



UNIVERSITI PUTRA MALAYSIA

FACTORS ASSOCIATED WITH THE RISK OF OBSTRUCTIVE SLEEP APNEA AMONG OPEN-ANGLE GLAUCOMA PATIENTS ATTENDING OPHTHALMOLOGY CLINIC IN A TEACHING HOSPITAL, MALAYSIA

OBED TWESAN MUTEB

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By

OBED TWESAN MUTEB

**Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia,
in Fulfilment of the Requirements for the Degree of Master of Science**

August 2021

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Science

FACTORS ASSOCIATED WITH THE RISK OF OBSTRUCTIVE SLEEP APNEA AMONG OPEN-ANGLE GLAUCOMA PATIENTS ATTENDING OPHTHALMOLOGY CLINIC IN A TEACHING HOSPITAL, MALAYSIA

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August 2021

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Glaucoma is the most prevalent cause of permanent vision loss in the world. There have been some findings that have shown an association between open-angle glaucoma (OAG) and obstructive sleep apnea (OSA) in Caucasian and Chinese people, however, there have been no any similar studies published from South-East Asia. Detection of OSA in a glaucoma patient and initiating optimal treatment for both conditions will arrest the progress of both medical problems. Therefore this study objective was to determine the factors (socio-demography, medical co-morbidities) associated with the risk of OSA in OAG patients, as well as the relationship between glaucoma parameters and OSA by using the STOP-BANG questionnaire. This study was a cross-sectional study that was carried out in the Ophthalmology clinic in Hospital Pengajar Universiti Putra Malaysia, Serdang, Seri Kembangan from November 2019 to January 2021 using a convenience sampling method to collect 442 respondents, with a response rate of 98.2% (males:245,55.4%, females:197,44,6%). Ethical approval was obtained from both National Medical Research Register (NMRR) and institutional Ethics Committee for Research Involving Human Subject (JKEUPM). Participants who fulfilled the inclusion criteria (aged ≥ 40 years with underlying open-angle glaucoma) were recruited. Research tools used were a validated questionnaire that had questions on socio-demography, ocular history, medical history, and also incorporated the STOP-BANG questionnaire. STOP-BANG questionnaire was used to classify patients as low risk (≤ 2) and moderate to high risk (score ≥ 3) of OSA. The patients also underwent a full ocular and complete ear, nose and throat examination. SPSS v25.0 was used to perform the statistical analysis. Level of significance was taken as ≤ 25.0 . The mean age was 64.2 ± 8.9 years. The prevalence of moderate to high risk of OSA was 247(55.9%) that includes females (n=51,11.54%), and male (n=196,44.34%). Predictors of moderate to high risk of OSA by using the multiple logistic regression analysis were males (odds ratio (OR) = 189.7, 95% confidence interval (CI) = 55.21, 651.69), individuals with a higher BMI (OR = 1.23, 95% CI =

1.14, 1.33), participants who were diabetics (OR = 3.1, 95% CI = 1.45, 6.63) and having hypertension (OR = 70.73, 95% CI = 22.59, 221.50). This study reported that in glaucoma patients, the prevalence of moderate to high risk of OSA is higher than that of the general population. The treating ophthalmologist should consider screening for OSA in glaucoma patients, especially in those with factors identified as predisposing to OSA.

Key words: Glaucoma, open-angle glaucoma (OAG), obstructive sleep apnea (OSA), STOP-BANG questionnaire, ophthalmology clinic.



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**FAKTOR-FAKTOR YANG BERKAITAN DENGAN RISIKO APNEA TIDUR
OBSTRUKTIF DALAM KALANGAN PESAKIT GLAUKOMA SUDUT
TERBUKA YANG MENGHADIRI KLINIK OPTALMOLOGI DI HOSPITAL
PENGAJARAN, MALAYSIA**

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Glaukoma adalah sumber kehilangan penglihatan kekal yang paling kerap berlaku di dunia. Terdapat beberapa penemuan yang menunjukkan hubungan antara glaukoma sudut terbuka (OAG) dan apnea tidur obstruktif (OSA) pada orang putih dan Cina, namun, belum ada kajian serupa yang diterbitkan dari Asia Tenggara. Pengesanan OSA pada pesakit glaukoma dan memulakan rawatan yang optimum untuk kedua-dua keadaan akan menghentikan perkembangan masalah perubatan ini. Oleh itu objektif kajian ini adalah untuk menentukan faktor-faktor (sosio-demografi, co-morbiditi perubatan) yang berkaitan dengan risiko OSA pada pesakit OAG, serta hubungan antara parameter glaukoma dan OSA dengan menggunakan borang soal-selidik STOP-BANG. Kajian ini adalah kajian keratan rentas yang dilakukan di klinik Oftalmologi di Hospital Pengajar Universiti Putra Malaysia, Serdang, Seri Kembangan. Jumlah peserta kajian adalah 442 orang. Kadar respons adalah 98.2% (lelaki: 245 (55.4%), perempuan: 197 (44.6%). Kajian ini dijalankan dari November 2019 hingga Januari 2021. Kelulusan etika diperoleh dari kedua-dua Daftar Penyelidikan Perubatan Nasional (NMRR) dan Jawatankuasa Etika Universiti Penyelidikan Melibatkan Manusia Univesiti Putra Malaysia(JKEUPM). Peserta yang memenuhi kriteria kemasukan (berumur ≥ 40 tahun dengan glaukoma sudut terbuka yang mendasari) telah direkrut. Alat kajian yang digunakan adalah borang soal-selidik yang telah disahkan penggunaannya yang mempunyai soalan-soalan mengenai sosio-demografi, sejarah okular, sejarah perubatan, dan juga melibatkan borang soal-selidik STOP-BANG. Borang soal selidik STOP-BANG digunakan untuk mengklasifikasikan pesakit sebagai risiko rendah (skor ≤ 2) dan risiko sederhana ke tinggi (skor ≥ 3) OSA. Pesakit juga menjalani pemeriksaan telinga, hidung dan tekak, dan juga mata yang lengkap. Pakej enyelidikan statistik Sains Sosial (SPSS) versi 25.0 telah digunakan untuk melakukan semua kajian statistik. Tahap signifikan diambil sebagai $p < 0.05$. Umur min ialah 64.2 ± 8.9 tahun. Prevalensi risiko sederhana ke tinggi OSA adalah 247 (55.9%) yang merangkumi wanita ($n = 51, 11.54\%$),

dan lelaki (n = 196,44.34%). Prediktor risiko sederhana ke tinggi OSA dengan menggunakan analisis regresi logistik berganda adalah lelaki [odds ratio (OR) = 189.7, keyakinan selang 95% (CI) = 55.21, 651.69], individu dengan indeks jisim badan (BMI) yang lebih tinggi (OR = 1.23, 95% CI = 1.14, 1.33), peserta yang menghidap diabetes (OR = 3.1, 95% CI = 1.45, 6.63) dan mempunyai hipertensi (OR = 70.73, 95% CI = 22.59.221.50). Kajian ini melaporkan bahawa pada pesakit glaukoma, prevalensi risiko sederhana ke tinggi OSA jauh lebih tinggi daripada populasi umum. Prediktor peningkatan risiko OSA pada pesakit ini harus mendorong doktor yang merawat untuk turut memeriksa kewujudan OSA pada pesakit glaukoma.

Kata kunci: Glaukoma, Glaukoma sudut terbuka (OAG), apnea tidur obstruktif (OSA), soal selidik STOP-BANG, klinik oftalmologi.

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- the research conducted and the writing of this thesis was under our supervision;
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LIST OF ABBREVIATIONS

AHI	Apnea Hypopnea Index
AASM	American Academy of Sleep Study
BMI	Body Mass Index
CDU	Color Doppler Ultrasound
CPAP	Continuous Positive Airway Pressure
DM	Diabetes Mellitus
REM	Rapid Eye Movement
OCT	Optical Coherence Tomography
VFI	Visual Field Index
RNFL	Retinal Nerve Fiber Layer
AH	Aqueous Humor
TM	Trabecular Meshwork
IOP	Intra-Ocular Pressure
OSA	Obstructive Sleep Apnea
OSAS	Obstructive Sleep Apnea Syndrome
OSAHS	Obstructive Sleep Apnea Hypopnea Syndrome
NTG	Normal Tension Glaucoma
ACG	Angle Closure Glaucoma
OAG	Open-Angle Glaucoma
CVD	Cardio Vascular Disease
PACG	Primary Angle Closure Glaucoma
SD-OCT	Spectral Domain Optical Coherence Tomography
PAC	Primary Angle Closure

WHO	World Health Organization
BQ	Berlin Questionnaire
SBQ	STOP-BANG Questionnaire
SQ	Stop Questionnaire
ESS	Epworth Sleepiness Scale
CSR	Central Serous Chorioretinopathy
CRVO	Central Retinal Vein Occlusion
CPAT	Continuous Positive Airway Therapy
PSD	Pattern strander Deviation
MD	Mean Deviation

CHAPTER 1

INTRODUCTION

This study is aimed to determine the factors that impact sleep apnea risk in patients with open-angle glaucoma who attended the Ophthalmology clinic in Hospital Pengajar Universiti Putra Malaysia (HPUPM). This chapter provides an overview of the research, as well as lists of problem statements, significance, hypotheses, objectives, and research questions.

1.1 Background

Globally, glaucoma is an important cause of irreversible loss of vision (Kaufman, 2020). Some studies have reported a strong connection between open-angle glaucoma (OAG) and obstructive sleep apnea (OSA) (Rao, 2017). Glaucoma is a category of pathological disorders that mainly involve the optic nerves which causes it to deteriorate over time, resulting in retinal ganglion cell dysfunction and vision loss. The most common type of glaucoma, which may or may not be related to elevated intraocular pressure is OAG. The treatment of glaucoma consist of medical or surgical methods to prevent damage to the optic nerve (Sena & Lindsley, 2017). Glaucoma is associated with progressive optic neuropathy and causes the optic disc to lose its original configuration when all retinal ganglion cells together with their axons degenerate, ultimately resulting in blindness (Bertaud et al., 2019).

Primary open-angle glaucoma mainly affects older-aged adults; however, congenital glaucoma maybe seen in infants. Primary open-angle glaucoma (POAG) is the most common type of glaucoma and is usually associated with elevated intraocular pressure (IOP), so lowering IOP remains the gold standard for treating most types of glaucoma, even normotensive glaucoma (NTG) which has normal IOP (Carreon et al., 2017). Normotensive glaucoma is classified as a multiple factor optic neuropathy, leading to gradual retinal ganglion's death and vision loss. While NTG and POAG may appear nearly the same, with similar cupping of the optic disc, retinal nerve fiber bundles defect, and deterioration of the visual field. NTG is a type of POAG which is distinguished by having an IOP which is within the normal limits. (Fan et al., 2019).

Globally in 2010, about 2.1 million patients were blind and 4.2 million patients suffered from moderate to severe vision impairment due to glaucoma (Bourne et al., 2016). Glaucoma remains the leading cause of irreversible loss of vision (Bourne et al., 2016). Age-related macular degeneration comes in third after cataract and glaucoma, causing blindness globally, and diabetic retinopathy occupies the fifth rank (Leasher et al., 2016). In 2015, cataracts, uncorrected refractive errors, glaucoma, corneal deficiency and age-related macular degeneration were identified as the main causes for blindness and visual impairment in Southeast Asian and Oceania countries specifically (Keeffe et al., 2019).

OSA is a breathing condition characterized by frequent upper airway attacks during sleep, resulting in reduced airflow, followed by hypoxemia and hypercapnia, arousals, sympathetic stimulation, and aggravated intrathoracic pressure fluctuation.

These levels of severity are the basis of the apnea-hypopnea index (AHI) measured in the overnight polysomnography (Won et al., 2018).

Symptomatic OSA affects two per cent of females and four per cent of males, but the prevalence of latent OSA is postulated to be much higher than these figures. The eye pathologies associated with OSA include keratoconus, floppy eyelid syndrome, non-arthritis anterior ischemic optic neuropathy, glaucoma, central serous chorioretinopathy, and papilledema (Skorin & Knutson, 2016).

Over the years, there have been several studies that proved a relationship between sleep apnea and OAG or NTG (Lin, 2013). OSA presence was confirmed as a significant risk factor for NTG (Gharraf et al., 2016). According to Huon and colleagues' meta-analyses, OSA patients have a higher risk of having glaucoma ($p = 0.001$) than non-OSA patients, and the average pooled OR (odds ratio) for OSA was 1.746 ($p = 0.002$) in the inverse direction, indicating a strong link between OSA and glaucoma (Huon et al., 2016).

Friedlander and co-researchers also showed that the prevalence of POAG was common among OSA patients. The POAG incidence in the general population is 2.5%, which is less than those with OSA. POAG was found to be significantly prevalent ($p < 0.001$) among OSA patients (Friedlander et al., 2018). Among elderly patients in Europe and America, the prevalence of OSA is estimated to be about 38%. A significant relationship between the male gender, age, and high BMI on the prevalence of OSA has also been identified (Senaratna et al., 2017).

In Taiwan, the risk for glaucoma is higher among people with OSA. However, following surgery for OSA, the risk for glaucoma was lowered (Chen et al., 2014).

Glaucoma is a common complication of OSA and it has become very clear that glaucoma cases are higher among OSA patients, and this is independent of the relationship between IOP and glaucoma. Therefore, OSA patients should be close monitored for glaucoma even during treatment with continuous positive airway pressure (CPAP) therapy which has also been demonstrated to cause injury to the optic disc (Chaitanya et al., 2016). These eye disorders have been documented among OSA patients with confirmed by polysomnography (Pedrotti et al., 2017). Recently, significant improvement in OSA symptoms is possible with bilateral hypoglossal nerve stimulation using the Genio-system, which may in turn, improve glaucoma symptoms as well (Eastwood et al., 2020).

However, some studies have also argued against the relationship between glaucoma and OSA, it demonstrated that an increased AHI did not increase the chances of glaucoma development. Therefore, there was no correlation was detected between the rate of visual field deterioration and the severity of OSA (Swaminathan et al., 2018). Another study also failed to establish any relationship between hospitalized OSA patients and the presence of OAG in the Caucasian populations (Keenan et al., 2017).

In contrast, high prevalence of OSA was found among POAG individuals as high as 33.3% (Balbay et al., 2014). Early in the disease process, glaucomatous optic nerve atrophy will present with thinning and atrophy of the retinal ganglion cell layer and thus, thinning of the nerve fiber layer above the ganglion cells. The nerve fiber layer consists of the unmyelinated ganglion cell axons; that will shrink concomitantly. In more advanced glaucomatous optic nerve atrophy there will be both cupping of the optic nerve as well as atrophy of the ganglion cell layer and subsequently the nerve fiber layer (Mahabadi et al., 2017).

In summary, from the above-mentioned discussion, it is clear that it has become highly necessary to identify OSA among glaucoma patients and to start treatment early, which can eventually will lead to the improvement of the quality of the patient's life. The aims of this research are to determine the association between OSA risk factors (socio-demography, medical co-morbidities) in OAG patients and also to determine the relationship between glaucoma parameters and OSA by using the STOP-BANG questionnaire.

1.2 Problem Statement

Globally, glaucoma is considered a major public health problem, which not only affects the patient but, also the economy, as it is the second most common cause of blindness. The number of patients suffering from both OAG and angle closure glaucoma (ACG) has increased to 79.6 million by 2020, where 74% were reported to have OAG (Quigley & Broman, 2006) (Sena & Lindsley, 2017). Although previous studies showed that glaucoma and OSA have a significant correlation, this association is still controversial (Sergi et al., 2007). Thus, this study aims to determine if OSA is significantly associated with the presence of glaucoma.

Malaysia is also known to have the highest rate of obesity in South East Asia with a rapid increase in the incidence of obesity over the years. This has created a concern for an increased prevalence of OSA among the Malaysian population that may go undetected. Studies assessing for the risk of OSA in Malaysia mainly assessed a specific group of the population such as bus drivers, pregnant ladies, or diabetic patients. According to Lim et al., 2016. and Yusoff et al., 2010, the prevalence for OSA found in these studies were 44.3%, 8.2%, and 32%, respectively. However, there was no specific study that assessed the risk for OSA among adults in our local population (Lim et al., 2016).

To the best of our knowledge, there is a limited information about the risk of OSA among OAG patients in Malaysia, with only a few Asian-based studies available (Mirrakhimov et al., 2013). Therefore, there is a need to identify significant factors associated with this risk in Malaysia. It is of extreme importance that this relationship should be understood and considered in advance by ophthalmologists, otolaryngologists, and relevant doctors to look for the presence of obstructive sleep apnea in patients with glaucoma.

1.3 Research Questions

1. What is the prevalence of having moderate to high-risk of OSA among patients with OAG?
2. Is there any association between socio-demographic factors with having a moderate to high-risk of OSA in patients with OAG?
3. Is there any association between medical comorbidities with having a moderate to high-risk of OSA in patients with OAG?
4. Is there any association between glaucoma parameters with having a moderate to high-risk of OSA in patients with OAG?

1.4 Research Objectives

1.4.1 General Objectives

The overall aim of this study is to assess the factors related to the risk of having moderate to high risk of OSA in patients with OAG (socio-demographic, medical, and comorbidity) attending the Ophthalmology clinic in Hospital Pengajar Universiti Putra Malaysia (HPUPM) during the study period in 2020.

1.4.2 Specific Objectives

- I. to determine the prevalence of having moderate to high-risk of OSA among patients with OAG.
- II. To determine the association between socio-demographic factors (age, sex, ethnicity, occupation, education level, income, smoking, BMI, alcohol consumption and family history) with having a moderate to high-risk of OSA among OAG patients.
- III. To determine the association between medical comorbidities (diabetes mellitus, hyperlipidemia, hypertension, ischemic heart disease, stroke, chronic renal failure, hypothyroidism, peripheral vascular disorders, depression, migraine, significant blood loss and asthma) with having a moderate to high-risk of OSA in OAG patients.
- IV. To determine the association between glaucoma parameters (type of glaucoma, intraocular pressure, intraocular pressure above target, visual field index, visual acuity, cup/disc ratio, Hoddap-Parrish-Anderson classification and clinical progression) with having a moderate to high-risk of OSA in OAG patients.

1.5 Research Hypothesis

1.5.1 Null Hypothesis

- There is a low prevalence of moderate to high-risk of OSA among OAG patients
- There is no significant association between socio-demographic factors (age, sex, ethnicity, occupation, education level, income, smoking, BMI, alcohol consumption and family history) and having a moderate to high-risk of OSA in patients with OAG.
- There is no significant association between medical comorbidities (diabetes mellitus, hyperlipidemia, hypertension, ischemic heart disease, stroke, chronic renal failure, hypothyroidism, peripheral vascular disorders, depression, migraine, significant blood loss and asthma) and having a moderate to high-risk of OSA in patients with OAG.
- There is no significant association between glaucoma parameters (type of glaucoma, intraocular pressure, intraocular pressure above target, visual field index, visual acuity, cup/disc ratio, Hoddap-Parrish-Anderson classification and clinical progression) and having a moderate to high-risk of OSA in patients with OAG.

1.5.2 Alternative Hypothesis

- There is high prevalence of moderate to high-risk of OSA among OAG patients
- There is a significant association between socio-demographic characteristics (age, sex, ethnicity, occupation, education level, income, smoking, BMI, alcohol consumption and family history) and having a moderate to high-risk of OSA in patients with OAG.
- There is a significant association between medical comorbidities (diabetes mellitus, hyperlipidemia, hypertension, ischemic heart disease, stroke, chronic renal failure, hypothyroidism, peripheral vascular disorders, depression, migraine, significant blood loss and asthma) and having a moderate to high-risk of OSA in patients with OAG.
- There is a significant association between glaucoma parameters (type of glaucoma, intraocular pressure, intraocular pressure above target, visual field index, visual acuity, cup/disc ratio, Hoddap-Parrish-Anderson classification and clinical progression) and having a moderate to high-risk of OSA in patients with OAG.

1.6 Research Significance

The rapid economic development of the communities leads to many changes in their lifestyle, including the increase proportion of unhealthy lifestyle habits, which in turn creates a suitable environment for developing many chronic illnesses. Among them are glaucoma and obstructive sleep apnea. Therefore, this research may be able to bridge this knowledge gap, so that there is an increased awareness of the increased risk of OSA among patients with OAG among clinicians. This can lead to early interventions and implementations of preventive measures and treatments to avoid the systemic complications of OSA and to avoid the progression of glaucoma. Furthermore, this study can potentially be a reference to guide ophthalmologists, otolaryngologists, and sleep physicians regarding the relationship between glaucoma and OSA, so that ocular disorders that may be associated with obstructive sleep apnea may be identified and treated early in their onset.

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