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Original Article

Association between the Severity of Glaucoma and Risk of Fractures: A Nationwide Cohort Study

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SUMMARY

Background: We evaluated the association between glaucoma and fracture risk in a retrospective cohort of individuals with (n = 3,810) and without (n = 3,810) glaucoma, matched 1:1 for age, sex, and index year obtained using Taiwan's National Health Insurance Research Database.
Methods: Patients with glaucoma were categorized into three groups reflecting the glaucoma severity: no more than two types of medical treatment, more than two types of medical treatment, and surgery. Data were analyzed using Cox proportional hazard regression models.
Results: During a mean follow-up period of 11.6 years, 750 participants with and 711 without glaucoma developed fractures. Glaucoma was significantly associated with increased fracture risk (adjusted HR [aHR] = 1.18, $p = 0.005$), particularly in the foot (aHR = 1.25, $p < 0.001$), femur (aHR = 1.24, $p = 0.021$), and hip (aHR = 1.30, $p = 0.001$), but not in the upper limbs and axial skeleton. Those who received more than two types of medical treatment showed a significant association with a higher fracture risk than did those who received no more than two types of medical treatment (aHR = 1.231, $p = 0.026$). However, patients with surgery showed a significant association with lower fracture risk than those who received medical treatment, with almost the same risk as that of patients without glaucoma.
Conclusion: Glaucoma seems independently associated with increased fracture risk, especially lower-limb fractures. In patients receiving medical treatment for glaucoma, a higher degree of severity of glaucoma was significantly associated with higher fracture risk. The fracture risk was decreased in those with severe glaucoma warranting surgery. This is the first nationwide study concerning the epidemiological correlation between two diseases.

1. Introduction

A bone fracture is a medical condition where the continuity of the bone is partially or completely broken. The most common fragile fracture sites are the hip, spine, and wrist.[1] Falls are a common and leading cause of fracture in older adults. For example, in 98% of patients with a hip fracture, the fracture is a result of a fall.[2] Fractures are a frequent and important cause of disability and medical costs in the aging population worldwide.[3] The estimated lifetime risk of osteoporotic fractures is as high as 50%, especially among white and Asian women.[4] In the USA, the cost of fragility fractures in 2005 was estimated to be $17 billion, which is estimated to increase to $25.3 billion by 2025.[5]

Glaucoma, an intraocular pressure (IOP)-associated optic neuropathy, is the second leading cause of blindness globally after cataracts.[6,7] Glaucoma causes gradual visual field loss (VFL)[8] and is the leading cause of such loss in people aged ≥ 55 years.[9] VFL resulting from glaucoma may increase the risk of fracture. A previous study demonstrated the association between VFL and the risk of fracture[10] but did not specifically evaluate the effect of glaucoma alone on fracture risk. There are various degrees of glaucoma, which require different treatment approaches; medical therapies constitute the first approach in the management of open-angle glaucoma, followed by laser therapies, which are followed by surgical therapies if the IOP remains uncontrolled.[11] Since the severity of glaucoma indicates different extents of VFL,[12] the degree of glaucoma severity might also relate to the risk of fracture, which has seldom been investigated before.

Therefore, we performed a nationwide, population-based, cohort study to examine the association between the severity of glaucoma and risk of fractures.

2. Materials and methods

2.1. Data sources

This study was conducted using the Longitudinal Health Insur-

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ance Database (LHID), which is a 2-million randomized dataset retrieved from the Taiwan's National Health Insurance Research Database (NHIRD). The LHID contains all medical claims for the outpatient, inpatient, and emergency departments. To protect privacy and ensure data security, the National Health Research Institute encrypted personal identifiers in the LHID before releasing the database. The Institutional Review Board of Tri-service General Hospital, National Defense Medical Center approved this study protocol (TSGHIRB No: 1-108-05-143). The study conformed to the guidelines of the Helsinki Declaration.

2.2. Study population

The study population included patients with glaucoma (case cohort) and individuals without glaucoma (control cohort). All individuals diagnosed with glaucoma between 2000 and 2015 in the LHID were included in the glaucoma cohort. The diagnosis of glaucoma was confirmed if there was at least one inpatient or two outpatient diagnoses of the condition by an ophthalmologist during the study period (ICD-9-CM code: 365.x). We defined the date of the first diagnosis of glaucoma as the index date and the year of first diagnosis of glaucoma as the index year. To increase the likelihood of identifying newly diagnosed cases, individuals diagnosed with glaucoma in 1999 were excluded, as were individuals diagnosed with any fracture (our primary outcome) before the index date. The control cohort was also selected from the LHID, matched 1:1 with the glaucoma cohort in terms of age, sex, and index year. As in the glaucoma cohort, individuals with a previous diagnosis of any fractures were excluded. Each control participant was assigned the same index date as that of the matched patient with glaucoma. Of 6,125 individuals initially identified with glaucoma, 2,315 were excluded; therefore 3,810 patients with glaucoma were enrolled as the study cohort, and another 3,810 individuals were selected as the control cohort (Figure 1).

2.3. Outcome measures

The primary outcome was defined as at least one new inpatient or outpatient diagnosis of fracture (ICD-9-CM codes: 800.x–829.x, 733.1x). All patients were followed up from the index date until the occurrence of the primary outcome, death, or December 31, 2015. In addition to the primary outcome, we analyzed each event separately. Fractures in the head (ICD-9-CM code: 800.x–804.x), humerus (733.11, 812.x), radius and ulna (733.12, 813.x), hand (814.x–817.x), vertebra (805.x, 806.x, 733.13), hip (820.x, 733.14), femur (733.14–733.15, 820.x–821.x), tibia and fibula (733.16, 823.x), foot (825.x–826.x), and other body parts (807.x–811.x, 818.x–819.x, 822.x, 824.x, 827.x–829.x, 733.10, 733.17–733.19) were defined as individual study outcomes.

To evaluate whether the severity of glaucoma influenced the risk of fracture in patients with glaucoma, we further divided the glaucoma cohort into (1) those who received no more than two types of medical treatment and no surgery for 6 months before the occurrence of fracture; (2) those who received more than two types of medical treatment and no surgery for 6 months before the occurrence of fracture; and (3) those who received surgery, including trabeculectomy, drainage device implant, cyclocoagulation, or cryotherapy, between the date of glaucoma diagnosis and 6 months before the occurrence of fracture. All these subgroups were compared with the control group in the analysis model. The medical treatment was defined as using topical eye drops, including brimonidine, carteolol, timolol, brinzolamide, dorzolamide, pilocarpine, bimatoprost, latanoprost, tafluprost, or travoprost, and oral drugs, including acetazolamide. If a patient used combination eye drops, such as COSOPT having timolol and dorzolamide, it was considered as using two types of medical treatment.

2.4. Covariates

We retrieved information on baseline characteristics and clinical details that were considered potential confounders (Table S1) according to the ICD-9-CM, along with the procedure and prescription codes from outpatient and inpatient reimbursement claims in the LHID. These factors may cause osteoporosis and thus further increase the risk of fractures. We listed diabetes mellitus, hyperthy-

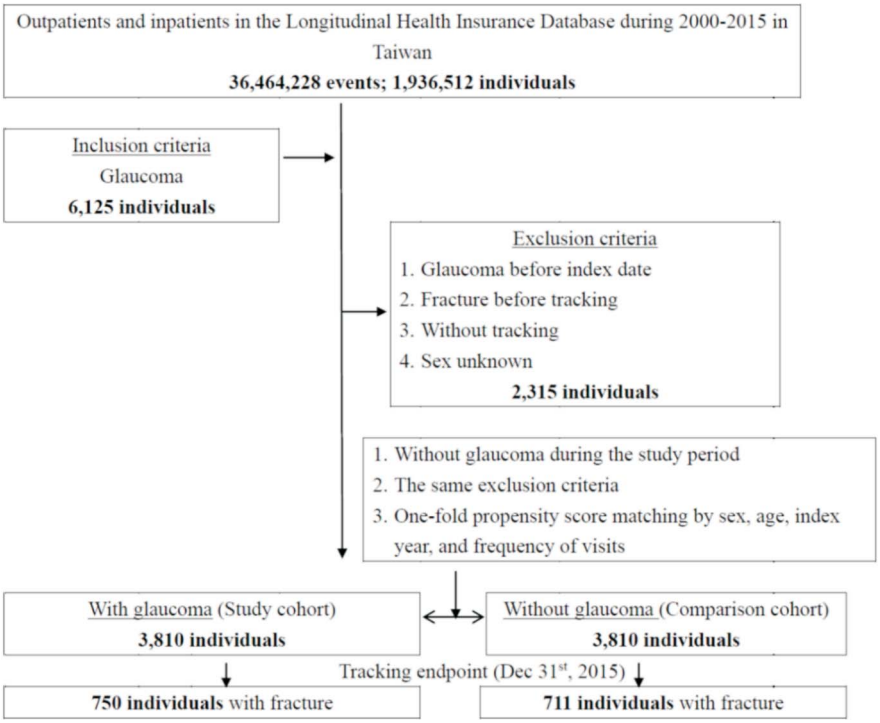

Figure 1. Flowchart of study sample selection.

roidism, tobacco use, drug use, and especially the use of systemic corticosteroids as potential confounders. Preexisting comorbidity was defined as a disease diagnosed during at least one inpatient or two outpatient services in the year preceding the index date. The Charlson Comorbidity Index was also calculated based on preexisting comorbidities.[13] A baseline medication was defined as a drug prescribed for at least 30 days within the year preceding the index date. Information on income and urbanization level of the place of living of a subject was considered as indicative of the individual's socioeconomic status. Income was categorized into four levels (New Taiwan dollars ≥ 35,000, 18,000–34,999, < 18,000, and financially dependent) based on income-related National Health Insurance (NHI) premiums. Urbanization was categorized into four levels (level 1, most urbanized; level 4, least urbanized). Detailed descriptions of how income and urbanization levels were assessed have been previously published.[14,15] To eliminate the possible confounding effect of healthcare use, we calculated the average number of outpatient visits, emergency department visits, and hospitalizations per year for each subject during the follow-up.

2.5. Statistical analyses

Continuous variables were compared using *t*-tests and categorical variables using Chi-square tests. The Kaplan-Meier method was used to estimate the cumulative incidences, which were compared using log-rank tests. Univariate and multivariate Cox proportional hazards regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals of the risk of developing fractures. When performing multivariate Cox proportional hazards regression analyses, all covariates listed in Table S1 were adjusted to avoid possible confounding effects. For continuous variables, the values of the variables were directly included for adjustment in the regression models; for categorical variables, each variable was treated as a separate dummy variable in the regression models. A two-sided *p*-value < 0.05 was considered statistically significant. We performed the analyses using IBM Statistical Product and Service Solutions for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Participant characteristics

The mean age of the glaucoma cohort was 62.5 ± 15.8 (standard deviation) years, and the mean age of the non-glaucoma cohort was 62.3 ± 16.4 years. The proportion of males was 50.9% in both cohorts. For other baseline characteristics, compared with the control cohort, the glaucoma cohort had higher levels of medical care and urbanization and higher risk of comorbidities such as diabetes mellitus, hypertension, cataract, and age-related macular degeneration, but a lower risk for comorbidities such as coronary artery disease, chronic heart failure, chronic obstructive pulmonary disease, chronic liver disease, and digestive ulcer or hemorrhage. Regarding other comorbidities, including stroke, thyroid disease, parathyroid disease, rheumatoid arthritis, dementia, depression, parkinsonism, epilepsy, disorders of menstruation, menopause, and tobacco use disorder; the use of medications, including systemic corticosteroids, proton pump inhibitors, thiazolidinediones, aromatase inhibitors, gonadotropin-releasing hormone agonists, and depot medroxyprogesterone acetate; income; the average number of outpatient visits; emergency department visits; and hospitalizations per year, we found no significant differences between the two cohorts (Table S1).

In the glaucoma cohort, 1,135 patients (29.8%) were included in the group that received no more than two types of medical treatment for 6 months before the occurrence of fracture, 1,084 patients (28.5%) were included in the group that received more than two types of medical treatment for 6 months before the occurrence of fracture, and 1,591 patients (41.8%) were included in the group that received surgery between the date of glaucoma diagnosis and 6 months before the occurrence of fracture.

3.2. Comparisons of participants with and without glaucoma

During the mean follow-up period of 11.6 years, 750 subjects in the glaucoma cohort and 711 subjects in the non-glaucoma cohort developed fractures (Figure 1 and Table 1). Kaplan-Meier analysis revealed that the cumulative incidence of developing fractures was significantly higher in the glaucoma cohort (22.4 vs. 18.0 per 1,000 person-years; log-rank test, $p = 0.009$; Figure 2a). Diagnosis of glaucoma was associated with a significantly increased risk of developing fractures, as assessed by univariate (crude HR = 1.23, $p = 0.002$) and multivariate (adjusted HR [aHR] = 1.18, $p = 0.005$) Cox proportional hazards regression models (Table 1).

After analyzing each event individually, we found that glaucoma was significantly associated with the risk of developing facture in the foot (aHR = 1.25, $p < 0.001$), femur (aHR = 1.24, $p = 0.021$), hip (aHR = 1.30, $p = 0.001$), and other body parts (aHR = 1.17, $p = 0.045$). Conversely, we found no significant association of glaucoma with the risk of developing factures in the tibia and fibula ($p = 0.60$), vertebra ($p = 0.68$), head ($p = 0.74$), hand ($p = 0.81$), radius and ulna ($p = 0.95$), or humerus ($p = 0.30$) (Table 2). The cumulative incidence curves for each event are shown in Figure 2b–2k.

3.3. Comparisons of participants with glaucoma of different severity and those without glaucoma

Compared with those without glaucoma, the subjects who received no more than two types of medical treatment had significantly increased risk of fractures (aHR = 1.189, $p < 0.001$), the subjects who received more than two types of medical treatment also had significantly increased risk of fractures (aHR = 1.669, $p < 0.001$), and the subjects who received surgery did not have any significant association with the risk of fracture (aHR = 0.900, $p = 0.164$) (Table 3).

3.4. Comparisons among participants with glaucoma of different severities

Compared with those who received surgery, those who received no more than two types of medical treatment (aHR = 1.100, *p*

Table 1
Risk of developing fractures according to glaucoma status.

Variables	No glaucoma (N = 3,810)	Glaucoma (N=3,810)
Events	711	750
Person-years	39,404.3	33,469.08
Incidence rate per 1,000 person-years	18.04	22.41
Multivariate Cox proportional hazards regression model, aHR (95% CI), p-value	Reference	1.18 (1.05–1.30), $p = 0.005$

aHR, adjusted hazard ratio; CI, confidence interval; N, number.

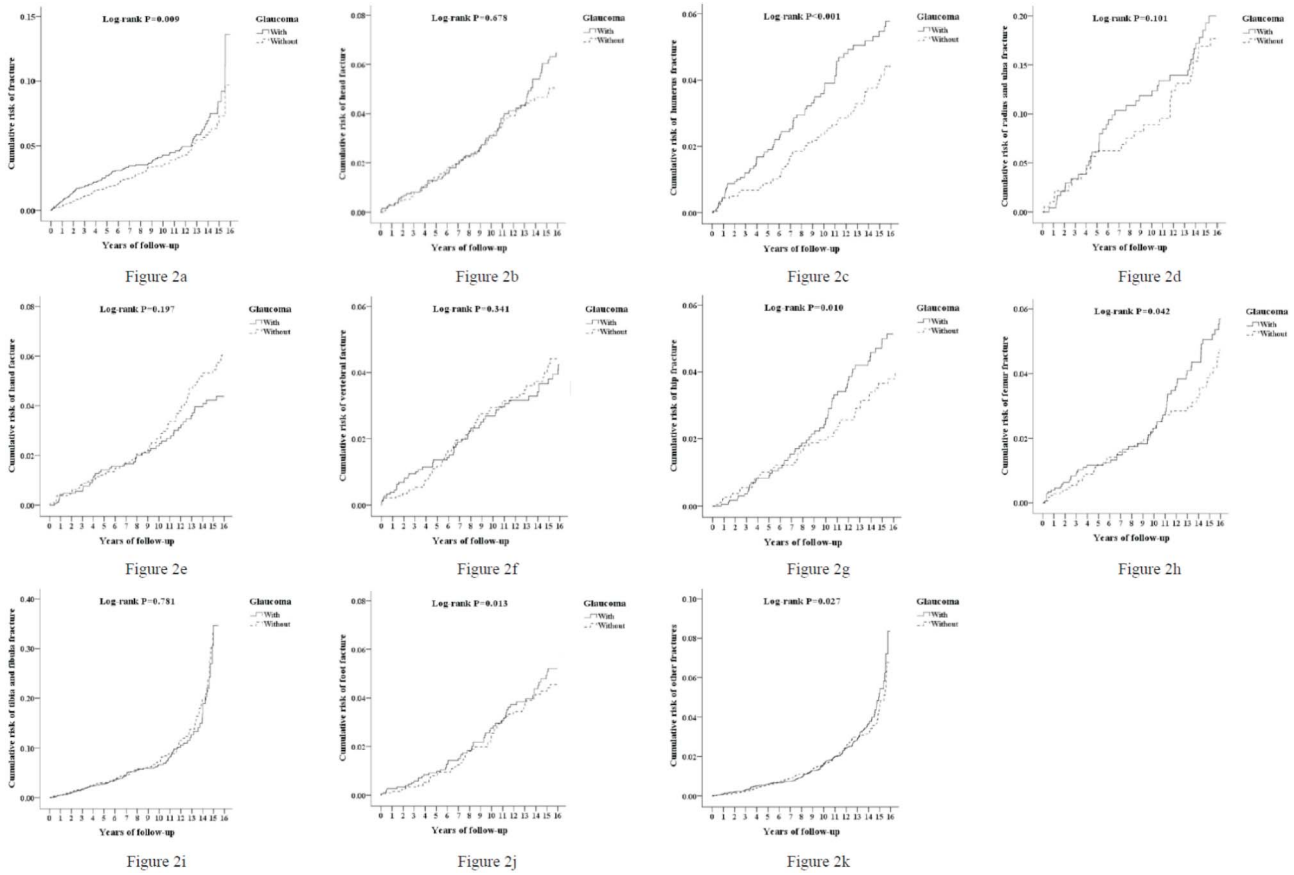

Figure 2. Kaplan-Meier analysis for the cumulative risk of fractures stratified by glaucoma using the log-rank test. (a) Overall, $p = 0.009$; (b) Head fracture, $p = 0.678$; (c) Humerus fracture, $p < 0.001$; (d) Radius and ulna fracture, $p = 0.101$; (e) Hand fracture, $p = 0.197$; (f) Vertebral fracture, $p = 0.341$; (g) Hip fracture, $p = 0.010$; (h) Femur fracture, $p = 0.042$; (i) Tibia and fibula fracture, $p = 0.781$; (j) Foot fracture, $p = 0.013$; (k) Other fractures, $p = 0.027$.

Table 2
Risk of different types of fracture according to glaucoma status.

Fractured body part	Glaucoma subgroup	Events	Incidence rate (per 1,000 PYs)	Multivariate model			
				aHR	95% CI	95% CI	p
Head	without glaucoma	30	0.8	reference			
	with glaucoma	32	1.0	1.08	0.56	1.72	0.737
Humerus	without glaucoma	50	1.3	reference			
	with glaucoma	40	1.2	0.78	0.49	1.25	0.300
Radius and ulna	without glaucoma	90	2.3	reference			
	with glaucoma	82	2.5	1.09	0.71	1.39	0.949
Hand	without glaucoma	145	3.7	reference			
	with glaucoma	125	3.7	1.10	0.80	1.37	0.811
Vertebra	without glaucoma	141	3.59	reference			
	with glaucoma	136	4.1	1.05	0.73	1.23	0.676
Hip	without glaucoma	179	4.5	reference			
	with glaucoma	234	7.0	1.30	1.07	1.59	0.001
Femur	without glaucoma	212	5.4	reference			
	with glaucoma	259	7.7	1.24	1.03	1.49	0.021
Tibia and fibula	without glaucoma	43	1.1	reference			
	with glaucoma	31	0.9	0.96	0.61	1.59	0.597
Foot	without glaucoma	278	7.1	reference			
	with glaucoma	318	9.5	1.25	1.11	1.60	< 0.001
Other	without glaucoma	397	10.1	reference			
	with glaucoma	391	11.7	1.17	1.01	1.50	0.045

aHR, adjusted hazard ratio (adjusted for the variables listed in Table S1); CI, confidence interval; PPYs, person-years.

= 0.007) and those who received more than two types of medical treatment (aHR = 1.362, $p < 0.001$) had significantly increased risk of fractures. Compared with those who received no more than two types of medical treatment, those who received more than two types of medical treatment had significantly increased risk of fractures (aHR = 1.231, $p = 0.026$) (Table 3).

4. Discussion

We evaluated the association between glaucoma and the risk of fractures using a nationwide population database over a long follow-up period. We found that glaucoma was independently associated with a high risk of fractures. Furthermore, sub-analysis for each

Table 3
Correlation between the severity of glaucoma and development of fractures.

Events	aHR for fracture			
	Control (N = 3,810)	No more than two medical treatments (N = 1,135)	More than two medical treatments (N = 1,084)	Surgery (N = 1,591)
Fracture	reference	1.189 ($p < 0.001$)	1.669 ($p < 0.001$)	0.900 ($p = 0.164$)
		1.100 ($p = 0.007$)	1.362 ($p < 0.001$)	reference
		reference	1.231 ($p = 0.026$)	

aHR, adjusted hazard ratio; N, number.

type of fracture showed that glaucoma was significantly associated with the risk of fracture in the foot, femur, and hip, but not in the hand, radius, ulna, humerus, vertebra, head, tibia, or fibula. Patients with glaucoma with different degrees of severity also showed different associations with a high risk of fracture: as the severity of glaucoma increased, patients who received more than two types of medical treatment showed a significant association with a higher risk of fracture compared with those who received no more than two types of medical treatment. However, when the severity of glaucoma increased to the severe stage that required surgery, it showed a significant association with a lower risk of fracture compared with glaucoma that required no more than two types of medical treatment or more than two types of medical treatment. Compared with patients without glaucoma, patients with glaucoma who received surgery did not show any significant association with the risk of fractures.

We found that individuals with glaucoma are at a higher risk of fractures than those without glaucoma. Previous studies have demonstrated the association between visual impairment and fracture risk of varying degrees.[10,16–18] Visual impairment mainly includes a decrease in visual acuity and VFL. For patients with glaucoma, VFL develops earlier than the decrease in visual acuity; this may explain why these patients tend to fall and have fractures. In their large-scale, retrospective cohort study, Coleman et al. included white and African-American women aged ≥ 65 years and showed that women with severe bilateral VFL (due to many ocular diseases) had an approximately 1.6-fold risk of a non-spine/non-hip fracture than those without any VFL (HR = 1.59; 95% confidence interval = 1.24–2.03).[10] This result is consistent with our findings, although our study included Asian patients of either sex with glaucoma. Glaucoma initially causes gradual VFL,[8] which in turn increases the risk of falls in the patient's daily life,[19–22] further increasing the risk of fractures. Since postural stability involves neural processing of visual inputs,[23,24] patients with glaucoma with peripheral visual loss may have postural instability in their daily lives, which may increase the risk of fall-related fractures. In the recent years, the association of glaucoma with cognitive dysfunction, such as that caused by Alzheimer's disease has been established, because both are neurodegenerative diseases.[25] Cognitive dysfunction can impair judgment, gait, visual-spatial perception, and the ability to recognize and avoid hazards, further increasing the risk of falling and fall-related fractures.[26]

Our study also examined the risk of fractures in different body parts. We found that glaucoma was significantly associated with the risk of developing fractures of the lower limbs, i.e., foot, femur, hip. However, there was no significant association between glaucoma and the risk of fractures for parts of the upper limb and the axial skeleton, such as the hand, radius, ulna, humerus, vertebra, and head. Consistent with our results, Ivers et al. demonstrated that VFL was not significantly associated with the risk of wrist or shoulder fractures but was associated with that of hip and ankle fractures.[27,28] VFL in patients with glaucoma first develops usually in the peripheral side of the visual field. Thus, body parts away from the center of the body (e.g., lower limbs) may be less visible in the visual fields of these patients, thus increasing the risk of bumping into an obstacle, which directly causes fracture of these body parts. Moreover, peripheral VFL in patients may increase the risk of falls because their foot may be at an increased risk of tripping by obstacles that they cannot see. Therefore, patients with glaucoma may have an increased risk of falls and fall-related fractures. The common types of fall-related fractures were the fractures of the lower limb, such as hip fractures. Mayo et al. conducted a matched case-control study, which showed that for patients with a history of falls, the fractures of the hip predominated, accounting for 42.6% of the total fractures.[29] Therefore, patients with glaucoma may have an increased risk of fractures of the lower limb, such as hip fracture, due to the increased risk of falls.

Our study also examined the risk of fractures according to different degrees of severity of glaucoma. For most types of glaucoma, surgery, including trabeculectomy, drainage device implantation, cyclocoagulation, or cryotherapy, is often the second-line therapy due to poor IOP control despite ophthalmic medications and laser trabeculoplasty.[30] Kuo et al. had established the ranking of the severity of glaucoma depending on the different treatment approaches found in the NHIRD. The severity in those who receive no more than two types of medical treatment is mild, in those who receive more than two types of medical treatment is moderate, and in those who receive surgery is severe.[31] We found that as the severity of glaucoma increased, the risk of fracture increased. However, when the severity of glaucoma increased to the most severe stage, which required surgery, the risk of fracture decreased to almost the same as that in individuals without glaucoma. For patients with glaucoma, VFL increases as the severity of glaucoma increases,[12] which can further increase the risk of falling.[32] This can explain the increase in the risk of fall-related fractures with an increase in the severity of glaucoma. However, when the severity of glaucoma increased to the most severe stage, which required surgery, a paradoxical protective effect was observed. Although these patients had worse visual acuity and VFL than patients who only used ophthalmic medications, they might have been performing fewer physical exercises due to poor vision and usually needed other people to help them with their daily activities, which might have prevented fall-related fractures. Conversely, patients who did not receive surgery might still be at an earlier stage of the disease and have continued to perform daily activities by themselves, which might have increased the risk of falls and fall-related fractures.

The strengths of this study are its nationwide population-based design, large sample size, and long follow-up period. Since glaucoma has a high prevalence and is the second leading cause of blindness globally, we believe that our study results have important public health implications. However, our study has some limitations. First, we could not access some potential confounding factors, such as lifestyle, substance use (e.g., smoking), and laboratory examination data in the claims-based dataset; therefore, we could not control or adjust these factors. Second, we did not examine the risk of fractures in patients with different types of glaucoma. Each type may entail a

different risk of fractures, as different types of glaucoma lead to different levels of VFL. However, as many doctors in Taiwan use the term "unspecified glaucoma" for recording the diagnosis regardless of the type of glaucoma, it is difficult to study the risk of fractures among different types of glaucoma. Third, in our study, the entry "other" for fractures in other body parts may have included fractures in any body part, as many doctors in Taiwan may use "other fractures" as the record of diagnoses instead of specifying the fractures. Fourth, using the claims-based dataset, we could not retrieve a detailed medical history of the fractures, including detailed imaging reports and resulting symptoms; therefore, we could not determine the specific types of fractures, such as vertebral, clinical, or morphometric. Fifth, using a claims-based dataset, we could not retrieve data on visual field tests or optical coherence tomography of the optic disc to precisely determine the severity of glaucoma. We used Kuo et al.'s approach of retrieving information on the different treatments administered to determine the severity of glaucoma.[31] However, these different treatment approaches would reflect difficulty in controlling the progression of glaucoma, which is not equivalent to the severity. Nevertheless, in most cases, these two issues would be correlated. Sixth, owing to the anonymity policies of the National Health Research Institute, only masked data could be accessed, and we could not directly approach the subjects to confirm their diagnosis. However, the accuracy of the diagnostic codes for fractures[33] and other diseases[34–36] has been previously validated. Additionally, the Bureau of the NHI routinely and randomly reviews a certain percentage of claims from every hospital to confirm diagnostic accuracy. If a hospital or doctor makes an incorrect diagnosis using incorrect codes, a large fine is imposed. Thus, we believe that the validity of diagnoses included in this study is acceptable. Finally, due to the observational nature of our study design, we could not confirm a causal association between glaucoma and the risk of fractures. Further studies will be needed to explore causality.

In conclusion, this population-based cohort study demonstrated a possible association between glaucoma and fractures. Glaucoma was independently associated with a higher risk of fractures, especially those of the lower limbs. In patients receiving medical treatment for glaucoma, a higher degree of severity of glaucoma was significantly associated with higher fracture risk. However, the fracture risk decreased in those with severe glaucoma warranting surgery. Therefore, the risk of fracture may be highest in patients with glaucoma, especially those with increased severity but not notably impaired visual acuity or normal life activities, and fall prevention is important in this population. Large-scale prospective studies or clinical trials will be needed to further confirm any cause-and-effect relationship between glaucoma and fractures.

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Conflicts of interest

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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Supplement

Table S1
Baseline characteristics of patients with and without glaucoma.

Variables	Study population						*p*
	Total		With glaucoma		Without glaucoma		
	N	%	N	%	N	%	
Total	7,620	100	3,810	50.0	3,810	50.0	
Sex							0.999
Male	3,882	50.9	1,941	50.9	1,941	50.9	
Female	3,738	49.1	1,869	49.1	1,869	49.1	
Age (years)	62.4 ± 16.1		62.5 ± 15.8		62.3 ± 16.4		0.511
Age group (years)							0.999
< 19	242	3.2	121	3.2	121	3.2	
20–29	202	2.7	101	2.7	101	2.7	
30–39	304	4.0	152	4.0	152	4.0	
40–49	544	7.1	272	7.1	272	7.1	
50–59	1,152	15.1	576	15.1	576	15.1	
≥ 60	5,176	67.9	2,588	67.9	2,588	67.9	
Insured premium (New Taiwan $)							0.134
< 18,000	7,512	98.6	3,760	98.7	3,752	98.5	
18,000–34,999	97	1.3	42	1.1	55	1.4	
≥ 35,000	11	0.1	8	0.2	3	0.1	
DM							0.002
Without	6,080	79.8	2,985	78.4	3,095	81.2	
With	1,540	20.2	825	21.7	715	18.8	
Hyperlipidemia							0.682
Without	7,468	98.0	3,737	98.1	3,731	97.9	
With	152	2.0	73	1.9	79	2.1	
HTN							0.027
Without	5,931	77.8	2,925	76.8	3,006	78.9	
With	1,689	22.2	885	23.2	804	21.1	
CKD							0.970
Without	6,847	89.9	3,424	89.9	3,423	89.8	
With	773	10.1	386	10.1	387	10.2	
CAD							0.041
Without	6,872	90.2	3,463	90.9	3,409	89.5	
With	748	9.8	347	9.1	401	10.5	
CHF							0.008
Without	7,130	93.6	3,594	94.3	3,536	92.8	
With	490	6.4	216	5.7	274	7.2	
Stroke							0.211
Without	6,946	91.2	3,489	91.6	3,457	90.7	
With	674	8.9	321	8.4	353	9.3	
COPD							0.034
Without	6,936	91.0	3,495	91.7	3,441	90.3	
With	684	9.0	315	8.3	369	9.7	
Chronic liver disease							< 0.001
Without	7,231	94.9	3,666	96.2	3,565	93.6	
With	389	5.1	144	3.8	245	6.4	
Hyperthyroidism							0.307
Without	7,597	99.7	3,796	99.6	3,801	99.8	
With	23	0.3	14	0.4	9	0.2	
Hypothyroidism							0.763
Without	7,609	99.9	3,805	99.9	3,804	99.8	
With	11	0.1	5	0.1	6	0.2	
Hyperparathyroidism							0.250
Without	7,617	100.0	3,807	99.9	3,810	100.0	
With	3	0.01	3	0.1	0	0.0	
Hypoparathyroidism							0.317
Without	7,619	100.0	3,809	100.0	3,810	100.0	
With	1	0.01	1	0.03	0	0.0	
RA							0.663
Without	7,600	99.7	3,801	99.8	3,799	99.7	
With	20	0.3	9	0.2	11	0.3	
Dementia							0.654
Without	7,438	97.6	3,716	97.5	3,722	97.7	
With	182	2.4	94	2.5	88	2.3	
Depression							0.510
Without	7,563	99.3	3,779	99.2	3,784	99.3	
With	57	0.8	31	0.8	26	0.7	
Parkinsonism							0.999
Without	7,612	99.9	3,806	99.9	3,806	99.9	
With	8	0.1	4	0.1	4	0.1	

Table S1 Continued.

Variables	Study population						*p*
	Total		With glaucoma		Without glaucoma		
	N	%	N	%	N	%	
Epilepsy							0.760
Without	7,577	99.4	3,790	99.5	3,787	99.4	
With	43	0.6	20	0.5	23	0.6	
Cataract							< 0.001
Without	7,315	96.0	3,532	92.7	3,783	99.3	
With	305	4.0	278	7.3	27	0.7	
ARMD							0.004
Without	7,604	99.8	3,796	99.6	3,808	100.0	
With	16	0.2	14	0.4	2	0.1	
Disorders of menstruation							0.317
Without	7,619	100.0	3,810	100.0	3,809	100.0	
With	1	0.01	0	0.0	1	0.03	
Menopause							0.999
Without	7,618	100.0	3,809	100.0	3,809	100.0	
With	2	0.03	1	0.03	1	0.03	
Digestive ulcer or hemorrhage							0.033
Without	7,119	93.4	3,583	94.0	3,536	92.8	
With	501	6.6	227	6.0	274	7.2	
Tobacco use disorder							0.999
Without	7,618	100.0	3,809	100.0	3,809	100.0	
With	2	0.03	1	0.03	1	0.03	
Charlson Comorbidity Index score	0.4 ± 1.4		0.6 ± 1.9		0.6 ± 1.9		
Systemic corticosteroids							0.307
Without	6,060	79.5	3,012	79.1	3,048	80.0	
With	1,560	20.5	798	20.9	762	20.0	
PPI							0.686
Without	6,385	83.8	3,199	84.0	3,186	83.6	
With	1,235	16.2	611	16.0	624	16.4	
TZD							0.834
Without	6,263	82.2	3,128	82.1	3,135	82.3	
With	1,357	17.8	682	17.9	675	17.7	
AI							0.648
Without	6,520	85.6	3,267	85.8	3,253	85.4	
With	1,100	14.4	543	14.3	557	14.6	
GnRH agonist							0.801
Without	6,424	84.3	3,208	84.2	3,216	84.4	
With	1,196	15.7	602	15.8	594	15.6	
DMPA							0.657
Without	6,639	87.1	3,326	87.3	3,313	87.0	
With	981	12.9	484	12.7	497	13.0	
Season							0.091
Spring (Mar–May)	2,030	26.6	1,008	26.5	1,022	26.8	
Summer (Jun–Aug)	1,785	23.4	875	23.0	910	23.9	
Autumn (Sep–Nov)	1,774	23.9	933	24.5	841	22.1	
Winter (Dec–Feb)	2,031	26.7	994	26.1	1,037	27.2	
Location							< 0.001
Northern Taiwan	3,366	44.2	1,840	48.3	1,526	40.1	
Middle Taiwan	1,733	22.7	665	17.5	1,068	28.0	
Southern Taiwan	2,181	28.6	1,187	31.2	994	26.1	
Eastern Taiwan	320	4.2	106	2.8	214	5.6	
Outlets islands	20	0.3	12	0.3	8	0.2	
Urbanization level							< 0.001
1 (highest)	3,125	41.0	1,840	48.3	1,285	33.7	
2	3,370	44.2	1,749	45.9	1,621	42.6	
3	326	4.3	55	1.4	271	7.1	
4 (lowest)	799	10.5	166	4.4	633	16.6	
Level of care							< 0.001
Hospital center	3,921	51.5	2,635	69.2	1,286	33.8	
Regional hospital	1,972	25.9	821	21.6	1,151	30.2	
Local hospital	1,727	22.7	354	9.3	1,373	36.0	
Frequency of OPD	7.2 ± 10.8		7.1 ± 10.3		7.2 ± 11.3		0.598
Frequency of ER	0.9 ± 1.0		0.9 ± 0.9		0.9 ± 1.1		0.091
Frequency of IPD	1.6 ± 2.0		1.6 ± 2.0		1.6 ± 2.0		0.663

Data are presented as mean ± standard deviation or number (N) and percentage (%).

p: Chi-square/Fisher's exact test for categorical variables and *t*-tests for continuous variables.

AI, aromatase inhibitors; ARMD, age-related macular degeneration; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; DMPA, depot medroxyprogesterone acetate; ER, emergency room; GnRH, gonadotropin-releasing hormone; HTN, hypertension; IPD, hospital inpatient care; OPD, hospital outpatient care; PPI, proton pump inhibitors; RA, rheumatoid arthritis; TZD, thiazolidinediones.