Original Article

Increased incidence of open-angle glaucoma among hypertensive patients: an 11-year nationwide retrospective cohort study

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Objective: To evaluate the risk of open-angle glaucoma (OAG) among patients with systemic hypertension (HTN).

Methods: This retrospective propensity-score–matched cohort study included patients with HTN and a matched comparison cohort from the Korean National Health Insurance Service National Sample Cohort database. The HTN group was defined as patients who were prescribed antihypertensive medication, or SBP at least 140 or DBP at least 90 mmHg. The OAG group was defined as patients satisfying OAG criteria during repeated visits to an ophthalmologist. The Charlson comorbidity index was used to control for systemic conditions. Cox proportional hazard regression analysis was performed.

Results: OAG occurred in 2.0% ($n = 1961$) in the HTN group, and 1.7% ($n = 1692$) in the comparison group ($P < 0.001$). The OAG incidence rates in patients with and without HTN were 19.0 and 16.4 per 10 000 person-years, respectively. HTN was associated with increased OAG incidence [adjusted hazard ratio (HR) = 1.16, 95% confidence interval: 1.09–1.24] from our multivariate Cox model. Participants with higher SBP (adjusted HR = 1.12 for 120–139 mmHg group; and adjusted HR = 1.20 for ≥140 mmHg group) was more likely to have subsequent OAG compared with participants with less than 120 mmHg blood pressure. Participants with higher DBP (adjusted HR = 1.11 for 80–89 mmHg group: and adjusted HR = 1.07 for ≥90 mmHg group) showed similar trends as participants with less than 80 mmHg blood pressure.

Conclusion: Patients diagnosed with HTN are more likely to experience subsequent OAG than those without HTN.

Keywords: antihypertensive medication, Charlson comorbidity index, glaucoma, National Health Insurance Service National Sample Cohort 2002–2013, open-angle glaucoma, systemic hypertension

Abbreviations: CI, confidence interval; HR, hazard ratio; KCD, Korean Classification of Diseases; KEDI, Korean electronic data interchange; KNHIS, Korea National Health Insurance Service; NHIS-NSC 2002–2013, National Health Insurance Service National Sample Cohort 2002–2013; OAG, open-angle glaucoma

INTRODUCTION

Although open-angle glaucoma (OAG) is associated with irreversible blindness [1], the exact cause and mechanism of optic nerve damage in OAG have not been determined. Epidemiological studies have thus been conducted to identify risk factors for OAG. Systemic hypertension (HTN) is one of the systemic diseases most studied as a risk factor of OAG development. Several mechanisms have been suggested to explain the relationship between OAG and HTN. One theory is that increased aqueous production, due to HTN-related enhancement of ciliary artery perfusion, causes increased intraocular pressure (IOP) [2]. Increased IOP can also be generated by the disturbance of aqueous humor outflow that results from elevation of episcleral venous pressure [3]. Circulatory disturbances related to the reduction of ocular perfusion to the optic nerve head (ONH) have also been suggested as a cause of optic nerve damage [4]. Reduction of the blood supply to the ONH could be induced by retinal vascular narrowing [5,6] or impairment of auto-regulation of the posterior ciliary circulation by HTN [6,7]. Treatment of HTN could result in lowered ocular perfusion to the ONH, due to the induced hypotensive status [8–10].

Many previous studies have investigated the correlation between blood pressure (BP) and IOP [5,11–14]; however, not all studies showed a significant correlation. Several studies have also evaluated the effect of HTN on the risk of OAG development [15–18] but also yielded inconsistent

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results. Recently, two meta-analyses of the relationship between HTN and OAG have shown that HTN increases the risk of OAG development [19,20]. However, only two longitudinal cohort studies investigating the association between OAG and HTN were included in these meta-analyses; moreover, these two longitudinal studies showed contradictory results. Additional longitudinal cohort studies will therefore be helpful to clarify the effect of HTN on OAG development.

In the present study, we investigated the risk of OAG development among patients with HTN, using a propensity-score matched sample of 200 124 adults from the National Health Insurance Service (NHIS) National Sample Cohort 2002–2013 (NHIS-NSC 2002–2013) in South Korea.

METHODS

Statement of ethics

This retrospective study was approved by our institutional review board, which waived the requirement for informed consent.

Database

South Korea started a nationwide health insurance system in 1989, and almost all South Koreans (ca. 97%) are currently enrolled. In South Korea, general health screening is recommended for all individuals above 40 years old. It is conducted once every 2 years, and the cost is borne fully by the NHIS. In 2016, the NHIS developed a new dataset using this general health screening results for research purposes. The health screening dataset included approximately 500 000 (10% of all South Korean adults) randomly selected adults aged 40–79 years among the 2002 NHIS beneficiaries. The dataset contains health examination results and all healthcare data of these randomly selected adults from 2002 to 2013. The Korea National Health Insurance Service and medical providers exchange all cost-related healthcare information via Korean electronic data interchange (KEDI) codes [e.g. the KEDI code for 'Visual Field Examination (Automated)' is E6691, and for 'Cosopt; Merck and Co., Inc.' is 655500390 (E09060211)]. Therefore, this database provides detailed information on procedures and prescription drugs, as well as diagnostic codes and personal information.

Systemic hypertension and glaucoma

In this study, we defined HTN as 'exposure to antihypertensive medication' or 'at least 140 mmHg SBP' or 'at least 90 mmHg DBP' based on health examination results in 2002. Antihypertensive medication comprised more than 200 types of generic antihypertensive drugs, including angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, diuretics, calcium channel blockers, and beta-blockers. Association between degree of high BP and OAG was evaluated on the basis of subgroups of SBP (<120/120–139/≥140 mmHg) and DBP (<80/80–89/≥90 mmHg).

Development of OAG was defined as a patient satisfying the following three criteria in more than one visit to an ophthalmologist: diagnosis with 'primary OAG' [Korean Classification of Diseases (KCD) H401, corresponding to International Classification of Diseases 9 Clinical Modification 365.11], receipt of a visual field test, and receipt of prescriptions for antiglaucoma medication. To include newly incident OAG, we excluded patients who were diagnosed with OAG in 2002. Diagnosis with OAG in 2003 or later was considered as OAG development.

Matching variables: sociodemographic factors and comorbidity

Sociodemographic factors were obtained from the database: age (40–49, 50–59, 60–69, ≥70 years), sex, residential area, and household income. The Charlson comorbidity index (CCI) (with the exception of acquired immune deficiency syndrome, which was not included in the NHIS-NSC 2002–2013 database to protect privacy), including a total of 15 comorbidities based on the KCD in 2002, was evaluated and matched between two groups. The list of diseases for the CCI is provided in Supplementary Table 1, http://links.lww.com/HJH/A714. The prevalence of chronic pulmonary disease, peptic ulcer, any form of liver disease, and any form of diabetes mellitus was relatively high (>2%), and these selected comorbidities were used for matching. The matching variables used were age group, sex, residential area, income level, chronic pulmonary disease, peptic ulcer, liver disease, diabetes mellitus, and CCI index.

Study sample

Of the 541 866 randomly selected adult patients in the NHIS-NSC 2002–2013 health screening dataset in 2002, we included all patients who had undergone general health screening in 2002 ($n = 294\,729$). Patients with missing BP data were excluded ($n = 169$), and trimming was done by deleting the top and bottom 1% for SBP or DBP ($n = 6150$). Thus, among the remaining 288 410 adults, there were 116 208 hypertensive patients, including 96 849 participants with high BP and an additional 19 359 participants with a history of antihypertensive medication. After propensity-score matching in 1 : 1 ratio, there were 100 062 patients with HTN and 100 062 matched patients without HTN in 2002.

Statistical analysis

Descriptive statistics of the dataset were prepared. Propensity score analysis, which can reduce the potential bias in estimated effects obtained from observational studies, is an effective covariate-balancing strategy; we therefore determined propensity scores by estimating a logistic regression to predict HTN using (and thus controlling for) sociodemographic factors, chronic pulmonary disease, peptic ulcer disease, liver disease, diabetes mellitus, and CCI. The estimated propensity scores were matched using a greedy algorithm. To identify the association between HTN and OAG, univariate and multivariate Cox proportional hazard regression analyses were performed and the results expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). The proportional hazards assumption was assessed by a Cox model with Schoenfeld residuals, and the assumption was not violated.

For subgroup analyses, groups were stratified into subgroups (40–64 years or ≥65 years of age; male or female

TABLE 1. Characteristics of the study population (systemic hypertension group and comparison group, $n = 200\,124$)

Variables	Comparison group ($n = 100\,062$)	HTN group ($n = 100\,062$)	*P* value
OAG			<0.001
Not occurred	98 370 (98.3)	98 101 (98.0)	
Occurred	1692 (1.7)	1961 (2.0)	
Comorbidities			
Chronic pulmonary diseases	3513 (3.5)	3606 (3.6)	0.262
Peptic ulcer	7013 (7.0)	7103 (7.1)	0.432
Liver diseases	2850 (2.9)	2986 (3.0)	0.071
DM	2695 (2.7)	2687 (2.7)	0.912
CCI			0.748
0	84 453 (84.4)	84 335 (84.3)	
1	11 571 (11.6)	11 597 (11.6)	
2	2988 (3.0)	3067 (3.1)	
≥3	1050 (1.1)	1063 (1.1)	
Variables for matching			
Age group (year)			0.870
40–49	41 788 (41.8)	41 760 (41.7)	
50–59	32 730 (32.7)	32 618 (32.6)	
60–69	20 380 (20.4)	20 459 (20.5)	
≥70	5164 (5.2)	5225 (5.2)	
Sex			0.515
Male	64 858 (64.8)	64 719 (64.7)	
Female	35 204 (35.2)	35 343 (35.3)	
Residence			0.631
Seoul (metropolitan)	16 712 (16.7)	16 765 (16.8)	
2nd area	16 386 (16.4)	16 493 (16.5)	
3rd area	24 414 (24.4)	24 171 (24.2)	
4th area	42 550 (42.5)	42 633 (42.6)	
Household income			0.458
0–30%	23 349 (23.3)	23 378 (23.4)	
30–70%	32 430 (32.4)	32 178 (32.2)	
70–100%	44 283 (44.3)	44 506 (44.5)	

CCI, Charlson comorbidity index; DM, diabetes mellitus; HTN, hypertension; OAG, open-angle glaucoma. Seoul, a metropolitan area in Korea; the second area includes the largest province, the third area includes the second largest city, and two second–third largest provinces; and the fourth area includes other areas in Korea.

sex; without comorbidity of CCI = 0 or with comorbidity of CCI ≥ 1; and presence of diabetes mellitus). Cumulative OAG incidence during the up-to-11-year follow-up period was described using a Kaplan–Meier curve. We defined the index date: the follow-up period began on 1 January 2003 for all patients. There were 153 patients who received medical care only in 2002 (mainly because of death); this population was excluded from the survival analysis. The follow-up ended at the time of OAG development, or at the date of last medical care, for the period through 2013. A significance level of 0.05 was selected. The statistical packages SAS System for Windows (Version 9.4; SAS Institute Inc., Cary, North Carolina, USA) and Stata/MP (Version 14.0; StataCorp, College Station, Texas, USA) were used.

RESULTS

Table 1 shows the characteristics of the study population (100 062 and 100 062 patients with and without HTN, respectively). Overall, patients with HTN were more likely than the comparison group to have a subsequent OAG diagnosis (2.0% for the HTN group, 1.7% for the comparison group, $P < 0.001$). There were no significant differences in matching variables, including comorbidities and sociodemographic factors, between the two groups.

Table 2 shows the HRs for OAG incidence during the up-to-11-year follow-up period using univariate and multivariate Cox proportional hazard regression. Based on multivariate Cox regression, patients with HTN were more likely to have OAG occurrence than those in the comparison group (adjusted HR = 1.16, 95% CI: 1.09–1.24) after adjusting for comorbidities and sociodemographic factors. Chronic pulmonary diseases, peptic ulcer, and liver diseases were not significantly associated with OAG; however, diabetes mellitus independently increased OAG risk (adjusted HR = 1.43, 95% CI: 1.17–1.75). Increasing CCI score, older age, male sex, and higher income were also associated with an increased risk of OAG, and there were regional disparities in OAG development.

A total of 2068 722 person-years (median: 10.9 years), including 1034 500 person-years for the HTN group and 1034 222 person-years for the comparison group, were examined (Fig. 1). OAG incidence for the HTN and comparison groups was 19.0 per 10 000 person-years and 16.4 per 10 000 person-years, respectively. The adjusted HRs, based on multivariate Cox regression in each subgroup, are described as a forest plot in Fig. 1. In subgroup analysis, although OAG occurred more frequently in individuals at least 65-years-old, the risk of OAG in those with HTN was higher in adults aged 40–64 years (adjusted HR = 1.17) than in those over 65 years (adjusted HR = 1.07) after adjustment for comorbidities and sociodemographic factors. The risk of OAG in patients with HTN was lower in women (adjusted HR = 1.13) than in men (adjusted HR = 1.18) after adjustment.

Subgroup analysis revealed that HTN independently increased the OAG risk (HR, 1.06–1.22) regardless of comorbidity or demographic status; the increased OAG risk in the HTN group was consistent across all subgroups (*P* for interaction: 0.332–0.491). However, the adjusted HR for OAG in the HTN group was only 1.06 in the subgroup with diabetes mellitus, indicative of the association between diabetes mellitus and OAG.

Kaplan–Meier survival curves for cumulative OAG incidence over time are given in Fig. 2. Figure 2a shows a faster increase in overall OAG development for the HTN group vs. the comparison group, whereas Fig. 2b shows that OAG occurred more frequently in patients with comorbidities than in those without comorbidities. However, consistent with the adjusted HRs in Fig. 1, the OAG rates between the HTN group and the comparison group were markedly different in both groups (comorbidity present or absent).

Figure 2c and d shows cumulative OAG development among participant with SBP of less than 120/120–139/at least 140 mmHg and DBP of less than 80/80–89/at least 90 mmHg. In our multivariate model, higher SBP was associated with higher risk of subsequent OAG development (adjusted HR = 1.12 for SBP 120–139 mmHg group, 95% CI: 1.02–1.22; and adjusted HR = 1.20 for SBP at least 140 mmHg group, 95% CI: 1.10–1.32). These trends were also clearly observed in Fig. 2c. However, somewhat different trends were observed in DBP subgroups. In the survival curve of Fig. 2d, midgroup of DBP 80–89 mmHg seemed to be higher risk of OAG among DBP subgroups.

TABLE 2. Predictive values for subsequent open-angle glaucoma development based on univariate and multivariate Cox regression ($n = 200\,124$)

Variables	Univariate Cox			Multivariate Cox		
	HR (95% CI)		*P* value	HR (95% CI)		*P* value
HTN						
No	1 (ref)			1 (ref)		
Yes	1.16	1.08–1.23	<0.001	1.16	1.09–1.24	<0.001
Chronic pulmonary diseases						
No	1 (ref)			1 (ref)		
Yes	1.41	1.21–1.64	<0.001	0.95	0.78–1.16	0.611
Peptic ulcer						
No	1 (ref)			1 (ref)		
Yes	1.45	1.30–1.62	<0.001	1.05	0.89–1.25	0.568
Liver diseases						
No	1 (ref)			1 (ref)		
Yes	1.57	1.34–1.84	<0.001	1.16	0.95–1.41	0.153
DM						
No	1 (ref)			1 (ref)		
Yes	2.15	1.87–2.48	<0.001	1.43	1.17–1.75	0.001
CCI						
0	1 (ref)			1 (ref)		
1	1.45	1.33–1.59	<0.001	1.22	1.04–1.43	0.015
2	1.75	1.50–2.05	<0.001	1.34	1.04–1.73	0.022
≥3	2.63	2.11–3.29	<0.001	1.76	1.27–2.46	0.001
Age group (year)						
40–49	1 (ref)			1 (ref)		
50–59	1.80	1.65–1.96	<0.001	1.82	1.67–1.98	<0.001
60–69	2.65	2.43–2.90	<0.001	2.76	2.53–3.02	<0.001
≥70	3.07	2.70–3.51	<0.001	3.18	2.78–3.64	<0.001
Sex						
Male	1 (ref)			1 (ref)		
Female	1.04	0.97–1.11	0.267	0.90	0.84–0.97	0.004
Residence						
Seoul (metropolitan)	1 (ref)			1 (ref)		
2nd area	0.76	0.68–0.85	<0.001	0.81	0.73–0.91	<0.001
3rd area	0.87	0.79–0.96	0.004	0.86	0.78–0.94	0.002
4th area	0.77	0.70–0.84	<0.001	0.75	0.69–0.82	<0.001
Household income						
0–30%	1 (ref)			1 (ref)		
30–70%	1.08	0.99–1.19	0.091	1.15	1.05–1.26	0.004
70–100%	1.26	1.16–1.38	<0.001	1.40	1.28–1.53	<0.001

CCI, Charlson comorbidity index; CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; HTN, hypertension; OAG, open-angle glaucoma. Seoul, a metropolitan area in Korea; the second area includes the largest province, the third area includes the second largest city, and two second–third largest provinces; and the fourth area includes other areas in Korea.

However, in our multivariate model, participants with DBP 80−89 mmHg (HR = 1.11, 95% CI: 1.02−1.20) and with at least 90 mmHg (HR = 1.07, 95% CI: 0.99−1.20) were more likely to have subsequent OAG than participants with DBP less than 80 mmHg as a reference group. The results for the DBP at least 90 mmHg group were marginal. Supplementary Table 2, http://links.lww.com/HJH/A714 shows these multivariate analyses in detail.

DISCUSSION

In the present longitudinal cohort study of 2068 722 person-years, we found that the risk of OAG development increased by 1.16-fold in patients with HTN as compared with control patients, during an up-to-11-year follow-up period. This increased risk was greater in participants with higher SBP or DBP than in participants with normal SBP or DBP, respectively.

Few longitudinal studies have assessed OAG development in patients with HTN. An earlier investigation that demonstrated a relationship between metabolic syndrome components, including HTN, is a representative study suggesting that HTN increases OAG risk [18]. Using claims data from the United States, this longitudinal cohort study showed increased risk of OAG development in persons with HTN (adjusted HR = 1.17) [18]. As mentioned above, two recent meta-analyses also showed a significant association between OAG and HTN [19,20]. One analysis, which included cross-sectional, case−control, and longitudinal studies, found that the pooled relative risk (RR) for OAG was 1.16 among patients with HTN [20]. The other meta-analysis, which included only population-based studies that were mainly cross-sectional, found a pooled odds ratio (OR) of 1.22 in patients with HTN compared with those without the condition [19]. These previous results of an increased risk of OAG development in the presence of HTN are similar to our results. Therefore, the present study contributes substantially to the evidence supporting the importance of HTN in the development of OAG.

The OAG incidence per 10 000 person-years in the presence and absence of HTN in our study was 19.0 and 16.4, respectively (Fig. 1). All average OAG incidence rates

	Subjects without HTN				Subjects with HTN			
	n	Cases	Person-years	Incidence	*n*	Cases	Person-years	Incidence
Whole cohort								
	100 062	1692	1 034 500	16.4	100 062	1961	1 034 222	19.0
Age group (year)							*P* for interaction = 0.332	
<65	88 762	1359	926 677	14.7	87 807	1574	918 570	17.1
≥65	11 300	333	107 823	30.9	12 255	387	115 653	33.5
Sex							*P* for interaction = 0.491	
Male	35 204	1059	664 533	15.9	64 719	1246	663 602	18.8
Female	11 300	633	369 968	17.1	35 343	715	370 621	19.3
Having comorbidity							*P* for interaction = 0.414	
No	84 453	1326	876 145	15.1	84 335	1513	875 238	17.3
Yes	15 609	366	158 356	23.1	15 727	448	158 984	28.2
Diabetes mellitus							*P* for interaction = 0.447	
No	97 367	1593	1 007 399	15.8	97 375	1861	1 007 359	18.5
Yes	2695	99	27 101	36.5	2687	100	26 864	37.2

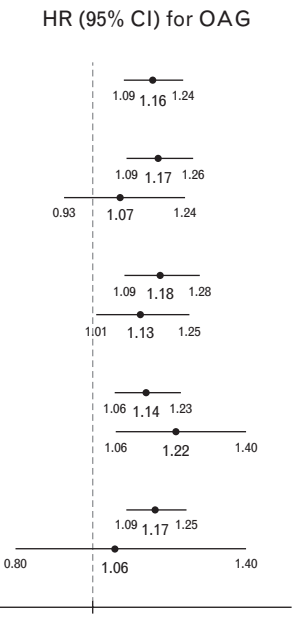

FIGURE 1 Incidence and risk of open-angle glaucoma in patients with and without systemic hypertension among the whole patient group, and per subgroup. Incidence rate per 10 000 person-years. Hazard ratios were calculated based on multivariate Cox regression after being adjusted for sociodemographic factors and comorbidities. The *P* for interaction was calculated using the interaction term for hypertension and each subgroup based on the Cox regression. CI, confidence interval; HR, hazard ratio; HTN, hypertension; OAG, open-angle glaucoma.

and the cumulative OAG incidence for the 11-year follow-up period (Fig. 2) were higher in patients with HTN than in those without the condition. These incidence rates do not completely reflect the actual incidence, as they were calculated using claims data; nevertheless, our findings clearly suggest that HTN is a risk factor for OAG.

Comorbidity of other diseases is an important factor, as it can confound analysis of the effect of HTN. As in a previous study [18], we used the CCI to adjust for systemic conditions. We found that an increased OAG incidence in patients with HTN with no comorbidity (CCI = 0) was similar to that in patients with comorbidity (CCI ≥ 1), with adjusted HRs of 1.14 and 1.22, respectively ($P = 0.414$ for interaction). This result suggests the possibility that HTN has an independent effect on OAG development, or that the effect of HTN in enhancing the development of OAG is larger than that of other systemic conditions. Although further studies are needed, this result provides evidence of the strong correlation between HTN and OAG. Interestingly, in the case of patients with diabetes mellitus, the incidence of OAG per 10 000 person-years was similar between patients with and without HTN (37.2 and 36.5, respectively; $P = 0.447$ for interaction). In addition, HTN did not markedly increase OAG risk among patients with diabetes mellitus (adjusted HR = 1.06). The weak effect of HTN on OAG risk in patients with diabetes mellitus and the increased OAG risk associated with diabetes mellitus (Table 2, HR = 1.43 in multivariate analysis, $P = 0.001$) show the importance of diabetes mellitus as a risk factor for OAG. Further studies on the effect of diabetes mellitus in OAG development are needed.

One of the interesting results of the present study is the relationship between BP and OAG risk. Previous studies on this relationship have shown varied results. In the Rotterdam study [8,21] and the Blue Mountain Eye Study [22], the OR for OAG development was high in the high-BP group; this was more marked for SBP than for DBP. However, in other longitudinal studies [17,23], the RR of OAG development was decreased in the high-BP group. Our study showed a correlation between high BP and a high risk of OAG development, and this trend was more specific for SBP than for DBP. In addition, because a large study sample was analyzed, the reliability of our study results would be high. Our results strongly suggest that lowering BP may be helpful for the prevention of OAG development in HTN patients.

There were differences in the adjusted HR for OAG development by HTN when we considered age and sex. Although those differences were small, middle-aged adults showed higher HRs for OAG development by HTN than did the elderly (adjusted HR = 1.17 and HR = 1.07, respectively), and male patients showed higher HR than did female patients (adjusted HR = 1.18 and HR = 1.13, respectively). A previous INTERHEART global case–control study from more than 50 countries showed that traditional risk factors, including HTN, diabetes mellitus, physical activity, and moderate alcohol use were more strongly associated with myocardial infarction, and these associations were generally stronger among younger adults than among older adults [24]. Association between HTN and glaucoma/ocular HTN was also evaluated in the Blue Mountains Eye Study. When those results are studied in detail, similar trends were observed: the difference in the prevalence of glaucoma between the HTN group and the non-HTN group was more prominent in younger patients than in older patients [22].

Yet, this more prominent effect of HTN on OAG among relatively younger adults may be caused by the relatively small incidence of OAG among these originally

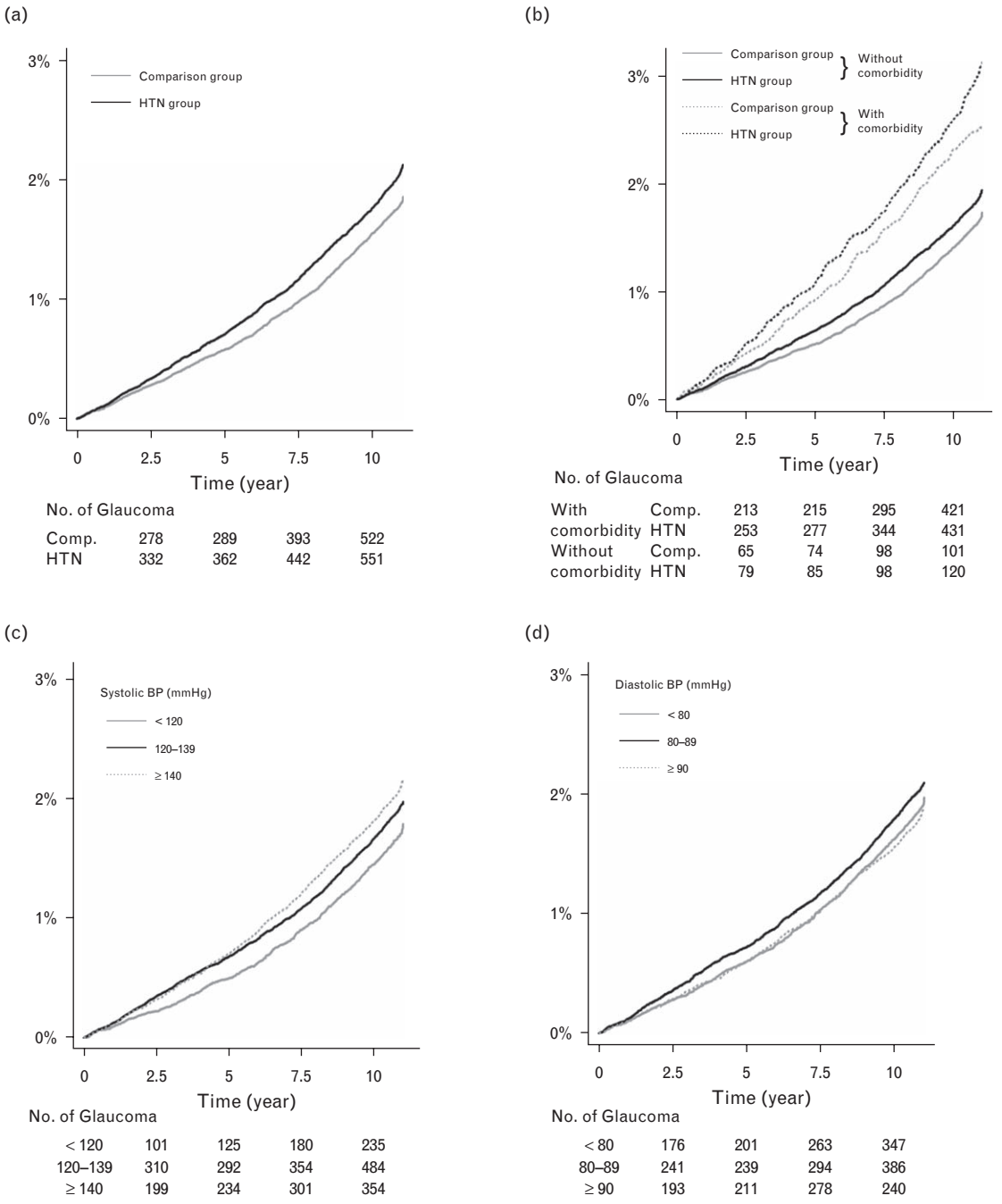

FIGURE 2 Kaplan–Meier survival curve for the up-to-11-year follow-up period. (a) Overall cumulative open-angle glaucoma incidence between the comparison group and the hypertension group. (b) Open-angle glaucoma incidence by Charlson comorbidity index score, (c and d) incidence by SBP or DBP subgroups, respectively. CCI, Charlson comorbidity index; HTN, hypertension.

not-susceptible groups. Moreover, HTN in young adults may imply a generally more severe unhealthy status, as HTN is relatively rare among young adults in the general population. However, caution is needed when interpreting these results, because the absolute number of individuals who develop OAG is still greater in elderly individuals, and the incidence of OAG is greater in those groups than in younger adults (Fig. 1). Although there are several points to be considered when we interpret our results, we can apply our results to the management of patients with HTN. When encountering such patients, particularly those who are relatively young, clinicians should take a more active approach to glaucoma surveillance.

Study strengths and limitations

Our study had a longer follow-up period than did previous longitudinal studies of the relationship between HTN and OAG. In addition, we used not only the OAG diagnosis code from claims data, but also other conditions suggesting OAG diagnosis, such as performance of a visual field examination and prescription of antiglaucoma medication. These factors may enhance the reliability of our study.

The limitations of the present study included the following: the possibility of a lack of consistency in defining OAG and HTN; the possibility of underestimation of OAG due to using insurance data based on hospital visits; the possibility that differences exist between South Korean and Western populations, limiting the generalizability of our findings; the mixed effect of chronic and newly developed HTN; the lack of access to data on the severity of glaucoma; and the possibility that medical claims and participants to general health screening may have included biased controls compared with general population-based controls, who may have neither received medical care nor had a specific diagnosis. Patients who did not visit a hospital could have been excluded from our study. However, the distinguishing features of the Korean medical system, such as the low medical expenses; the fact that it is a government-run, universal, single-payer healthcare; and its high health-service accessibility, may reduce the possibility of underestimating the effect of HTN on OAG. Moreover, the annual incidence of OAG among patients with HTN is 19.0 per 10 000. Our findings also contributed new information about the epidemiological characteristics of OAG risk in patients with HTN.

In conclusion, this nationwide, 11-year cohort study demonstrated that patients with HTN exhibit a significantly higher rate of OAG incidence. In addition, younger patients (<65 years of age) with HTN were more susceptible to OAG than were older patients (≥65 years of age) with HTN. These findings may be clinically important, because HTN has a high prevalence in the general population, and because OAG can lead to blindness if not treated.

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Conflicts of interest

C.Y.K. is a consultant for Allergan, Santen, and Alcon. The authors do not have any conflict of interest, financial or otherwise, to report.

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Reviewers' Summary Evaluation

Reviewer 3

Using a population-based, representative cohort study of over 200,000 adults living in South Korea, Rim *et al*. demonstrate hypertension predicts incidence of open-angle glaucoma. Major strengths of the study include the large, representative sample, follow-up of nearly 11 years, and use of objective blood pressure assessments and use of prescription antihypertensive medication to define the hypertension group. The study also employed sophisticated statistical analyses including propensity score matching and multivariable Cox regression models to carefully consider multiple potential confounding factors and to test for differential effects in subgroups. Although causality is always difficult to establish, this study provides high-quality epidemiological evidence for hypertension as a robust, distinct risk factor for the development of open-angle glaucoma.