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Increased risk of open angle glaucoma in patients with moyamoya disease from a nationwide population-based cohort in Korea

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This nationwide population-based retrospective cohort study aims to investigate the association between Moyamoya disease (MMD) and open-angle glaucoma (OAG). In this study using the Korean National Health Insurance Service database, a total of 36,432 patients having diagnostic code with MMD between 2002 and 2022, and their age-, sex-matched non-MMD controls ($n = 346,769$) were included. We used a Cox proportional hazard model to determine the association between MMD and subsequent OAG after excluding cases with preexisting diagnosis of MMD for the initial 2-year. Kaplan-Meier survival analyses with log-rank test were performed to compare the incidence probability of OAG based on the MMD diagnosis. Cox regression analysis showed that the diagnosis of MMD was associated with increased risk of subsequent diagnosis of OAG (adjusted HR, 1.26; 95% CI, 1.14–1.38; $P < 0.001$). The cumulative incidence probability of OAG was 3.7% in MMD group and 2.9% in control group at the end of the study period, and was significantly higher among MMD patients than controls consistently during the study period ($P < 0.001$).

In conclusion, the nationwide longitudinal data of Korean population revealed a significant association between MMD and OAG. Presence of MMD may increase the risk of developing OAG.

Keywords Glaucoma, Risk factor, Moyamoya disease

Moyamoya disease (MMD) is a rare neurological disorder characterized by progressive narrowing or blockage of the internal carotid arteries (ICA) at the base of the brain, leading to reduced blood flow and formation of collateral vessels, often resulting in ischemic stroke[1,2].

Glaucoma is an optic nerve head (ONH) disease characterized by progressive damage of the retinal ganglion cell axons, which results in a gradual loss of visual field. Its pathogenesis is multifactorial, and decreased ocular blood flow has been demonstrated as one of the risk factors contributing to the development and progression of open-angle glaucoma (OAG)[3–6].

The association between MMD and OAG could potentially be predicted by a shared mechanism of reduced blood flow in branches of the ICA. The ONH is supplied by the short posterior ciliary artery and central retinal artery, which are both the downstream of the ICA. Therefore, decreased flow in the ICA may also affect the perfusion of the ONH. However, so far, only a few cases of glaucoma associated with MMD have been reported in the literature[7–10]. Given the higher prevalence and incidence of MMD in Korea compared to other countries, utilizing population claims data from Korea is highly suitable for establishing epidemiologic evidence of associations between MMD and other diseases.

Therefore, this study investigated the association between MMD and OAG using a large, nationwide, longitudinal cohort that encompasses the entire population of South Korea.

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Methods

Data source

The National Health Insurance Service (NHIS) is a single-payer, mandatory health insurance system implemented in South Korea covering about 97% of all residents[11,12]. Under this system, healthcare providers are required to submit medical claims to the NHIS for reimbursement. These claims include demographics, diagnostic codes according to the Korean Classification of Disease system (8th edition), which is a modified version of the International Classification of Diseases-10 system, procedure codes, prescription records, and details of healthcare facilities[12]. We conducted a retrospective cohort study using this NHIS database from 2002 to 2022.

Cohort definition and study variables

Patients having diagnostic code with MMD between January 1, 2002 and December 31, 2022 were identified from the NHIS database. Control subjects were selected from the same database to match the age and sex of the each MMD patient at a ratio of 10 to 1. This control group included individuals who did not receive a diagnosis of MMD during the study period. Subjects diagnosed with MMD were identified using the diagnostic code I675 and the registration code V128, the latter being registered in the Korean government's assistance program for rare and incurable diseases. For OAG diagnosis, the diagnostic code of OAG (H401, which includes normal tension glaucoma and primary open-angle glaucoma) was used. Individuals were classified as having OAG if they had diagnostic code of H401, and a history of medication prescriptions for glaucoma. Medications for glaucoma included prescriptions of any of the following topical agents: prostaglandin analogues, beta-blockers, carbonic anhydrase inhibitors, or alpha-agonists.

Statistical analysis

We employed a Cox proportional hazard model to investigate the association between MMD and the subsequent diagnosis of OAG. To ensure the exclusion of preexisting MMD cases, patients with MMD claims during the initial two-year period (January 1, 2002 – December 31, 2003) were excluded from the analysis. Additionally, patients with glaucoma prior to the diagnosis of MMD were excluded. Through this exclusion, we aimed to access the risk of OAG diagnosis following the diagnosis of MMD. Among the control cohort without MMD, the subjects who had been diagnosed with OAG before entering the cohort were excluded. The outcome for survival analysis was defined as the time to first diagnosis of OAG after entering the cohort. Cases that died or reached the end of the follow-up without the event were considered censored. Crude and adjusted hazard ratios for OAG were calculated. Model 1 used crude values; model 2 adjusted for age and sex, model 3 adjusted for age, sex, and other systemic comorbidities (i.e. hypertension, diabetes, hyperlipidemia, heart failure, atrial fibrillation, myocardial infarction, ischemic stroke, peripheral artery disease, cancer, sleep apnea, and hypotension). Kaplan-Meier survival analyses with log-rank test were performed to compare the incidence probability of OAG based on the MMD diagnosis.

Statistical analyses were carried out using SAS version 9.4 (SAS Inc., Cary, NC) and R programming version 4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org). Results were deemed statistically significant at a significance level of $P < 0.05$.

Ethics statement

This study was conducted with the approval of the Institutional Review Board of the Seoul National University Bundang Hospital (No. X-2306-837-903). The study adhered to the tenets of the Declaration of Helsinki and followed good clinical practice guidelines.

Results

A total of 36,432 MMD patients were included in the study (women, 62.5%), along with 346,769 controls (women, 63.1%). Figure 1 illustrates the flow chart displaying the eligibility criteria. The prevalence of systemic comorbidities was significantly higher in the MMD group as compared to the control group (Table 1).

In the Cox regression analysis, MMD was associated with an increased risk of subsequent diagnosis of OAG (Model 1: hazard ratio [HR], 1.43; 95% confidence interval [CI], 1.31–1.57; $P < 0.001$; Model 2: HR, 1.48; 95% CI, 1.35–1.62; $P < 0.001$; Model 3: HR, 1.26; 95% CI, 1.14–1.38; $P < 0.001$) (Table 2). Men, older age group, comorbidities including hypertension, diabetes, dyslipidemia, peripheral artery disease, and cancer were also associated with an increased risk of OAG in model 3. The mean interval between the diagnosis of MMD and OAG was 5.5 ± 4.3 years.

Incidence probability of OAG was significantly higher among MMD patients than controls consistently during the study period of 18 years ($P < 0.001$, log-rank test) (Fig. 2). The cumulative incidence probability was 3.7% in MMD group and 2.9% in control group at the end of the study period.

Discussion

In this nationwide population-based cohort study, we observed individuals newly diagnosed with MMD showed an elevated risk of subsequent diagnosis of OAG even after adjusting for confounding factors. This is the first study to report the association between MMD and OAG using big medical claims data.

There have been several reports of concurrent retinal vascular occlusion in patients with MMD[13–21]. The authors speculated that reduced blood flow in the ophthalmic artery, presumably caused by MMD, contributes to the development of retinal vascular occlusion. In a review article, it was reported that 57.1% of patients with concurrent retinal vascular occlusion and MMD had stenosis of the carotid artery proximal to the ophthalmic artery bifurcation[19].

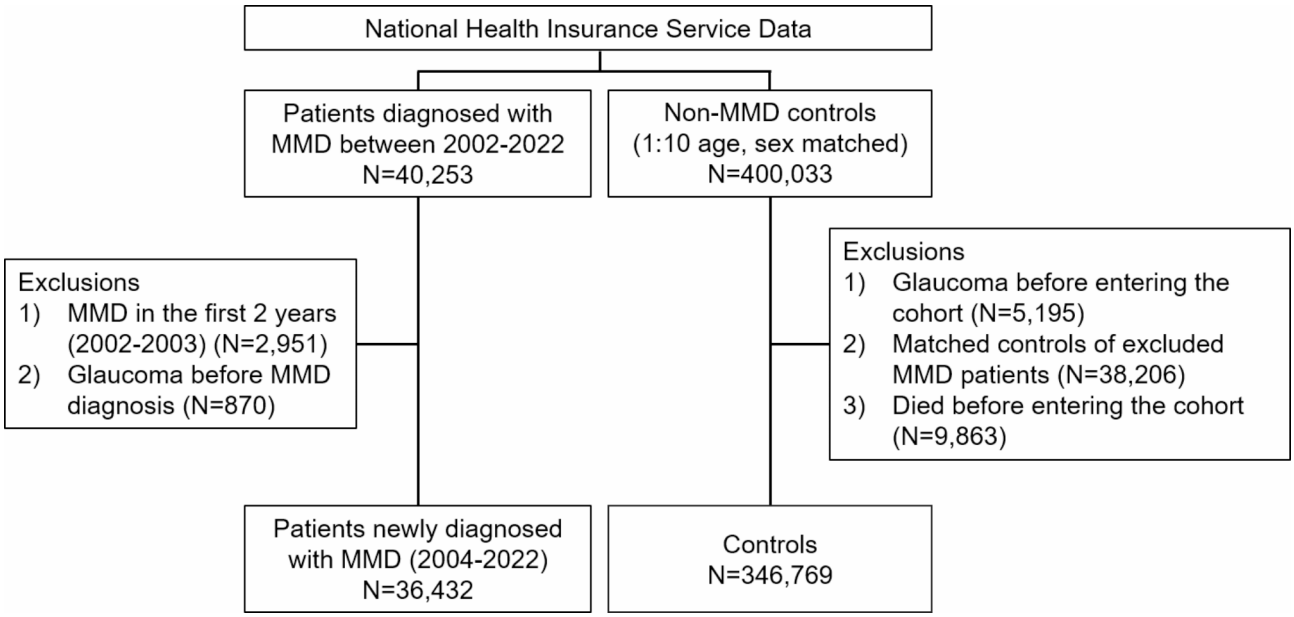

Fig. 1. Flow diagram showing eligible patients' selection for Moyamoya disease and control.

	Total ($n=383,201$)	Moyamoya disease ($n=36,432$)	Control ($n=346,769$)	*P*-value
Sex, n (%)				
Men	141,460 (36.9)	13,654 (37.5)	127,806 (36.9)	0.019
Women	241,741 (63.1)	22,778 (62.5)	218,963 (63.1)	
Age, n (%)				< 0.001
< 40	160,609 (41.9)	14,919 (41)	145,690 (42)	
40–59	156,624 (40.9)	14,662 (40.2)	141,962 (40.9)	
≥ 60	65,968 (17.2)	6,851 (18.8)	59,117 (17)	
Comorbidities, n (%)				
Hypertension	96,549 (25.2)	16,568 (45.5)	79,981 (23.1)	< 0.001
Diabetes	37,193 (9.7)	5,593 (15.4)	31,600 (9.1)	< 0.001
Dyslipidemia	93,715 (24.5)	13,535 (37.2)	80,180 (23.1)	< 0.001
Heart failure	10,565 (2.8)	1,845 (5.1)	8,720 (2.5)	< 0.001
Atrial fibrillation	5,715 (1.5)	1,029 (2.8)	4,686 (1.4)	< 0.001
Myocardial infarction	5,356 (1.4)	1,018 (2.8)	4,338 (1.3)	< 0.001
Ischemic stroke	19,534 (5.1)	8,695 (23.9)	10,839 (3.1)	< 0.001
Peripheral artery disease	61,231 (16)	8,778 (24.1)	52,453 (15.1)	< 0.001
Cancer	34,440 (9)	3,855 (10.6)	30,585 (8.8)	< 0.001
Sleep apnea	2,215 (0.6)	260 (0.7)	1,955 (0.6)	< 0.001
Hypotension	3,345 (0.9)	565 (1.6)	2,780 (0.8)	< 0.001

Table 1. Baseline characteristics.

Meanwhile, population-based epidemiological and clinical studies have highlighted altered ocular hemodynamics (e.g., decreased ocular blood flow), as a significant risk factor for both the prevalence and progression of glaucoma[3,22]. Evidence supporting low ocular blood flow as a causative factor in glaucoma has been demonstrated in studies such as the Blue Mountains Eye Study, Beijing Eye Study, Singapore Malay Eye Study, Los Angeles Latino Eye Study, Barbados Studies, and Rotterdam Study [4–6,23–25]. Reliable instruments such as fluorescein angiography, laser doppler velocimetry, color doppler imaging, laser doppler flowmetry, laser speckle flowgraphy and optical coherence tomography angiography have also confirmed decreased ocular blood flow in glaucoma patients[26–29].

Chou et al. suggested that carotid artery stenosis serves as an independent risk factor for the development of OAG[30]. They observed that individuals with carotid artery stenosis exhibited an elevated risk of OAG (adjusted HR = 1.5) using claims data from Taiwan. Additionally, increased carotid arterial stiffness was found to be

	Model 1		Model 2		Model 3	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Moyamoya disease	1.43 (1.31–1.57)	< 0.001	1.48 (1.35–1.62)	< 0.001	1.26 (1.14–1.38)	< 0.001
Sex						
Men	NA		1 (reference)		1 (reference)	
Women	NA		0.86 (0.81–0.91)	< 0.001	0.88 (0.83–0.94)	< 0.001
Age						
< 40	NA		1 (reference)		1 (reference)	
40–59	NA		4.99 (4.55–5.48)	< 0.001	4.07 (3.7–4.48)	< 0.001
≥ 60	NA		13.37 (12.15–14.71)	< 0.001	8.4 (7.53–9.37)	< 0.001
Comorbidity						
Hypertension	NA		NA		1.31 (1.21–1.41)	< 0.001
Diabetes	NA		NA		1.54 (1.42–1.66)	< 0.001
Dyslipidemia	NA		NA		1.22 (1.14–1.31)	< 0.001
Heart failure	NA		NA		1.08 (0.94–1.25)	0.275
Atrial fibrillation	NA		NA		1.08 (0.9–1.31)	0.405
Myocardial infarction	NA		NA		0.98 (0.81–1.18)	0.802
Ischemic stroke	NA		NA		1.03 (0.93–1.15)	0.531
Peripheral artery disease	NA		NA		1.19 (1.1–1.27)	< 0.001
Cancer	NA		NA		1.16 (1.05–1.27)	0.002
Sleep apnea	NA		NA		1.35 (0.94–1.95)	0.109
Hypotension	NA		NA		1.09 (0.81–1.46)	0.580

Table 2. Results of Cox proportional hazard models for open-angle glaucoma. HR = hazard ratio, CI = confidence interval.

associated with high-tension OAG in the Rotterdam study[6]. Given that the ONH is supplied by the downstream of the ICA, it is not surprising that disturbance in blood flow in the carotid artery could be linked to the development or presence of glaucoma. We speculate that the reduced ocular blood flow associated with MMD contributed to the development of OAG by imposing chronic ischemia on the ONH. Since there are currently no studies directly observing ocular blood flow in MMD, further research in this area is needed. Analyzing ophthalmic artery flow in MMD patients via magnetic resonance angiography or using animal models of MMD could be an effective approach. This approach would provide direct evidence of ocular blood flow changes associated with MMD, supporting our hypothesis that compromised blood flow due to ICA impairment could contribute to OAG risk in these patients.

Previous studies have indicated that the prevalence of diabetes mellitus (DM) tends to be higher, or significantly elevated, in patients with MMD compared to healthy individuals. However, no studies have clearly elucidated the correlation between MMD and DM[31,32]. In contrast, several studies have reported associations between dyslipidemia and MMD. Although the specific mechanisms through which lipid metabolism affects the onset and progression of MMD remain unclear, it is hypothesized that persistent inflammatory states, such as those caused by dyslipidemia, may contribute to vascular immune injury. It is speculated that MMD could be a consequence of such vascular injury[32,33]. Furthermore, we found no reports exploring the relationship between MMD and cancer. While the underlying reasons for any potential association between these diseases remain uncertain, it is plausible that increased healthcare utilization by MMD patients may result in more opportunities for comprehensive health evaluations, thereby leading to the incidental detection of malignancies.

Genome-wide association studies and exome analysis have identified RNF213 as a susceptibility gene for MMD, with p.R4810K and p.R4859K variants recognized as Asian-specific founder variants, as these mutations are absent in Caucasian populations[34]. Numerous animal models, including zebrafish, mice, rats, rabbits, primates, felines, canines, and peripheral blood cells, have been developed to replicate MMD, primarily via genetic, immunological/inflammatory, or ischemic mechanisms[35]. However, no studies have examined the genetic linkage between MMD and glaucoma, nor have they investigated glaucoma or other ophthalmic diseases in MMD animal models. Further research in this area is warranted.

In a meta-analysis, the pooled primary angle-closure glaucoma to primary OAG prevalence ratio was 2.204, showing high heterogeneity in the Asian population[36]. The Namil study, a population-based prevalence study initiated by the Korean Glaucoma Society, reported that in those aged 40 and older, the prevalence of primary OAG was 3.5%, while the prevalence of primary angle closure suspects, primary angle closure, primary angle-closure glaucoma, and overall angle closure were 2%, 0.5%, 0.7%, and 3.2%, respectively[37,38]. OAG and angle-closure glaucoma have different pathophysiologies, and ongoing studies will further explore the impact of MMD on angle-closure glaucoma.

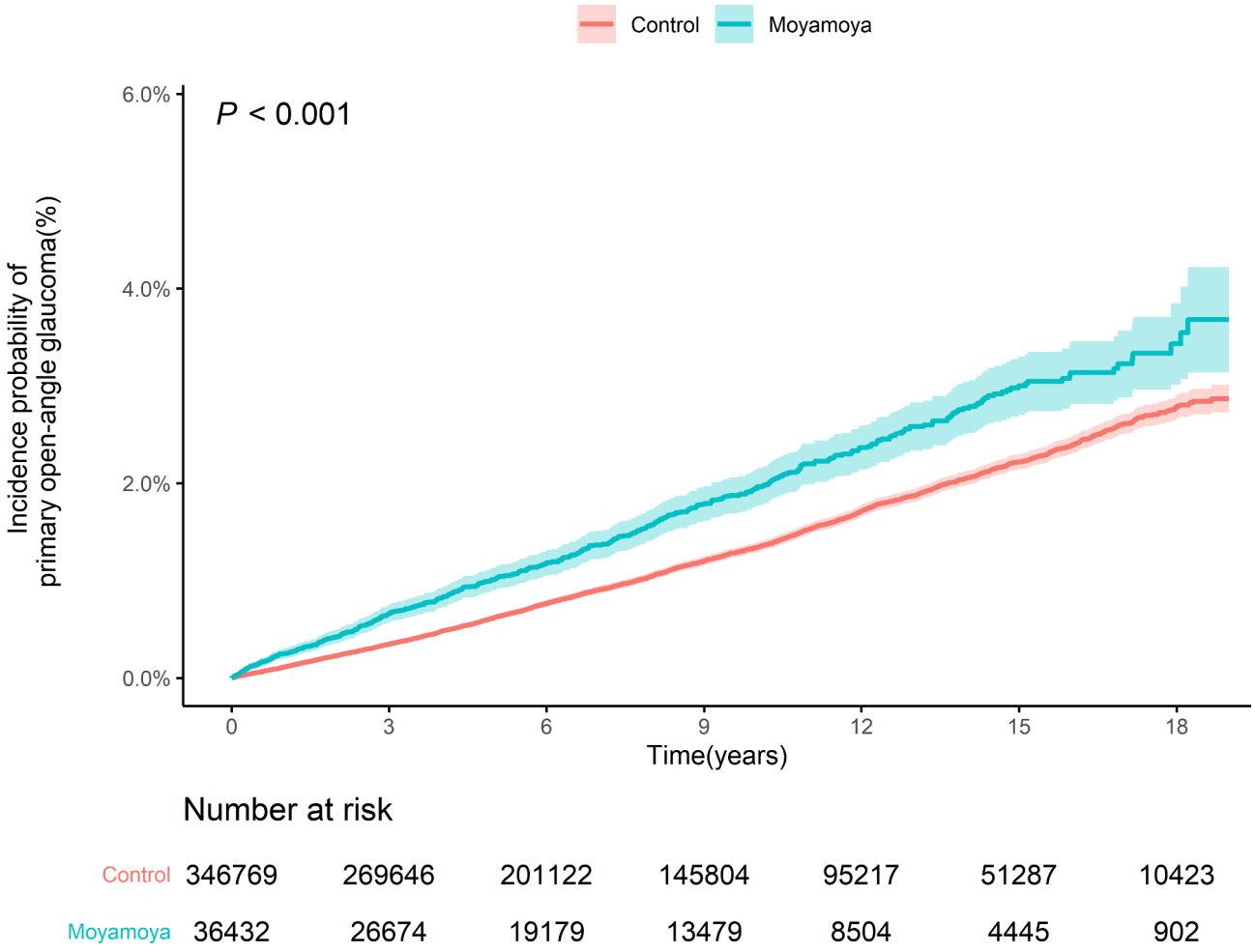

Fig. 2. Kaplan–Meier curves of open-angle glaucoma incidence in the Moyamoya group and the control group.

This study has several limitations. First, the diagnosis of OAG relied on diagnostic codes, which raises the possibility of diagnostic uncertainty. Particularly, due to the absence of clinical information such as intraocular pressure, optical coherence tomography, and visual field test, we were unable to distinguish normal-tension glaucoma or ischemic optic nerve head atrophy separately and assess the severity of glaucoma in this study. To ensure a more accurate diagnosis of OAG, we define OAG not only based on the diagnostic code but also on the concurrent medication prescriptions. Further studies are required to examine the intraocular pressure in glaucoma associated with MMD. Similarly, relying solely on diagnostic codes for the diagnosis of MMD may lead to potential overestimation or underestimation of MMD. Second, individuals with MMD might be more likely to visit clinics than those without MMD, which could have led to a higher rate of glaucoma detection among MMD patients. Lastly, since the exact mechanism was not explored in this study, further research investigating ocular blood flow in patients with MMD is warranted.

In conclusion, patients with MMD in Korea showed an association and increased risk of OAG, indicating that MMD could be considered as one of the risk factors for OAG. Given that OAG frequently presents without acute symptoms, physicians should keep in mind the possibility of OAG in MMD patients.

Data availability

Data are accessible from NHIS database, but the access to data used in this study is only available for the researchers who have applied for and have been granted. Further information is available in online homepage of National Health Insurance Sharing Service (https://nhiss.nhis.or.kr). For data requests, contact the correspond ing author.

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Author contributions

KJ and MSK contributed to the conception or design of work. JL and SN contributed to the data collection.

MSK, EJL, SUL, TWK, SJP, SJW and SN contributed to the data analysis and/or interpretation. MSK, EJL, SUL, KJ contributed to the drafting of the article and critical review of the article. The final version was reviewed by all authors.

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Declarations

Ethics approval
Institutional Review Board of the Seoul National University Bundang Hospital (No. X-2306-837-903).

Competing interests
The authors declare no competing interests.

Additional information
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