Association of Systemic Hypertension With Primary Open-angle Glaucoma: A Population-based Case-Control Study

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• PURPOSE: To examine the association between systemic hypertension (HTN) and primary open-angle glaucoma (POAG) using Taiwan's nationwide health insurance claims data.
• DESIGN: A case-control study.
• METHODS: Data for this case-control study were retrieved from the Taiwan National Health Insurance Research Database for all 112,929 newly diagnosed patients with POAG from January 2010 through December 2015 (cases), and 449,840 propensity score-matched controls from Taiwan's National Health Insurance system. We performed multiple logistic regression analysis to estimate the odds (ORs) of prior HTN among cases vs controls.
• RESULTS: Of total 562,300 study patients, 296,975 (52.81%) had HTN prior to the index date, 63,528 (56.49%) among cases and 233,447 (51.90%) among controls ($P < .001$). POAG was significantly associated with prior HTN (OR 1.31, 95% CI 1.29-1.33) after adjusting for age, sex, monthly income, geographic location and residential urbanization level, hyperlipidemia, diabetes, coronary heart disease, migraine, hypotension, and obstructive sleep apnea syndrome.
• CONCLUSIONS: POAG is associated with pre-existing HTN, suggesting that internal medicine/family medicine physicians should refer patients with hypertension periodically for regular ophthalmological examinations and ophthalmologists should alert patients with glaucoma to have their blood pressure regularly monitored. (Am J Ophthalmol 2020;218:99–104. © 2020 Elsevier Inc. All rights reserved.)

INTRODUCTION

SYSTEMIC HYPERTENSION (HTN) AFFECTS MORE THAN 25% of the adult population worldwide and is a major public health concern.[1,2] Although it is well established that HTN adversely affects the heart and the kidney,[3,4] its association with primary open-angle glaucoma (POAG) has been inconclusive. Glaucoma is the second leading cause of blindness globally,[5] causing irreversible damage of the retinal ganglion cells and nerve fiber layer. The Blue Mountains Eye Study[6] demonstrated a positive association between HTN and POAG. The Rotterdam study[7] showed no association between systolic blood pressure and POAG, but high diastolic blood pressure was associated with increased risk of low pressure glaucoma. The Baltimore Eye Survey[8] reported an increased risk of glaucoma with increasing (diastolic or systolic) hypertension. In contrast, the Barbados Eye Study[9] found that HTN was not associated with prevalence of POAG at baseline. Further the relative risk of POAG decreased with increasing baseline systolic blood pressure levels. In light of these conflicting results, this study investigated the association of HTN with POAG using population-based nationwide data from Taiwan.

METHODS

• DATABASE: Data were retrieved from the Taiwan National Health Insurance (NHI) Research Database (NHIRD), which is a database of all NHI beneficiaries, over 99% of the Taiwanese population. This database includes the registration files and all medical claims data for approximately 23 million NHI enrollees since 1995 when the NHI program was implemented. The NHIRD provides de-identified data to Taiwanese researchers, enabling longitudinal studies of patients with medical conditions. A large volume of research has been published based on the NHIRD in peer-reviewed international

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TABLE 1. Demographic Characteristics of Patients with Primary Open-Angle Glaucoma (Cases) Diagnosed in 2010-2015 and Matched Controls in Taiwan (n = 562,300)

	Patients with Primary Open-Angle Glaucoma (n = 112,460)		Controls (n = 449,840)		
Variable	Total no.	%	Total no.	%	*P* Value
Age, mean (standard deviation)	59.16 (16.23)	59.49 (16.29)			<.001
Males	59,744	53.12	236,401	52.55	.001
Monthly income					<.001
No income	327	0.29	1,068	0.24	
NT$1-15,840	29,583	26.31	113,841	25.31	
NT$15,841-25,000	40,698	36.19	168,527	37.46	
≥NT$25,001	41,852	37.22	166,404	36.99	
Geographic region					<.001
Northern	59,611	53.01	235,810	52.42	
Central	23,561	20.95	98,590	21.92	
Eastern	2,238	1.99	7,999	1.78	
Southern	27,050	24.05	107,441	23.88	
Urbanization level					<.001
1 (most urbanized)	50,782	45.16	200,325	44.53	
2	40,470	35.99	162,105	36.04	
3	15,061	13.39	61,025	13.57	
4	2,984	2.65	10,277	2.28	
5 (least urbanized)	3,163	2.81	16,108	3.58	
Hyperlipidemia	39,419	35.05	157,718	35.06	.956
Diabetes	34,068	30.29	134,784	29.96	.031
Migraine	3,381	3.01	11,509	2.56	<.001
Obstructive sleep apnea syndrome	1,980	1.76	6,304	1.40	<.001
Hypotension	774	0.69	1,968	0.44	<.001
Coronary heart disease	19,030	16.92	74,859	16.64	.024

journals. This study was approved by the Institutional Review Board of Taipei Medical University (TMU-JIRB N201912007). This study adhered to the Declaration of Helsinki.

• **STUDY SAMPLE:** This study used a retrospective case control design. To select cases, we first identified 122,025 patients with a first-time diagnosis of POAG appearing in a claim for a clinic visit or hospital outpatient department visit from January 1, 2010, to December 31, 2015 (ICD-9-CM codes 365.1, 365.10, and 365.11). We used a look-back period of 3 years to exclude patients with POAG appearing in any claim prior to the index date during the study period. We selected patients with at least 2 claims showing a POAG diagnoses and showing a prescription for topical antiglaucoma medications (for diagnostic validity) and assigned the date of first POAG diagnosis as their index date. We excluded 3,114 patients under 18 years of age because of the low prevalence of POAG and HTN in that age group. The analytic study sample included 112,929 cases with POAG.

To select controls, we first excluded all patients with a medical claim showing a POAG diagnosis during the study period or aged less than 18 years. Out of the remaining NHI beneficiaries we selected a comparison group (controls) similar to cases on demographic and comorbidity variables at baseline. We selected four controls per POAG case by propensity score matching (n = 449,840) using age, sex, monthly income, geographic location (northern, central, southern, and eastern) residential urbanization level, and selected comorbidities expected to be associated with either POAG or HTN, hyperlipidemia, diabetes, coronary heart disease, migraine, hypotension, and obstructive sleep apnea syndrome. We assigned the date of their first utilization of ambulatory care during the index year of the matched case as the control patient's index date. The final study sample included 112,460 POAG patients and 449,840 patients without POAG as controls.

• **EXPOSURE DETERMINATION:** The exposure of interest was HTN preceding the index date (for cases, POAG diagnosis date, and for controls, date of the first ambulatory care claim during the year of diagnosis of their matched case). The outcome of interest was POAG. We identified prior HTN by ICD-9-CM codes 401-405 in ambulatory care visit claims prior to the index date. To strengthen diagnostic validity we identified HTN only if a prescription for antihypertensive medication could be found in the claims.

• **STATISTICAL ANALYSIS:** Analyses were performed using the SAS statistical package (SAS System for Windows, V.9.4, SAS Institute, Cary, NC, USA). We used

TABLE 2. Prevalence of Prior Hypertension Among Sample Patients

	Total (n = 562,300)		Patients with Primary Open-Angle Glaucoma (n = 112,460)		Controls (n = 449,840)	
Prior Hypertension	n, %		n, %		n, %	
Yes	296,975	52.81	63,528	56.49	233,447	51.90
No	265,325	47.19	48,932	43.51	216,393	48.10

chi-squared tests to compare cases and controls on sex, monthly income (<NT$15,841, 15,841-25,000, ≥25,001), geographic location (northern, central, eastern, and southern Taiwan), urbanization level (5 levels: 1 most urbanized and 5 least urbanized), hyperlipidemia, migraine, obstructive sleep apnea syndrome, diabetes, coronary heart disease, and hypotension between patients with POAG and their matched controls. We performed multiple logistic regression analysis were to estimate the odds (ORs) of prior HTN among cases vs controls. A value of $P = .05$ was used to determine statistical significance.

RESULTS

TABLE 1 PRESENTS THE DEMOGRAPHIC CHARACTERISTICS and medical comorbidities of cases and controls. After selecting controls by propensity score matching, we found small but statistically significant differences in age, sex, monthly income, geographical location, and urbanization level of the patient's residence between cases and controls (all $P < .001$), significance largely attributable to large sample size. Cases were also slightly more likely to have diabetes (30.3% vs 30.0%, $P = .031$), migraine (3.0% vs 2.6%, $P < .001$), hypotension (0.7% vs 0.4%, $P < .001$), obstructive sleep apnea syndrome (1.8% vs 1.4%, $P < .001$), and coronary heart disease (16.9% vs 16.6%, $P = .024$) than controls.

Table 2 shows the prevalence of prior HTN among cases and controls; 296,975 sample patients (52.8% of 562,300) had HTN prior to the index date. Prevalence of prior HTN was higher among cases than controls: 63,528 (56.5%) among cases and 233,447 (51.9%) among controls, $P<.001$.

Table 3 presents the covariate-adjusted odds of HTN among POAG vs controls. POAG was significantly associated with prior HTN (OR 1.31, 95% CI 1.29-1.33) after adjusting for age, sex, monthly income, geographic location and residential urbanization level, hyperlipidemia, diabetes, coronary heart disease, migraine, hypotension, and obstructive sleep apnea syndrome. It may be noted that although patients with POAG showed a 31% increased risk of prior HTN compared with controls after adjusting for covariates, the actual magnitude of difference in HTN prevalence between cases and controls was small, 4.6% (56.5% vs 51.9%).

As expected, POAG was significantly associated with prior migraine (OR 1.17, 95% CI 1.12-1.21), hypotension (OR 1.61, 95% CI 1.48-1.75) and obstructive sleep apnea syndrome (OR 1.25, 95% CI 1.18-1.31).

DISCUSSION

THIS POPULATION-BASED CASE-CONTROL STUDY SHOWED that among a population of mostly Han-Chinese ethnicity, persons with HTN are about 31% more likely than controls to develop POAG (OR 1.31).This finding is consistent with a recent meta-analysis[10] which showed that individuals with HTN have about 20% higher risk of developing POAG than individuals without HTN. Another meta-analysis[11] also identified a significant association between HTN and POAG while noting significant heterogeneity of study designs.

This study also adds to the evidence that POAG is associated with prior migraine (OR 1.17, 95% CI 1.12-1.21), obstructive sleep apnea syndrome (OR 1.25, 95% CI 1.18-1.31), and hypotension (OR 1.61, 95% CI 1.48-1.75). It should be noted that high tension open-angle glaucoma and normal tension glaucoma are represented by the same ICD-9-CM codes. Migraine, sleep apnea syndrome, and hypotension are well-documented risk factors[12–15] for low tension glaucoma, and Asians are more susceptible to develop this condition.[12,16]

The observed association between migraine and POAG is consistent with the literature. Migraine is a disorder of the central nervous system with both neural and vascular involvement.[17] During the interictal period, transient abnormal changes in blood vessel diameter also occur in peripheral organs such as fingers and eyes.[18,19] These changes in blood vessel caliber are considered indicative of vasospasm or "vascular dysregulation."[20] Broadway and Drance found that the prevalence of vasospasm and migraine was higher in glaucoma patients with focal ischemia of the optic nerve head and subsequent focal loss of the neuroretinal rim than among glaucoma patients without evidence of these forms of optic tissue damage.[21] Emre and associates also demonstrated that ocular blood flow alteration in glaucoma patients is related to systemic vascular dysregulation.[22]

Our study also reinforces the notion that it is the hypoxia induced by obstructive sleep apnea syndrome that

TABLE 3. Covariate-Adjusted Odds Ratio for Prior Hypertension Among Open-Angle Glaucoma vs Matched Controls (n = 562,300)

Variables	Presence of Primary Open-ANGLE glaucoma	
	Univariate OR, 95% CI	Adjusted OR, 95% CI
Hypertension	1.20[a] (1.19-1.22)	1.31[a] (1.29-1.33)
Age	0.99[a] (0.99-0.99)	0.99[a] (0.99-0.99)
Sex	1.02[a] (1.01-1.04)	1.02[a] (1.01-1.03)
Monthly income		
No income (reference group)	1.00	1.00
NT$1-15,840	0.85 (0.75-0.96)	0.86 (0.76-0.97)
NT$15,841-25,000	0.79[a] (0.70-0.89)	0.80[a] (0.71-0.91)
≥NT$25,001	0.82 (0.73-0.93)	0.82 (0.20-0.93)
Geographic region		
Northern (reference group)	1.00	1.00
Central	0.95[a] (0.93-0.96)	0.97[a] (0.95-0.99)
Eastern	1.11[a] (1.06-1.16)	0.91 (0.84-1.00)
Southern	1.00 (0.98-1.01)	1.01 (0.99-1.03)
Urbanization level		
1 (reference group)	1.00	1.00
2	0.98 (0.97-1.00)	0.99 (0.97-1.00)
3	0.97 (0.95-0.99)	1.00 (0.97-1.02)
4	1.15[a] (1.10-1.20)	1.22[a] (1.13-1.32)
5	0.77[a] (0.74-0.81)	0.80[a] (0.77-0.84)
Hyperlipidemia	1.00 (0.99-1.01)	0.95[a] (0.93-0.96)
Diabetes	1.02 (1.00-1.03)	0.98 (0.97-1.00)
Migraine	1.18[a] (1.14-1.23)	1.17[a] (1.12-1.21)
Obstructive sleep apnea syndrome	1.26[a] (1.20-1.33)	1.25[a] (1.18-1.31)
Hypotension	1.58[a] (1.45-1.72)	1.61[a] (1.48-1.75)
Coronary heart disease	1.02 (1.00-1.04)	0.99 (0.97-1.01)

OR = odds ratio; CI = confidence interval.
[a]$P < .001$.

increases sleep apnea patients' risk of coronary artery disease, heart failure, stroke, and ocular conditions including glaucoma, both NTG and POAG.[23] During repeated and prolonged episodes of breath cessation, the optic nerve head is likely susceptible to ischemia and damage through hypoxia, hemodynamic changes to retinal blood vessels, oxidative stress, mitochondrial dysregulation, and inflammation.[20,24]

In one meta-analysis, Zhao and associates reported a J-shaped association between blood pressure and the risk of POAG.[11] This further lends support to a conjecture that in addition to high blood pressure being associated with POAG, low blood pressure may also be a risk factor for POAG. The pathways through which HTN predisposes to POAG remain to be understood, a relationship that may be complex, involving multiple pathways. High blood pressure may increase intraocular pressure by increased production of aqueous humor (through elevated ciliary blood flow and capillary pressure),[11,25] and decreased aqueous humor drainage as a result of increased episcleral venous pressure.[11,26] Low blood pressure, on the other hand, may reduce ocular perfusion pressure leading to ischemic damage of the optic nerve.[16,27,28]

Population-based studies[29,30] and randomized clinical trials[31,32] have documented evidence that lower systemic blood pressure and lower ocular perfusion pressure is strongly associated with increased risk of POAG, a 6-fold excess risk of POAG for those in the lowest quantile of perfusion pressure in the Baltimore Eye Study.[29] In the Barbados Eye Study, Leske and associates noted that lower ocular perfusion pressure more than doubled the risk of developing POAG.[30] The Thessaloniki Eye Study revealed that a diastolic BP of less than 90 mm Hg produced by antihypertensive treatment was associated with increased cupping and decreased rim area of the optic disc. The use of systemic antihypertensive medication may be associated with exaggerated nocturnal blood pressure reduction which further compromises optic nerve head blood flow.[33,34] Our analysis provides strong evidence that hypotension is highly correlated with hypertension. However, data on intraocular pressure are not available in administrative claims databases and, hence, the relationship between ocular perfusion pressure and POAG requires further assessment based on data from medical records.

Although age is a documented risk factor for glaucoma, our data did not support this finding of other studies. In

the Barbados Eye Study, the prevalence of POAG was especially high at older ages and in men. Among participants 50 years old or older, 1 in 11 had POAG, and prevalence increased to 1 in 6 at age 70 years or older.[35] Similarly, in the National Health and Nutrition Examination Survey 2005-2008, older age (OR 1.09 per year) was significantly associated with glaucoma.[36] In a 11-year follow-up study using nationwide, population-based data, the National Danish Registry of Medicinal Products Statistics confirmed the known positive association between age and glaucoma.[37] It is intriguing that our study does not agree with other studies. This may be due to ethnic differences of a Han-Chinese population and deserves further evaluation.

Besides being an independent risk factor for POAG, age is also documented to be associated with atherosclerosis and hyperlipidemia, risk factors for coronary heart disease. Again our results deviate from the documented literature. Lipids, inflammatory cells, and connective tissue build-up within arterial walls that leads to plaque formation and obstruction of blood flow that affects systemic vasculature also affects ocular vasculature.[38] Ronkko and associates found that in the ocular tissue of POAG patients, there is overexpression of a specific enzyme which indicates atherosclerosis.[39] In our study, coronary heart disease (assumed to be a proxy for atherosclerosis) was not a statistically significant predictor of POAG risk after adjusting for covariates such as obstructive sleep apnea syndrome and hyperlipidemia.

The study has several strengths. We used medical claims data from NHIRD, a population-based database that covers approximately 23 million participants, the entire population of Taiwan, providing a large study sample without loss to follow-up as all citizens avail care from NHI-approved providers for most medical care. We minimized bias by using propensity score matching to establish a comparable control group based on demographics and comorbidities. Documented comorbidity risk factors for POAG were accounted for in regression analysis. The study has some limitations. First, the number of patients with glaucoma may be underestimated given that it is asymptomatic, especially in the early and moderately advanced stages. Patients with HTN are seldom referred for routine ophthalmic evaluation and screening, unlike diabetes mellitus patients. We anticipate some undiagnosed POAG among the control group although the magnitude of underdiagnosis among controls is likely to be low, given that about 70% of controls show evidence of eye examination by an ophthalmologist during the study period. Despite the potential for POAG underdiagnosis among those who missed their eye exams, the associated bias would have little effect on the essential conclusion of the study. However, such bias would likely drive the result towards the null hypothesis, indicating that our detected difference may be smaller than the actual difference between the groups. A second limitation is that untreated low tension glaucoma cases (without a prescription) were excluded from the study. Finally, more than 95% of the Taiwanese population is of Han Chinese ethnicity, which may limit generalizability of the findings to other ethnic groups.

The study finds that HTN may be a risk factor for subsequent development of POAG. Findings suggest that ophthalmologist should alert patients with glaucoma to have their blood pressure regularly monitored and internists should refer hypertensive patients periodically for complete ophthalmological evaluation.

KEY POINTS

- A total of 56.49% patients with POAG had prior hypertension.
- Prevalence of prior hypertension was higher among patients with POAG than controls.
- POAG was significantly associated with pre-existing hypertension (adjusted OR 1.31).

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