

Original Article

Obstructive sleep apnea and chronic pain as risk factors of cognitive impairment in elderly population: A study from Indonesia

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Abstract

Obstructive sleep apnea (OSA), one of the most prevalent sleep-related breathing disorders in the elderly, seems to be underdiagnosed. Meanwhile, the resulting complication on cognitive function could impact on patient's quality of life. Association between OSA and cognitive function in the elderly varies highly, depending on study type, setting, and possibly by demographic differences. Therefore, this study sought to determine the risk of OSA among elderly and to assess the association of OSA risk and other plausible factors with cognitive function. In this cross-sectional study, patients aged 60 years and above who visited the outpatient clinic at two main hospitals in Surabaya of Indonesia were examined. A total of 178 participants were interviewed to evaluate the OSA risk using STOP-Bang questionnaire, the cognitive dysfunction using Montreal Cognitive Assessment Indonesian version (MoCA-Ina), depressive symptoms using Geriatric Depression Scale-15 (GDS-15), and sleep disorder using Insomnia Screening Questionnaire (ISQ). The Mann-Whitney and Chi-square tests were used to assess factors associated with cognitive impairment. In addition, logistic regression analyses were performed to evaluate the role of high risk of OSA on cognitive impairment. A total of 120 patients were considered having high risk of OSA (STOP-Bang score ≥ 3), and 129 had mild cognitive impairment (MCI) (MoCA-Ina < 26). Among the elderly who had high risk of OSA, 94 were diagnosed with MCI (78.3%). Multivariate logistic regression analysis showed that high risk of OSA (OR: 2.99; 95%CI: 1.39, 6.46, $p=0.005$), chronic pain (OR: 5.53; 95%CI: 1.19, 25.64, $p=0.029$), and low education level (OR: 4.57; 95%CI: 1.79, 11.63) were associated with MCI. In conclusion, our data suggests a high prevalence of MCI among high risk OSA elderly. Screening and comprehensive management might be beneficial to improve or to preserve cognitive function in elderly group.

Keywords: Obstructive sleep apnea, OSA, STOP-Bang, depression, cognitive impairment

Introduction

According to WHO estimates, in 2020 the number of people aged 60 years and older outnumbered children younger than 5 years, and it was estimated to further increase and will approximately reach 2.1 billion by 2050, in which 80% of them will be living in low and middle-income countries [1]. Indonesia will also enter an ageing society. In 2020, the proportion of elderly in Indonesia was already 9.92% [2]. East Java became a province with the third highest



proportion of the elderly population (13.4%) and in its capital Surabaya, the proportion was 10.5% [2]. The impact of this demographic change on health, economic and social sector needs to be considered. In the health sector, the prevalence of cognitive impairment including dementia in the elderly has increased in Asia, and will be the highest in India, China, South Asia, and western Pacific region. Predictors of cognitive impairment in elderly are very diverse and include race, ethnicity, culture, lifestyle, economic and social status. The initial management for modifiable factors causing cognitive impairment in the elderly will be beneficial.

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder characterized by partial or complete obstruction of the airways, despite an ongoing effort to breathe. The blockage is caused by increased collapsibility of soft tissue because of upper airway muscle relaxation during sleep. This condition causes complete pauses (apnea) or partial reduction (hypopnea) in breathing for at least ten seconds, leads to blood oxygen desaturation and brief arousal as a consequence [3]. OSA is a common primary sleep disorder in the elderly and the intermittent hypoxemia due to OSA is expected subsequently become one of the primary causes of cognitive impairment in the elderly [4].

Several studies assessing the relationship between OSA and cognitive function in the elderly have been conducted with conflicting results. In one study, OSA was associated with impaired verbal episodic memory and microvascular damage in the elderly with depression and cognitive impairment [5]. Other studies have shown that elderly with OSA were at higher risk for early onset of cognitive impairment or Alzheimer Dementia than controls of the same age and sex [5,6]. However, some other studies did not find a relationship between OSA and cognitive impairment [7,8].

OSA screening is usually obtained as a part of comprehensive evaluation of patients with high risk for OSA, for example those who are obese, have atrial fibrillation, congestive heart failure (CHF), refractory hypertension, type 2 diabetes, stroke, or nocturnal dysrhythmias, high-risk driving populations, and those being evaluated for bariatric surgery [3]. Meanwhile OSA is associated with cardiovascular and metabolic system complications (hypertension, coronary heart disease, type 2 diabetes mellitus, cerebrovascular infarction), neurocognitive dysfunction (cognitive impairment, vascular dementia and neurodegenerative diseases such as Alzheimer Dementia), depression and increased mortality [6,9-12].

The prevalence of undiagnosed and treated OSA is still high. The gold standard for the diagnosis of OSA is polysomnography (PSG); however, PSG is expensive, time-consuming and requires trained operators. In addition, the prevalence of OSA is much higher than the number of patients that could be handled by sleep laboratories worldwide. Therefore, another method has been developed, in the form of a questionnaire, STOP-Bang, as a simpler and lower-cost screening tool to prioritize patients with high risk of OSA for PSG [9,13].

Since OSA is a treatable and proper OSA management in the early stage could reduce the progression of dementia [14]; therefore, early recognition of these disorders is important to prevent the morbidity in elderly. This study was conducted to determine the risk of OSA among elderly and to assess the association of OSA risk and other plausible factors with cognitive impairment.

Methods

Study setting and participants

A cross-sectional study was conducted at two main hospitals in Surabaya of Indonesia, Dr Soetomo Hospital and Universitas Airlangga Hospital, between September and October 2021. Elderly who visited the Neurology, Cardiology, Geriatric, and Physical and Rehabilitation were consecutively enrolled. Eligibility criteria for the study participants were: elderly (aged 60 years and above), able to speak the national language Bahasa Indonesia, literate, had minimal six years of education, and able to comprehend investigator instructions. Individuals with history of head trauma, brain infection or neoplasm, Parkinson disease, epilepsy, stroke (less than three months with NIH Stroke Scale (NIHSS) >14, chronic obstructive pulmonary disease (COPD),

history of continuous positive airway pressure (CPAP) therapy, and chronic pain (more than three months with pain scale >4) were excluded. Patients were also excluded if they had history of alcohol consumption, used of sedative-hypnotic, anticonvulsant or antidepressant, or opioid drugs for the past one month.

Data collection

Individuals who met eligibility criteria were interviewed and sociodemographic and clinical information were collected during clinic visits and also from electronic medical records. These data included age, sex, ethnic, education level, job description, smoking status, neck circumference, body mass index (BMI), history of hypertension, diabetes, dyslipidemia, stroke, coronary artery disease (CAD), arrhythmia, congestive heart failure (CHF), and the chronic pain. Patients were interviewed and screened for OSA risk with STOP-Bang questionnaire and cognitive dysfunction with a validated Montreal Cognitive Assessment Indonesian version (MoCA-Ina). Other confounding factors evaluated including depression symptoms, which was evaluated with Indonesian Geriatric Depression scale-15 (GDS-15), and other sleep disturbance using Insomnia Screening Questionnaire (ISQ).

OSA risk assessment

OSA risk was measured with STOP-Bang questionnaire. The questionnaire, first developed in 2008, is a simple and self-reportable screening tool for OSA risk. STOP-Bang questionnaire includes four subjective items on STOP parameters (snoring, tiredness, observed apnea, and high blood pressure) and four demographic items on Bang parameters (BMI >35 kg/m², age >50, neck circumference >40 cm, and male gender). Each “yes” answer was scored 1, and “no” answer was scored 0, with total maximum score was 8. Score 3 and above is considered as having a high risk of OSA. The questionnaire is able to predict moderate to severe OSA (Apnea – Hypopnea Index - AHI ≥ 15) and severe OSA (AHI ≥ 30) with sensitivity of 92.9% and 100%, respectively [15]. For patients who came alone to the hospital, the information of snoring and witnessed apnea was collected from a proxy informant, typically spouse or their sleep partners, by telephone call.

Cognitive function assessment

Cognitive function was evaluated using a validated Montreal Cognitive Assessment Indonesian version (MoCA-Ina) [16]. MoCA is very sensitive to screen for mild cognitive impairment (MCI) better than MMSE. It evaluates eight cognitive domains: executive function, visuospatial, attention, concentration, memory, language, abstraction, calculation, and orientation with total point of 30. Score <26 was considered MCI, whereas ≥ 26 was considered normal. With a cut-off point of 26, it has better sensitivity to detect MCI and Alzheimer dementia (90% and 100%) better than Mini-Mental State Examination (MMSE) (18% and 78%), with equal specificity (87% and 100%, respectively) [17].

Depression assessment

Depression was assessed using a GDS-15 Indonesian version. GDS-15 is a validated tool to screen depressive symptoms in elderly. It consists of 15 questions, in which each question answered “yes” is scored as 1, and “no” as 0. Having a total score >5 is considered as having depression, with sensitivity of 71.8%, and specificity 87.6% [18].

Insomnia assessment

Insomnia was assessed using ISQ that screens the primary sleep disorder or secondary causes of insomnia [19]. It consists of 17 items, and grouped into six different sleep disorders (insomnia, psychiatric disorder, circadian rhythm disorder, movement disorder, parasomnia, and sleep apnea). The details of the number of questions are as follows: (1) insomnia (question 1-6 (Q1-6)); (2) psychiatric disorder (Q7-10); (3) circadian rhythm disorder (Q11); (4) movement disorder (Q12-13); (5) parasomnia (Q14); and (6) sleep apnea (Q15-17). The possible answers for each question are: “Never (1)”, “Rarely (2)”, “Occasionally (3)”, “Most nights/days (4)” and “Always (5)”. Those who responded 3, 4, or 5 on any questions likely suffer from insomnia. Details of the interpretation have been described elsewhere [19].

Covariates

The covariates that could possibly affect cognitive function based on the current literature were assessed. The covariates were age, gender, level of education, BMI, neck circumference, working status, smoking status, and clinical comorbidities such as hypertension, diabetes, dyslipidemia, CAD, arrhythmia, CHF, stroke (>3 months, NIHSS <14), and chronic pain (pain >3 months, pain scale ≤ 4).

Data analysis

The continuous variables were presented as mean \pm standard deviation (SD), and categorical variables as frequency (%). The continuous variables were tested for normality with Kolmogorov-Smirnov test. The Mann-Whitney non parametric test was used to analyze difference in continuous variables and Chi-square test was used for categorical data. Risk factors associated with cognitive function was analyzed using backward L-R multiple logistic regression. A $p < 0.05$ (two sided) was considered significant. Statistical analysis was performed using SPSS version 28.0.

Results

Sample characteristics

A total of 178 individuals aged 60 years old and above, presented at outpatient clinics and met eligibility criteria, were evaluated. The mean age was 67 ± 5 years (range 60–88) (**Table 1**). Higher proportion of the samples was male (61.8%), Javanese (73.6%), completed at least 12 years of education (40.4%), and were housewife or without formal job (44.4%). Majority of the patients had normal BMI (59%), had neck circumference ≤ 40 cm (88.8%), non-smoker (61.2%), and had hypertension (62.4%). Approximately 43.3% of patients had history of CAD, and 18.0% had chronic pain. According to GDS-15 scores, depression was found in 7 out of 178 patients (3.9%) and all of them had cognitive impairment and a (**Table 1**). There were 11.2% (20/178) of patients had insomnia and all patients with insomnia also had cognitive impairment. There were 67.4% of patients had STOP-Bang score ≥ 3 which was considered as having high OSA risk; the mean STOP-Bang score was 3.

No patients were classified as having psychiatric disorders, circadian rhythm disorder, movement disorder, or parasomnia according to ISQ. Patients who were classified as having insomnia caused by sleep apnea based on ISQ were not included in the analysis as it could affect the multicollinearity on regression analysis because our independent variable was OSA risk.

The prevalence of cognitive impairment and associated factors

The mean score of MoCA-Ina was 23 and 129 (72.5%) of respondents had MoCA-Ina score below 26, which was considered as mild cognitive impairment (MCI) while rest had normal cognitive function. Based on MoCA-Ina assessment, majority of impaired domains were delayed memory recall (98.3%) and visuospatial – executive function (69.1%) followed by language (56.2%), abstraction (41.6%), attention (41.0%), orientation or calculation (10.1%) and language or naming (8.4%). Age, BMI, neck circumference, gender, ethnicity, working status, smoking status and comorbidities had no association with cognitive impairment (**Table 1**). Our data suggested that low education level, having chronic pain and having high OSA risk were associated with cognitive impairment (**Table 1**).

In a multivariate analysis, controlling for age, education, smoking status, BMI, CHF, arrhythmia, stroke, chronic pain, and insomnia, we found that the high OSA risk, chronic pain and have completed 9 years of education only were significantly associated with cognitive dysfunction. The adjusted odds ratio (OR) for having 9 years of education, chronic pain, and high OSA risk were 4.57 (95%CI: 1.79, 11.63), 5.53 (95%CI: 1.19, 25.64) and 2.99 (95%CI: 1.39, 6.46), respectively (**Table 2**).

Table 1. Factors associated with cognitive impairment and normal cognitive

Variable	Overall (n=178) n (%)	MCI (n=129) n (%)	Normal cognitive (n=49) n (%)	p-value
Age (years), mean (\pm SD)	67.3 (\pm 5.5)	67.7 (\pm 5.8)	66.3 (4.3)	0.178 ^a
Body mass index (BMI), mean (\pm SD)	24.5 (\pm 4.3)	24.3 (\pm 4.4)	25.1 (3.9)	0.196 ^a
Neck circumference, mean (\pm SD)	36.5 (\pm 2.9)	36.4 (\pm 3.0)	36.7 (2.6)	0.596 ^a
Male	110 (61.8)	78 (60.5)	32 (65.3)	0.674 ^b
Education level				0.007 ^{b**}
Completed 9 years of education	57 (32)	50 (38.8)	7 (14.3)	
Completed 12 years of education	72 (40.4)	48 (37.2)	24 (49.0)	
Completed >12 years of education	49 (27.5)	31 (24.0)	18 (36.7)	
Ethnicity – Java	131 (73.6)	95 (73.6)	36 (73.5)	1.000 ^b
Working status				0.390 ^b
Working	58 (32.6)	41 (31.8)	17 (34.7)	
Retired	41 (23.0)	27 (20.9)	14 (28.6)	
Housewife/ no work	79 (44.4)	61 (47.3)	18 (36.7)	
Smoking status				0.228 ^b
Smoker	10 (5.6)	8 (6.2)	2 (4.1)	
Ex-smoker	59 (33.1)	47 (36.4)	12 (24.5)	
Never smoke	109 (61.2)	74 (57.4)	35 (71.4)	
Comorbidity				
Hypertension	111 (62.4)	82 (63.6)	29 (59.2)	0.714 ^b
Diabetes	48 (27.0)	37 (28.7)	11 (22.4)	0.517 ^b
Dyslipidemia	59 (33.1)	45 (34.9)	14 (28.6)	0.535 ^b
Stroke	31 (17.4)	27 (20.9)	4 (8.2)	0.074 ^b
Coronary artery disease (CAD)	77 (43.3)	58 (45.0)	19 (38.8)	0.566 ^b
Arrhythmia	26 (14.6)	23 (17.8)	3 (6.1)	0.082 ^b
Congestive heart failure (CHF)	27 (15.2)	24 (18.6)	3 (6.1)	0.066 ^b
Chronic pain	32 (18.0)	30 (23.3)	2 (4.1)	0.006 ^{b**}
Depression	7 (3.9)	7 (5.4)	0 (0.0)	NA ^b
Insomnia	20 (11.2)	20 (15.5)	0 (0.0)	NA ^b
OSA risk – High	120 (67.4)	94 (72.9)	26 (53.1)	0.019 ^{b*}

MCI: mild cognitive impairment; SD: standard deviation

^a Analyzed using a Mann-Whitney test^b Analyzed using a Chi-square test* Significant at $p < 0.05$ **Significant at $p < 0.01$

Table 2. Multivariable logistic regression analysis of variables associated to cognitive impairment

Model	Variable	aOR (95% CI)	p-value
Model 1 (Initial) R ² = 0.263	Age	1.06 (0.99, 1.14)	0.105
	Body mass index (BMI)	0.96 (0.87, 1.05)	0.379
	Smoking status - current	1.86 (0.32, 10.89)	0.490
	Stroke	1.60 (0.46, 5.55)	0.456
	Arrhythmia	3.26 (0.77, 13.73)	0.108
	Congestive heart failure (CHF)	1.18 (0.28, 5.04)	0.819
	Completed 9 years of education	4.29 (1.66, 11.09)	0.003 ^{**}
	Chronic Pain	5.03 (1.04, 24.41)	0.045 [*]
	OSA risk – High	3.09 (1.39, 6.91)	0.006 ^{**}
Model 5 (Final) R ² = 0.250	Completed 9 years of education	4.57 (1.79, 11.63)	0.001 ^{**}
	Chronic pain	5.53 (1.19, 25.64)	0.029 [*]
	OSA risk – High	2.99 (1.39, 6.46)	0.005 ^{**}

* Significant at $p < 0.05$ **Significant at $p < 0.01$

Discussion

Our data found that 67.4% of the elderly had high risk of developing OSA and 72.9% had MCI. A study in Chinese population found the OSA prevalence was 63.7% [21] and a study found that MCI prevalence among those with high risk of OSA was ranging from 11-70%, slightly lower from our study (72.9%) [21]. Our data suggests that age was not associated with cognitive impairment and this is different from a previous study [22]. A study suggested that not all

cognitive abilities decline with age in which the concentration decreases but orientation and executive inhibition improve with age [23].

In the present study, having only nine years of education was associated with cognitive impairment. This is in accordance with previous studies in which high educational level was found to be associated with more cognitive reserve [24-26]. Moreover, individuals with a higher education would likely working in a higher cognitive function environmental, and therefore the pathological neurodegenerative would be inhibited in longer time before the functional or clinical symptoms manifest [27].

In this study we found that having chronic pain was a risk factor for cognitive impairment. A previous study found that pain was associated with cognitive impairment, especially in memory, attention, processing speed, and executive function.²⁸ From the previous imaging evidence, patient with chronic pain showed decrease of cortical gray matter volume of the prefrontal cortex and thalamus. It was suggested that chronic pain was associated with regional abnormalities of cerebral blood flow and areas associated with emotional decision making [28].

Our study found that elderly that had high risk of OSA were associated with MCI in which those who had high OSA risk would have 2.99 times higher risk to develop cognitive impairment. A study found that MoCA score was negatively related with severity of OSA [29]. The mechanism of cognitive impairment in the elderly who are at risk of OSA might be related to the neuroinflammatory process, hypoperfusion, and endothelial dysfunction [30]. In the neuroinflammatory process, hypoxia and repeated reoxygenation conditions will trigger oxidative stress which results in blood brain barrier hyperpermeability and neuroinflammation. This condition will result in leakage of plasma proteins into the arteriolar walls and perivascular cavities (Virchow-Robin spaces) as well as the accumulation of macrophages and fibrosis in the arteriolar walls, resulting in cerebral small vessel disease (CSVD) [30].

Hypoxia will induce ischemic condition and eventually activate inflammatory factors. These will activate microglia to become a toxic proinflammatory phenotype that will cause disruption of white matter and lacunar infarct and eventually lead to progressive neuronal synaptic plasticity dysfunction [30]. Meanwhile, there will be cerebral hypoperfusion in bad collateral circulation area, which will eventually also cause lacunar infarct. Sleep fragmentation and thoracic pressure swings which happened in OSA will cause amyloid deposition on accumulation of Alzheimer Dementia neuropathology. All of these mechanisms will lead to neuronal dysfunction and decrease of neuronal plasticity which will eventually cause cognitive impairment [30].

Study limitations

As a cross-sectional study, this study could not establish a causal relationship. A longitudinal prospective therefore might be needed. Furthermore, we used self-reported questionnaire to evaluate OSA risk, depression, and other sleep disorders which could potentially cause bias. A follow-up study with direct examination of OSA could provide more accurate result. Although we had already adjusted the confounding factors, based on R^2 value, this study could only explain approximately 25% of the association possibility between those risk factors, meaning that there might be other confounders which were not assessed in this study.

Conclusion

The present study suggests a high prevalence of MCI among high-risk of OSA elderly patients in Surabaya and there was a strong association between those with high risk of OSA and cognitive dysfunction. Therefore, screening and comprehensive management of OSA high-risk individuals might be beneficial to improve or preserve their cognitive function. Meanwhile, chronic pain as another risk factor of having MCI also need to be carefully evaluated and managed.

Ethics approval

Written informed consent was obtained from all eligible participants. This study was approved by the Research Ethics Committee of the Dr. Soetomo General Hospital (0253/KEPK/IX/2021) and Universitas Airlangga Hospital (171/KEP/2021).

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Conflict of interest

The authors declare that they have no competing interests.

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Underlying data

Derived data supporting the findings of this study are available from the first author on request.

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