neurological deficits after an anterior stroke.[27] In this study, stroke severity was between 7.3 and 8.32 for AIS with or without OSA. This finding indicates that NIHSS is a predictor of neurological deficits in AIS with or without OSA and does account for stroke severity and neurologic outcome among our AIS population with OSA.

Table 2: Baseline characteristics of an National Institutes of Health Stroke Scale score >7 in ischemic stroke patients stratified by absence or presence of sleep apnea

Characteristic	No sleep apnea		*P*	Sleep apnea		*P*
	NIHSS ≤7, *n* (%)	NIHSS >7, *n* (%)		NIHSS ≤7, *n* (%)	NIHSS >7, *n* (%)	
Number of patients	2865	1811		102	56	
Age group (years)						
<50	391 (13.6)	182 (10.0)	<0.001*,a	8 (7.8)	5 (8.9)	0.662
50-59	552 (19.3)	298 (16.5)		28 (27.5)	10 (17.9)	
60-69	738 (25.8)	358 (19.8)		26 (25.5)	14 (25.0)	
70-79	650 (22.7)	404 (22.3)		29 (28.4)	18 (32.1)	
≥80	534 (18.6)	569 (31.4)		11 (10.8)	9 (16.1)	
Age, mean±SD	65.62±14.37	69.8±15.08	<0.001*,b	65.69±12.11	67.23±12.49	0.449
Race						
White	2262 (79.0)	1401 (77.4)	0.318	92 (90.2)	45 (80.4)	0.081
Black	514 (17.9)	342 (18.9)		10 (9.8)	11 (19.6)	
Other	89 (3.1)	68 (3.8)		0	0	
Gender						
Female	1398 (48.8)	1018 (56.2)	<0.001*,a	37 (36.3)	25 (44.6)	0.303
Male	1467 (51.2)	793 (43.8)		65 (63.7)	31 (55.4)	
Hispanic ethnicity	51 (1.8)	28 (1.5)	0.545	0	0	
BMI, mean±SD	28.72±6.9	27.55±6.73	<0.001*,b	33.86±7.27	34.73±9.02	0.515
Medical history						
Atrial fib	361 (13.6)	423 (23.4)	<0.001*,a	15 (14.7)	21 (37.5)	0.001*,a
CAD	852 (29.7)	548 (30.3)	0.705	40 (39.2)	27 (48.2)	0.274
Carotid artery stenosis	167 (5.8)	105 (5.8)	0.965	9 (8.8)	4 (7.1)	0.713
Depression	355 (12.4)	236 (13.0)	0.521	52 (51.0)	28 (50.0)	0.906
Diabetes	1029 (35.9)	573 (31.6)	0.003*,a	63 (61.8)	31 (55.4)	0.433
Drugs or alcohol	163 (5.7)	121 (6.7)	0.166	5 (4.9)	4 (7.1)	0.561
Dyslipidemia	1464 (51.1)	877 (48.4)	0.075	68 (66.7)	43 (76.8)	0.183
Stroke family history	322 (11.2)	114 (6.3)	<0.001*,a	15 (14.7)	5 (8.9)	0.296
Heart failure	231 (8.1)	240 (13.3)	<0.001*,a	16 (15.7)	15 (26.8)	0.093
Hormonal replacement therapy	41 (1.4)	27 (1.5)	0.868	2 (2.0)	2 (3.6)	0.538
HTN	2224 (77.6)	1423 (78.6)	0.446	92 (90.2)	53 (94.6)	0.331
Migraine	86 (3.0)	29 (1.6)	0.003*,a	6 (5.9)	4 (7.1)	0.756
Obesity	1291 (45.1)	701 (38.7)	<0.001*,a	90 (88.2)	52 (92.9)	0.357
Previous stroke	710 (24.8)	507 (28.0)	0.015*,a	32 (31.4)	15 (26.8)	0.546
Previous TIA (>24 h)	260 (9.1)	156 (8.6)	0.590	9 (8.8)	6 (10.7)	0.698
Prosthetic heart valve	35 (1.2)	25 (1.4)	0.638	0	0	
Peripheral vascular disease	192 (6.7)	117 (6.5)	0.747	12 (11.8)	9 (16.1)	0.446
Chronic renal disease	227 (7.9)	130 (7.2)	0.350	16 (15.7)	10 (17.9)	0.725
Sickle cell disease	3 (0.1)	1 (0.1)	0.573	0	0	
Smoker	846 (29.5)	454 (25.1)	0.001*,a	15 (14.7)	7 (12.5)	0.702
Medication history						
HTN medication	1951 (68.1)	1270 (70.1)	0.144	80 (78.4)	51 (91.1)	0.043*,a
Cholesterol reducer	1302 (45.4)	770 (42.5)	0.050	57 (55.9)	39 (69.6)	0.090
Diabetes medication	802 (28.0)	431 (23.8)	0.002*,a	50 (49.0)	28 (50.0)	0.906
Antidepressant	352 (12.3)	242 (13.4)	0.282	50 (49.0)	27 (48.2)	0.923
Laboratory values, mean±SD						
Total cholesterol	174.73±54.01	168.41±47.29	<0.001*,b	174.31±47.45	158.98±50.36	0.070
Triglycerides	147.58±114.88	126.39±91.33	<0.001*,b	168.29±88.99	136.39±78.77	0.033*,b
HDL	41.33±13.4	43.13±14.33	<0.001*,b	38.15±11.77	36.92±11.51	0.546
LDL	106.58±41.14	102.42±40.37	0.001*,b	105.42±39.87	97.9±41	0.279
Lipids	6.55±2.74	6.4±2.3	0.073	7.19±2.22	6.65±1.77	0.132
Blood glucose	143.23±74.84	149.52±82.46	0.007*,b	170.58±105.52	157.91±69.36	0.421
Serum creatinine	1.23±1.09	1.25±1.07	0.405	1.26±0.61	1.36±1.05	0.470
INR	1.11±0.43	1.16±0.54	0.001*,b	1.1±0.19	1.18±0.32	0.130

Contd...

Table 2: Contd...

Characteristic	No sleep apnea		*P*	Sleep apnea		*P*
	NIHSS ≤7, *n* (%)	NIHSS >7, *n* (%)		NIHSS ≤7, *n* (%)	NIHSS >7, *n* (%)	
Vital signs, mean±SD						
Heart rate	79.02±16.39	85±19.84	<0.001*,b	79.14±15.01	84.71±17.75	0.038*,b
BP systolic	153.46±28.04	151.71±29.4	0.043*,b	153.88±29.87	149.63±25.86	0.371
BP diastolic	82.31±17.79	83.44±20.07	0.052	82.14±20.83	83.89±21.01	0.614
Ambulation status prior to event						
Ambulate independently	2721 (95.0)	1534 (84.7)	<0.001*,a	97 (95.1)	49 (87.5)	0.117
Ambulate with assistance	81 (2.8)	79 (4.4)		3 (2.9)	1 (1.8)	
Unable to ambulate	43 (1.5)	109 (6.0)		1 (1.0)	3 (5.4)	
Not documented	20 (0.7)	88 (4.9)		1 (1.0)	3 (5.4)	
Ambulation status on admission						
Ambulate independently	1050 (36.6)	94 (5.2)	<0.001*,a	48 (47.1)	2 (3.6)	<0.001*,a
Ambulate with assistance	1133 (39.5)	283 (15.6)		41 (40.2)	12 (21.4)	
Unable to ambulate	222 (7.7)	1196 (66.0)		6 (5.9)	40 (71.4)	
Not documented	460 (16.1)	238 (13.1)		7 (6.9)	2 (3.6)	
Ambulation status on discharge						
Ambulate independently	1618 (56.5)	339 (18.7)	<0.001*,a	65 (63.7)	10 (17.9)	<0.001*,a
Ambulate with assistance	1009 (35.2)	546 (30.1)		27 (26.5)	21 (37.5)	
Unable to ambulate	178 (6.2)	694 (38.3)		6 (5.9)	18 (32.1)	
Not documented	60 (2.1)	232 (12.8)		4 (3.9)	7 (12.5)	
rtPA administration	602 (21.0)	670 (37.0)	<0.001*,a	25 (24.5)	20 (35.7)	0.136
First care received						
Emergency department	2226 (78.4)	1489 (82.9)	<0.001*,a	82 (81.2)	49 (87.5)	0.308
Direct admission	612 (21.6)	307 (17.1)		19 (18.8)	7 (12.5)	
Improved ambulation	940 (33.4)	684 (43.0)	<0.001*,a	26 (26.3)	24 (49.0)	0.006*,a
Diastolic BP ≥80 mmHg	1535 (53.6)	977 (54.1)	0.772	51 (50.0)	31 (55.4)	0.519

Results for continuous variables are presented as mean±SD, while discrete data are presented as percentage frequency. [a]Pearson's Chi-square test, [b]Student's *t*-test, *P<0.05. NIHSS: National Institutes of Health Stroke Scale, SD: Standard deviation, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, INR: International normalized ratio, HTN: Hypertension, TIA: Transient ischemic attack, CAD: Coronary artery disease, BP: Blood pressure, rtPA: recombinant tissue plasminogen activator

In the adjusted analysis, AIS patients without OSA that present with a worsening neurologic outcome were more likely to be older female patients with a history of heart failure, AF, previous stroke, antidepressant use, higher blood glucose, increased heart rate, and rtPA administration. Because females have longer life expectancies, the majority of stroke deaths are known to occur in women compared with men.[28] While stroke incidence rates are higher for men than women in most age groups,[29] as age increases, the incidence of stroke in females increases drastically such that after the age of 85 years, more women suffer from strokes than men.[30] In addition, several studies have reported risk factors associated with poor neurologic outcome in elderly stroke populations.[31-33] Findings indicate that women were more likely to have a poor outcome than men. While hormonal factors and comorbid function are known to contribute to the poor functional recovery in older women, our study reveals that well-established factors including previous stroke,[34,35] AF,[36] heart failure,[37] antidepressant use,[38] higher blood glucose level,[39] higher heart rate,[40] and rtPA administration[41] are all linked to worsening outcome in the elderly patient population. After adjusting for the effect of confounding variables, our findings reveal that several clinical risk factors contribute to the continuous decline in neurologic outcome in older female AIS patients, which suggests that long-term management strategies are needed for older stroke populations.

We observed that AIS patients without OSA, and with a family history of stroke, obesity, diabetic medication use, higher triglyceride levels, higher systolic BP, and direct admission, were associated with an improvement in neurologic outcomes. A similar finding demonstrating an increased risk in AIS patients with a family or parental history of stroke has been reported.[42] In addition, high triglyceride levels have been reported to be associated with low NIHSS scores and improving neurologic outcome,[43] while a systolic BP ≥185 mmHg was considered to be a contraindication for thrombolytic therapy and associated with poor outcomes.[44] However, in our current study, we observed a systolic BP of 153.46 mmHg to be associated with poor outcomes which is significantly lower than previously reported values.[44] There is a J- and U-shape relationship between BP variables and outcomes,[44] indicating that higher BP levels linked with worse or improved clinical outcomes may not produce direct evidence for causality of neurologic outcome with certainty.[45] Therefore, future studies will be necessary to definitively determine the

Table 3: Factors associated with a National Institutes of Health Stroke Scale score >7 for ischemic stroke patients without sleep apnea

Variables	*B*	Wald	OR	95% CI		*P*
				Lower	Upper	
Increasing age	0.022	40.877	1.022	1.015	1.029	<0.001*
Female	0.316	14.147	1.372	1.163	1.617	<0.001*
Atrial fibrillation	0.323	8.281	1.381	1.108	1.72	0.004*
History of drugs or alcohol abuse	0.34	3.705	1.405	0.994	1.987	0.054
Family history of stroke	−0.481	10.463	0.618	0.462	0.827	0.001*
Heart failure	0.277	4.271	1.319	1.014	1.716	0.039*
Migraines	−0.536	3.739	0.585	0.34	1.007	0.053
Obesity	−0.209	5.882	0.811	0.685	0.961	0.015*
History of previous stroke	0.315	11.572	1.371	1.143	1.644	0.001*
History of smoking	0.186	3.4	1.204	0.988	1.466	0.065
Cholesterol reducer	−0.151	3.043	0.86	0.726	1.019	0.081
Diabetic medication	−0.233	4.789	0.792	0.643	0.976	0.029*
Antidepressant	0.267	4.694	1.306	1.026	1.662	0.03*
Triglycerides	−0.002	11.774	0.998	0.998	0.999	0.001*
Blood glucose	0.002	11.206	1.002	1.001	1.003	0.001*
Heart rate	0.017	43.7	1.017	1.012	1.022	<0.001*
Systolic BP	−0.004	5.301	0.996	0.993	0.999	0.021*
Diastolic BP	0.005	3.508	1.005	1	1.011	0.061
rtPA	0.918	109.91	2.505	2.11	2.975	<0.001*
Direct admission	−0.387	10.55	0.679	0.538	0.858	0.001*
Changes in ambulation	0.394	22.175	1.482	1.258	1.746	<0.001*

Adjusted OR <1 denotes factors that are associated with not having a NIHSS score >7 while OR >1 denotes factors that are associated with having a NIHSS score >7. *Statistical significance (P<0.05) with a 95% CI. Backward stepwise model based on likelihood ratio was applied. Model assumptions were fulfilled. Multicollinearity and interactions among independent variables were checked, and no significant interactions were found. Hosmer-Lemeshow test (P=0.069), Cox and Snell (R^2=0.123). OR: Odds ratio, CI: Confidence interval, NIHSS: National Institutes of Health Stroke Scale, BP: Blood pressure, rtPA: Recombinant tissue plasminogen activator

Table 4: Factors associated with a National Institutes of Health Stroke Scale score >7 for ischemic stroke patients with sleep apnea

Variables	*B*	Wald	OR	95% CI (lower-upper)		*P*
				Lower	Upper	
Caucasian	−1.542	5.609	0.214	0.06	0.767	0.018*
Atrial fibrillation	1.212	6.145	3.36	1.289	8.762	0.013*
Dyslipidemia	0.822	2.707	2.274	0.855	6.053	0.1
Heart failure	0.897	2.753	2.451	0.85	7.067	0.097
Lipids	−0.21	2.91	0.81	0.636	1.032	0.088
Changes in ambulation	1.034	4.878	2.813	1.123	7.041	0.027*

Adjusted OR <1 denotes factors that are associated with not having a NIHSS score >7 while OR >1 denotes factors that are associated with having a NIHSS score >7. *Statistical significance (P<0.05) with a 95% CI. Backward stepwise model based on likelihood ratio was applied. Model assumptions were fulfilled. Multicollinearity and interactions among independent variables were checked, and no significant interactions were found. Hosmer-Lemeshow test (P=0.988), Cox and Snell (R^2=0.191). OR: Odds ratio, CI: Confidence interval, NIHSS: National Institutes of Health Stroke Scale, rtPA: Recombinant tissue plasminogen activator

potential association of BP variables and improved neurologic outcomes in AIS.

We found that a direct admission of patients was associated with improving neurologic outcomes. In general, direct admission is known to contribute to shorter onset-to-need times and therefore better outcomes in AIS patients undergoing thrombolysis.[46-48] This is because direct admission has been shown to reduce the door-to-needle time to <60 min in >70% of AIS patients and to <50 min in >45% of AIS patients.[49-51] Such a time improvement could be helpful when implementing the protocol of mixing and administering rtPA thrombolytic therapy to stroke patients, resulting in timely intervention that could lead to improved neurologic outcome.

Our finding that AF was associated with the odds of a worse neurologic outcome in AIS patients with OSA is not surprising. This is because AF is a common cardiac arrhythmia and is known to increase stroke severity while OSA represents an independent risk factor for stroke.[52] The pathophysiology of AF and OSA is complex and bidirectional, such that while OSA may contribute to the development of AF, AF may also promote OSA.[53] Although the mechanism for the pathological effects of AF and OSA on stroke severity and neurologic outcome is beyond the scope of the current study,

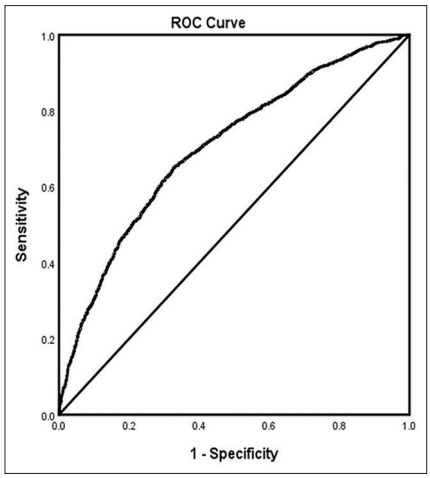

Figure 2: ROC curve associated with prediction of a National Institutes of Health Stroke Scale score >7 for acute ischemic stroke patients without sleep apnea. Classification table (overall correctly classified percentage = 68.8%) and area under the ROC curve (Area under the ROC Curve = 0.704, 0.687–0.721) were applied to check model fitness

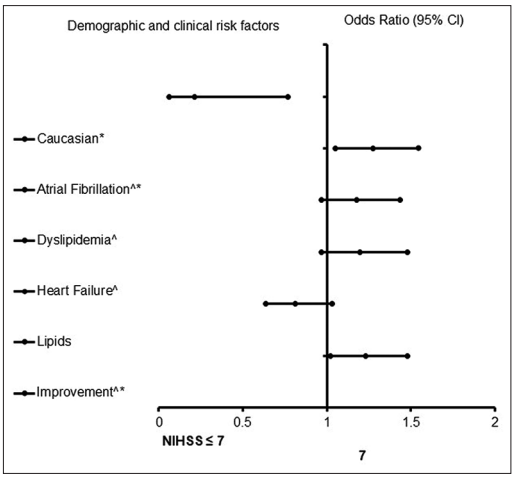

Figure 3: Forest plot representation of Table 4. Confidence interval band below 1 denotes factors that are associated with a National Institutes of Health Stroke Scale score ≤7 while confidence interval band above 1 denotes factors that are associated with National Institutes of Health Stroke Scale score >7. *Indicates statistical significance ($P < 0.05$) with a 95% confidence interval. ^Indicates that data were modified by taking the 5th square root

there is extensive evidence[24,54] that these comorbidities are linked, and can independently worsen neurologic outcomes in AIS patients. Our finding that AIS patients with worsening neurologic outcomes are associated with AF indicates that the pathophysiology linking AF, OSA, and AIS is complex and likely multifactorial. We know that the pathophysiologic changes associated with sleep apnea, such as changes in intrathoracic pressure and blood gas levels, may cause structural and electrical changes that predispose patients to arrhythmias like AF.[53] While OSA is considered to be an independent risk for AIS, it is possible that its effect could also contribute to cardiac conduction abnormalities in the rate of AF. The abnormality in AF not only leads to stasis and abnormal cardiac circulation but also leads to increased endothelial activation, and coagulation factor release,[55] which may contribute to worsening neurologic outcome in AIS populations with OSA. This possibility demonstrates the multidirectional interplay between OSA and AF in AIS which may lead to the observed result of worsening neurologic outcomes in our AIS population with OSA. This possibility also suggests the need to develop care and management plans to address OSA and AF in AIS patients.

Our finding that Caucasian AIS patients with OSA were more likely to present with improving neurologic outcomes is not surprising. It is well documented that African Americans are twice as likely to have a stroke, with worsening neurologic outcome, and the mortality rate is 35% greater than that of Caucasian AIS patients.[56-58] Other studies[59,60] note that this disparity also affects Hispanics, Native Americans, and Asian Americans.[61] A retrospective study found that when insurance, access to health care, and treatment plans were controlled for, African Americans still had worsening neurologic outcome when compared to Caucasians[59] indicating the possibility that race contributes to worsening neurologic outcome in AIS patients with OSA. This possibility suggests that race needs to be considered in developing treatment plans for OSA to reduce the likelihood of worsening neurological outcomes in AIS patients with OSA.

Changes in ambulatory outcome were predictive of worsening neurologic outcomes in AIS patients with OSA. NIHSS scores are traditionally used to measure the severity of stroke, and several studies have shown its efficacy in being used for the prediction of worsening neurologic outcomes.[9,10] Other models including modified Rankin score and Barthel's index try to quantify functional outcomes of stroke recovery,[11,48,49] but none of these tests specifically measure motor recovery.[18,50] Our finding that changes in ambulatory outcome were associated with higher NIHSS scores and worsening neurologic outcome reveals that ambulatory function may serve as a significant quantitative measure and predictor of future outcomes following an anterior stroke in AIS patients with OSA.[27]

There are several limitations that must be taken into consideration. In this study, only patients with a diagnosis of OSA prior to stroke were classified as having OSA. Experts estimate that approximately 80% of OSA cases go undiagnosed, and many patients are not diagnosed with sleep apnea until after hospitalization for AIS. This could have led to the misclassification of some patients with undiagnosed OSA as patients without OSA leading to decreased differences between the two groups. This data set also lacked information about severity of OSA, treatment of OSA, and compliance with treatment

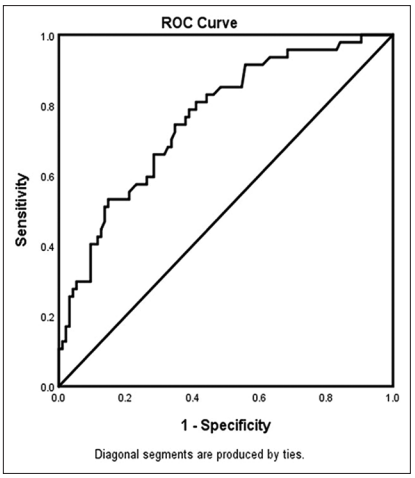

Figure 4: ROC curve associated with prediction of having a National Institutes of Health Stroke Scale score >7 for acute ischemic stroke patients with sleep apnea. Classification table (overall correctly classified percentage = 71.9%) and area under the ROC curve (Area under the ROC Curve = 0.761, 0.679–0.843) were applied to check model fitness

of OSA limiting our ability for further study. Because this was a retrospective study, there is always the possibility of selection bias. One strength of this study is the use of a large data set from a primary stroke center. Data from the primary stroke center contributed to the get with the guidelines national stroke registry. Another strength is the use of logistic regression which allows us to make predictions about future patients.

Conclusion

This study reveals that baseline clinical and demographic factors influence stroke severity differently in AIS patients with and without incidence of OSA. Our findings suggest that in patients with a history of OSA, AF and changes in ambulation are associated with worsening neurological outcomes while Caucasian AIS patients with OSA were associated with improving neurological outcome. These findings may have significant implications for patient stratification when determining treatment protocols with respect to neurologic outcomes in AIS patients with OSA.

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Conflicts of interest
There are no conflicts of interest.

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