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Incidence and outcome of pediatric moyamoya disease in the Republic of Korea: A nationwide study

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Abstract

Background: Moyamoya disease (MMD) is a rare cerebrovascular disorder for which nationwide epidemiological data on the pediatric population are limited. In Korea, the majority of published epidemiologic data on MMD entailed brief study periods and were published many years ago. Moreover, the majority of prior epidemiological studies on MMD have not examined the clinical outcomes associated with cerebral revascularization.

Aims: To provide a comprehensive analysis of the recent epidemiological trends and cerebrovascular outcomes associated with pediatric moyamoya disease in the Republic of Korea.

Methods: A retrospective cohort study was conducted using the Korean National Health Insurance Database, analyzing 4323 pediatric patients diagnosed with MMD between 2006 and 2021. Prevalence and incidence were assessed in all 4323 patients, and cerebrovascular outcomes were analyzed in 3656 of these patients. Patients were categorized into surgical and non-surgical groups, with surgical techniques including indirect bypass (IB), direct bypass (DB), and combined bypass (CB). To evaluate year-to-year variations, linear regression analyses were performed to identify and quantify temporal trends for all measured outcomes.

Results: The mean observation period for the subjects was 10.3 years, with 12.1 years for the non-surgical group and 9.7 years for the surgical group. The prevalence of pediatric MMD increased from 9.3 to 24.8 per 100,000 between 2006 and 2021. Concurrently, the incidence rate has remained stable at approximately 2.0 per 100,000 since 2010. The surgical rate among prevalent cases has exhibited a gradual increase and has remained at approximately 88% since 2018. Furthermore, the case event rate for stroke has exhibited a downward trend over time, and a statistically significant reduction in hemorrhagic stroke was observed.

Conclusions: In Korea, the prevalence rate of MMD continues to rise, while the incidence rate remains stable despite a reduction in absolute case numbers, reflecting demographic shifts and improved survival. The mortality rate among pediatric MMD patients remained unchanged; however, the incidence of hemorrhagic stroke was found to have decreased. Further multi-institution-based cohort studies are needed to clarify long-term cerebrovascular outcomes in this population.

Data access statement: Researchers can access the NHIS database by submitting a request to the National Health Insurance Service Big Data Platforms (http://nhiss.nhis.or.kr).

Keywords

Epidemiology, mortality, morbidity, stroke, moyamoya disease, pediatric

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Introduction

Moyamoya disease (MMD) is a rare cerebrovascular condition characterized by progressive stenosis or occlusion of distal internal carotid arteries.[1] The disease has a bimodal age distribution, with incidence peaking at approximately 10 and 40 years of age.[2] Although pediatric and adult MMD share similar radiographic features, they differ in their clinical presentations, surgical methods, and prognoses.[3,4] In children, MMD predominantly manifests as ischemic symptoms, with cerebral infarction being more common and occurring in approximately 39% of cases, whereas cerebral hemorrhage is less frequent than in adults, affecting only approximately 3% of cases.[3] Surgical revascularization through indirect bypass (IB) surgery is the main treatment modality for pediatric patients, whereas adult patients commonly undergo direct bypass (DB) or combined bypass (CB) procedures.[5–10] Pediatric patients have favorable long-term outcomes, but young patients (<3 years of age) tend to have more rapid disease progression and worse prognoses.[4,7]

MMD has distinct regional variations, with higher incidence rates reported in East Asian countries such as Korea, Japan, Taiwan and China.[11,12] Several previous studies have examined the epidemiologic features of MMD using nationwide cohort data from each country.[11–16] However, many of these studies do not fully account for the impact of recent demographic changes and advancements in treatment that have improved clinical outcomes. In Korea, most published epidemiologic data on MMD involve short study periods and are more than a decade old.[13,15] In addition, most prior epidemiologic studies on MMD have not investigated the clinical outcomes associated with cerebral revascularization.

Aims

This study was performed to examine epidemiologic trends, treatment modalities, and cerebrovascular outcomes associated with patients with MMD. Using data from the National Health Insurance Service (NHIS) in Korea, this study focused specifically on the pediatric population.

Methods

Study design and population

This study utilized a retrospective cohort design to assess the prevalence, incidence, therapeutic modalities, mortality, and morbidity among pediatric patients diagnosed with MMD in Korea. We used the National Health Insurance Database (NHID) which covers 97% of the Korean population, and integrates insurance and healthcare utilization data.[17]

The study population included pediatric patients with MMD aged 18 years or younger with an index date from 2002 to 2021. We specifically focused on children, as their clinical presentation, natural history, and treatment strategies differ substantially from adults, necessitating a pediatric-specific analysis. Patients were identified using the Rare Intractable Disease (RID, V128) and the International Classification of Disease (ICD)-10 (I675) codes to ensure diagnostic accuracy.[13] As the policy to support medical expenses for patients with rare diseases in Korea was gradually implemented starting in 2005, the analysis was conducted with 2005 as a wash-out period. The final cohort included 4323 patients, to investigate prevalence and incidence and to analyze clinical outcomes (Figure 1). For the cerebrovascular outcome analysis, 3656 patients were included after excluding 667 patients who had any claims with MMD during 2002-2005 or a history of cerebral infarction or intracranial hemorrhage within five years prior to study enrollment. The occurrence of a new stroke event was defined as the primary outcome.

Patients were categorized by the initial surgical intervention: IB, DB, CB (both IB and DB), and non-surgical

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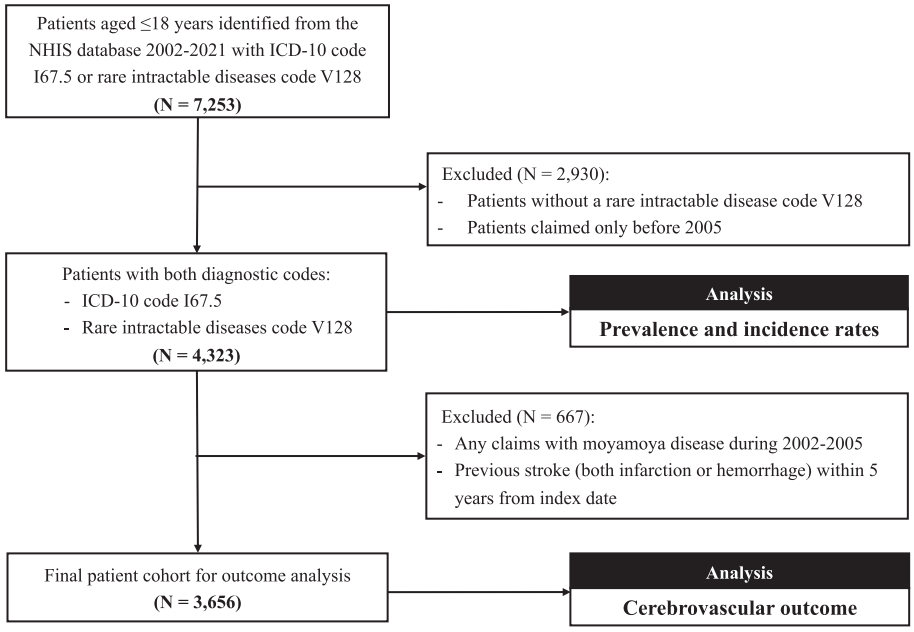
Figure 1. Selection process for children with moyamoya disease from the South Korean National Health Insurance database.



intervention. All data related to healthcare utilization were subjected to analysis until the end of the observation period (31 December 2021), the occurrence of cerebrovascular events, or the death of the patient.

The study protocol received an exemption from review by the Institutional Review Board at Seoul National University Hospital (IRB No. E-2307-060-1448), and the stipulation for informed consent was annulled given the retrospective characteristics of the study. The NHIS granted authorization for the utilization of their database for this research subsequent to an internal examination of the study protocol (NHIS-2024-1-471).

Baseline characteristics and outcomes

Baseline characteristics included the age at the initial diagnosis of MMD, sex, category of surgical intervention, and comorbid conditions. The comorbid conditions were moyamoya syndrome–associated conditions or diseases that were predominantly accompanied by MMD.[18,19] They were defined by any health insurance claims utilizing the ICD-10 classifications during the year preceding cohort enrollment (Supplemental Table S1).

The prevalence and incidence rates of pediatric MMD were calculated from the data. The annual pediatric population size was provided by the Korean Statistical Information Service (KOSIS, https://kosis.kr), which was the denominator used for the calculation of the incidence and prevalence of MMD in the pediatric population. The annual population was defined as the population on 1 July, representing the mid-year point. Mortality data were ascertained from the national mortality statistics repository of the KOSIS, which was connected to the NHIS utilizing the national identification number as the linking key.

Medical expenditures during the postoperative observation period were calculated from the claims data, and these costs were classified into those incurred at consultations where MMD was the principal diagnosis and those where it was not. The durations of hospitalization and outpatient visits were also gathered and differentiated into those attributable to MMD and those not attributable to MMD.

Statistical analysis

Group comparisons and survival analysis used standard statistical tests. The prevalence rate was calculated by dividing the number of patients with MMD by the total population for each year and the result per 100,000 persons. The incidence rate was determined by dividing the number of new cases by the total population for the corresponding year. The operation rate was defined as the proportion of new patients who underwent revascularization surgery among prevalent patients in each year and expressed as a percentage. Furthermore, an appropriate reference population had to be selected in order to reflect the changing demographics of the pediatric population and facilitate comparison of statistically adjusted prevalence and incidence rates. The 2021 Korean pediatric population and the

World Health Organization (WHO) standard population[20] were selected for domestic and international comparisons, respectively. In addition, structural changes based on sex were incorporated in the calculation of the domestic standardization rate.

In order to ascertain survival and stroke incidence rates during the observation period, a comprehensive review was conducted of the number of prevalent patients, as well as the number of cases. The incidence rate among patients with the disease was subsequently calculated to facilitate an analysis of temporal changes. To evaluate year-to-year variations, linear regression analyses were conducted to identify and quantify temporal trends for all measured outcomes.

All the statistical analyses were performed using SAS Version 9.4, SAS Enterprise Guide (SAS Institute, Inc., Cary, NC, USA), and R software (version 4.5.0, R Foundation for Statistical Computing, Vienna, Austria). A two-sided significance level of 0.05 was used for all tests.

Results

Demography, prevalence, and incidence of MMD in children

A total of 4323 patients in the cohort comprised 3328 (77.0%) surgical patients and 995 (23.0%) non-surgical patients (Table 1). Among first surgical interventions, IB was predominant (n = 3082 patients, 92.6%), followed by CB (n = 177, 5.3%) and DB (n = 69, 2.0%). Female predominance was observed in both surgical (57.6%) and non-surgical groups (54.4%). The surgical group showed a significantly younger mean age (9.5 ± 4.1 years) compared with the non-surgical group (12.4 ± 4.1 years). Age distribution varied by surgical method: patients with IB were younger (9.2 years) than DB (14.5 years), CB (12.4 years), and the non-surgical group (12.4 years). IB was most common in patients aged 5–9 years (45.6%), DB in 15–18 years (62.3%), and CB predominantly equal to or older than 10 years (77.4%).

Hematologic diseases were the most frequent comorbidities (36.0%), especially in the surgical group (38.3%), followed by central nervous system (CNS) infections (10.5%). The non-surgical group had higher proportions of hypertension (9.5%) and arteriovenous malformations (1.4%). Nutritional anemia (49.4%) and coagulopathy (40.0%) were the most common hematologic subtypes (Supplemental Table S2). The incidence rate of nutritional anemia was highest among patients aged 0–4 years at 59.0% (102 of 173), decreasing with age to 52.2%, 47.6%, and 39.4% in the subsequent age groups (Supplemental Table S3).

The prevalence of MMD has increased since 2006 and peaked in 2015, when 2249 cases (23.1 per 100,000 children) were observed (Table 2). Since then, the prevalence has slowly declined, with the most recent data reporting 2002 cases. Despite this decrease in absolute numbers, the prevalence rate continues to rise due to a decline in the overall population from 9.3 per 100,000 in 2006 to 24.8 per 100,000 in 2021 (Figure 2). The annual number of incident cases has steadily decreased since 2006. However, the incidence rate has remained stable, approximately 2.0 per 100,000 after 2010. The operation rate among prevalent cases gradually increased and has remained at approximately 88% since 2018. Moreover, the operation rate among incident cases peaked at 88.8% in 2012, fluctuated at a similar level thereafter, and dropped to 75.8% in 2021.

The mortality rate for pediatric MMD showed a stable trend from 2006 to 2021. While the mortality rate was higher in 2007 (3.6 per 1000 person-years), in most other years, the rate fluctuated within a narrow range of 0.5 to 1.5 per 1000 person-years. Given the rarity of mortality in pediatric patients with MMD, the observed trend was not statistically significant ($p = 0.5084$). On the contrary, the incidence of stroke showed a decreasing trend. While there was no significant change in ischemic stroke ($p = 0.1730$), a significant decrease was observed in hemorrhagic stroke ($p = 0.0419$, Table 3).

Discussion

We analyzed epidemiologic trends and cerebrovascular outcomes in pediatric MMD using the NHID. Most pediatric patients with MMD in Korea are treated at tertiary hospitals, where relatively standardized treatment strategies and surgical methods are employed. These factors increase the precision and robustness of our findings, despite the inherent limitations of claims-based data.

Epidemiologic features of MMD in children

Consistent with prior national reports, we observed a continued increase in the prevalence of pediatric MMD cases between 2006 and 2021, increasing from 9.3 to 24.8 per 100,000. However, the number of new cases declined over the same period. This divergence likely reflects demographic shifts, most notably declining birth and fertility rates, as well as improved survival and early diagnosis. The incidence rate in our cohort stabilized at approximately 2.0 per 100,000 after 2010, which is in line with earlier studies.[13,15,21]

Comparative data from Japan, where most epidemiologic analyses are derived from nationwide surveys, show similar trends but lower prevalence rates.[2,11] Between 2015 and 2019, the pediatric MMD prevalence ranged from 7.3 to 9.7 per 100,000 children, whereas the incidence increased slightly from 1.4 to 2.5 per 100,000. In contrast, Taiwan[22] and China[12] reported substantially lower rates, and Western countries, including the United States and Denmark, reported incidence and prevalence that were more than 10-fold lower than those reported in East Asia.[23,24] These

Table 1. The baseline characteristics of the pediatric patient cohort with moyamoya disease (N=4323).

	Total (n=4323)	Non-Surgical treatment (n=995)	Surgical treatment (n=3328)	p-value	Type of surgical treatment			P-value
					Indirect (n=3082)	Direct (n=69)	Combined (n=177)	
Age, mean ± SD, years	10.1 ± 4.2	12.4 ± 4.1	9.5 ± 4.1	<0.0001	9.2 ± 3.9	14.5 ± 3.4	12.4 ± 4.1	<0.0001
Age group, N (%), years								
0-4	392 (9.1)	51 (5.1)	341 (10.2)	<0.0001	332 (10.8)	1 (1.4)	8 (4.5)	<0.0001
5-9	1634 (37.8)	190 (11.6)	1444 (43.4)		1407 (45.6)	5 (7.3)	32 (18.1)	
10-14	1485 (34.3)	937 (39.9)	1088 (32.7)		1004 (32.6)	20 (29.0)	64 (36.2)	
15-18	812 (18.8)	357 (35.9)	455 (13.7)		339 (11.0)	43 (62.3)	73 (41.2)	
Sex, N (%)								
Male	1865 (43.1)	454 (45.6)	1411 (42.4)	0.0711	1310 (42.5)	28 (40.6)	73 (41.2)	0.3257
Female	2458 (56.9)	541 (54.4)	1917 (57.6)		1772 (57.5)	41 (59.4)	104 (58.8)	
Comorbidity, N (%)								
Alagille syndrome	-	-	-	-	-	-	-	-
Arterial dissection	11 (0.3)	1 (0.1)	10 (0.3)	0.4745	9 (0.3)	-	1 (0.6)	0.3318
Arteriovenous malformation	27 (0.6)	14 (1.4)	13 (0.4)	<0.0001	10 (0.3)	2 (2.9)	1 (0.6)	0.0002
Central nervous system infection	423 (9.8)	73 (7.3)	350 (10.5)	0.0031	320 (10.4)	15 (21.7)	15 (8.5)	0.0002
Cerebral aneurysm	9 (0.2)	4 (0.4)	5 (0.2)	0.2252	4 (0.1)	-	1 (0.6)	0.1558
Down Syndrome	16 (0.4)	6 (0.6)	10 (0.3)	0.1679	10 (0.3)	-	-	0.4924
Graves' disease	22 (0.5)	4 (0.4)	18 (0.5)	0.5891	15 (0.5)	-	3 (1.7)	0.2021
Hematological disease[a]	1557 (36.0)	282 (28.3)	1275 (38.3)	<0.0001	1171 (38.0)	27 (39.1)	77 (43.5)	<0.0001
Hypertension	260 (6.0)	94 (9.5)	166 (5.0)	<0.0001	146 (4.7)	7 (10.1)	13 (7.3)	<0.0001
Inflammatory vasculopathy	24 (0.6)	10 (1.0)	14 (0.4)	0.0295	13 (0.4)	-	1 (0.6)	0.1741

(continued)

Table 1. (continued)

	Total (n = 4323)	Non-Surgical treatment (n = 995)	Surgical treatment (n = 3328)	p-value	Type of surgical treatment			P-value
					Indirect (n = 3082)	Direct (n = 69)	Combined (n = 177)	
Morning glory disk anomaly	-	-	-	-	-	-	-	-
Neurofibromatosis	66 (1.5)	19 (1.9)	47 (1.4)	0.2617	43 (1.4)	2 (2.9)	2 (1.13)	0.3737
Noonan syndrome	11 (0.3)	5 (0.5)	6 (0.2)	0.0767	6 (0.2)	-	-	0.3715
Prothrombotic condition	-	-	-	-	-	-	-	-
Renal artery stenosis	8 (0.2)	3 (0.3)	5 (0.2)	0.3958	4 (0.1)	1 (1.4)	-	0.133
Renovascular hypertension	49 (1.1)	19 (1.9)	30 (0.9)	0.0084	23 (0.8)	2 (2.9)	5 (2.8)	0.0009
Sickle cell anemia	1 (0.0)	-	1 (0.0)	-	1 (0.03)	-	-	-
Systemic lupus erythematosus	2 (0.0)	-	2 (0.1)	-	2 (0.06)	-	-	-
Systemic vasculitis	76 (1.8)	13 (1.3)	63 (1.9)	0.2168	59 (1.9)	1 (1.4)	3 (1.7)	0.6262
Turner syndrome	-	-	-	-	-	-	-	-
Observation periods, mean ± SD, years	10.3 (5.3)	12.1 (5.4)	9.7 (5.2)	<0.0001	9.9 (5.2)	9.9 (4.9)	6.7 (4.4)	<0.0001

[a]Hematological disease included anemia and coagulation disorders and certain disorders involving the immune mechanism.

Table 2. Prevalence incidence of pediatric moyamoya disease, and the operation rate among newly diagnosed patients from 2006–2021.

Outcome	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	Beta (β)[a]	P-value[a]
Prevalent case (N)	1083	1398	1654	1863	2027	2132	2219	2232	2243	2249	2247	2203	2167	2160	2069	2002	48.11	0.0044
Prevalence rate[b]	9.3	12.1	14.5	16.6	18.5	19.9	21.1	21.8	22.4	23.1	23.7	23.9	24.2	25.0	24.8	24.8	0.95	<0.0001
Standardized prevalence rate[b]																		
Korea pediatric population[c]	8.5	11.2	13.6	15.5	17.2	18.5	19.8	20.4	21.2	22.0	22.8	23.1	23.5	24.3	24.2	23.9	0.97	<0.0001
WHO population	6.4	8.5	10.3	12	13.5	14.8	16	17	18	19.1	20.3	21.2	22.1	22.7	24.3	24.8	1.18	<0.0001
Operation among prevalent case																		
Indirect	664	871	1053	1214	1373	1506	1619	1695	1753	1791	1820	1825	1811	1796	1723	1660	65.99	<0.0001
Direct	10	17	21	23	28	31	29	25	22	18	21	18	18	15	15	15	–0.32	0.3220
Combined[d]	12	15	16	18	25	30	38	47	55	56	72	77	84	95	92	91	6.30	<0.0001
All surgical treatment	686	903	1090	1255	1426	1567	1686	1767	1830	1865	1913	1920	1913	1906	1830	1766	71.97	<0.0001
Operation rate for prevalent patients (%)	63.3	64.6	65.9	67.4	70.4	73.5	76	79.2	81.6	82.9	85.1	87.2	88.3	88.2	88.4	88.2	1.93	<0.0001
Incident case (N)	306	315	286	264	234	215	215	195	189	198	220	207	191	200	154	157	–9.05	<0.0001
Incidence rate[b]	2.6	2.7	2.5	2.4	2.1	2.0	2.0	1.9	1.9	2.0	2.3	2.2	2.1	2.3	1.8	1.9	–0.04	0.0076
Standardized prevalence rate[b]																		
Korea pediatric population[c]	2.6	2.7	2.6	2.4	2.2	2.1	2.2	2.0	2.0	2.2	2.5	2.4	2.2	2.4	1.9	1.9	–0.03	0.0107
WHO population	2.4	2.5	2.4	2.2	2.1	2.0	2.0	1.9	1.8	2.0	2.3	2.2	2.1	2.2	1.7	1.7	–0.03	0.016

(continued)

Table 2. (continued)

Outcome	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	Beta (β)[a]	P-value[a]
Operation among incident case																		
Indirect	191	207	192	182	185	167	175	157	149	154	166	166	150	143	122	103	–5.09	<0.0001
Direct	3	7	4	4	7	8	5	3	2	4	5	0	2	2	3	3	–0.24	0.0359
Combined[d]	2	3	2	4	9	6	11	13	13	12	23	13	14	19	10	13	0.95	0.0006
All surgical treatment	196	217	198	190	201	181	191	173	164	170	194	179	166	164	135	119	–4.37	<0.0001
Operation rate for incident patients (%)	64.1	68.9	69.2	72.0	85.9	84.2	88.8	88.7	86.8	85.9	88.2	86.5	86.9	82.0	87.7	75.8	1.04	0.0156

WHO: World Health Organization.
[a]The reported Beta (β) and p-value are indicative of the observed trend and its statistical significance.
[b]The rate is expressed as the value per 100,000 persons.
[c]For the purpose of year-to-year comparisons, the standard population is set to the cohort population in the last year of the study.
[d]The Combined refers to cases where both indirect and direct methods were used.

regional differences highlight the likely contributions of genetic and ethnic predispositions to MMD pathogenesis.

In our nationwide cohort, stroke incidence decreased over time and mortality remained rare. Compared with large surgical series evaluating long-term outcomes of surgically treated pediatric MMD patients, our observed stroke incidence (~0.9–1.1% per year) was higher than the rates reported in previous series (0.08–0.04% per year).[7] This discrepancy may reflect the inclusion of both surgically and conservatively managed patients in our cohort, as well as differences inherent to claim-based data collection. Nonetheless, the declining trend of stroke incidence and the rarity of mortality in our cohort are consistent with the favorable long-term outcomes reported in surgical cohorts.

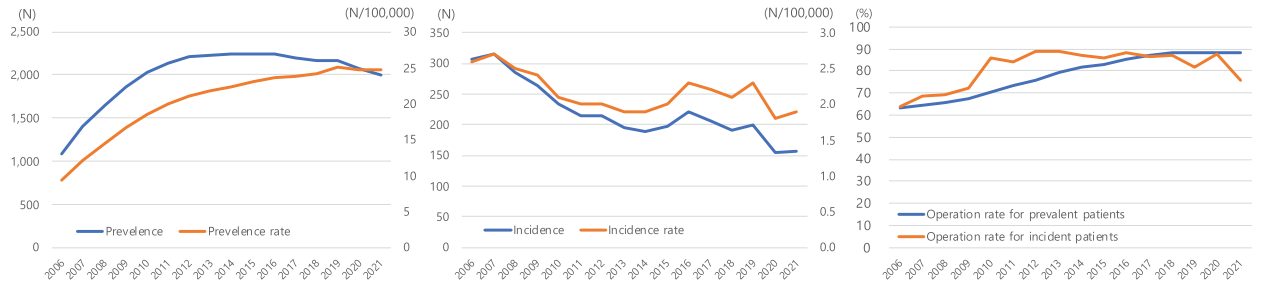
Comorbid conditions of MMD in children

Hematologic disease, including nutritional anemias (49.4%) and coagulopathy (40.0%), was the most common comorbid condition reported in this study and no patients had hematologic malignancies. Although severe coagulation disorders are rare, mild abnormalities detected with laboratory tests are relatively common in children, and are observed in approximately 5.8–15.6% of pediatric patients undergoing elective surgery.[25] The prevalence of hematologic disease appears to be elevated because of its high prevalence in the general pediatric population rather than being directly associated with MMD. In addition, blood transfusions are often performed during surgery in patients with MMD to maintain normal hemoglobin levels (hemoglobin level >13 g/dL immediately after surgery) to reduce postoperative cerebral infarction.[6] Anemia diagnoses are often required for the reimbursement of transfusions, potentially inflating administrative prevalence rates.

Hypertension was noted in 6.0% of patients, and renovascular hypertension was noted in 1.1%. While renovascular hypertension is a recognized complication of MMD,[26] the observed prevalence is likely underestimated. Prior reports indicate that systemic hypertension, unrelated to renovascular pathology, may occur in up to 29% of pediatric patients with MMD.[18] In our cohort, hypertension was identified using insurance claims with ICD-10 codes I10-I15. However, this method may not align with clinical guidelines, which define pediatric hypertension based on age, sex, and growth status.[27] As a result, many children who were not on medication may have been excluded from being classified as hypertensive.

Neurofibromatosis type 1 (NF-1) was identified in 1.5% of the cohort. Although rare, NF-1 is a well-established risk factor for moyamoya syndrome, with cerebral vasculopathy observed in 5% of patients.[19,28] Graves' disease and Down syndrome, which are commonly associated with moyamoya syndrome were less common in this study.[19,29] Given the reliance on diagnostic codes, we could not reliably distinguish between idiopathic MMD and moyamoya

Figure 2. Annual trends in prevalence, incidence, and the operation rate for pediatric moyamoya disease from 2006-2021.



syndrome, although we cross-referenced comorbidities when feasible.

Limitations

This study has several limitations. First, the use of claims data precludes detailed clinical and radiographic analyses. We relied on insurance system variables, and applied ICD–10 and RID codes to ensure strict patient selection. However, these may not fully capture the clinical spectrum of MMD. To address these challenges, it is imperative to construct a comprehensive database that integrates clinical data with insurance claim data. This database could be used to identify patients with unilateral disease, determine the severity of disease, and provide associated imaging data. However, conducting such a study is challenging given Korea's current legal framework. Second, the definition of stroke occurrence used in this study has not been externally validated. However, this definition provides more stringent operational criterion than claims-based stroke research.[30] Therefore, the probability of underestimation of annual prevalence and incidence of stroke remains. Nevertheless, the same type of misclassification occurred across all study years, and the observed trends would be significantly affected even if a different definition were applied, thus maintaining the comparability of the result. Third, indication bias may affect the observed efficacy of surgery. While randomized controlled trials (RCTs) offer stronger causal inferences, they are difficult to implement in pediatric populations. This is due to ethical concerns regarding assignment to non-surgical groups, as substantial evidence already supports the effectiveness of surgical intervention in preventing strokes. Furthermore, the high likelihood of crossover from non-surgical to surgical groups introduces an additional layer of complexity in trial implementation. In such cases, large–scale retrospective studies implementing target trial emulation could serve as alternatives. Fourth, our outcome analysis focused on the first surgical procedure, potentially overestimating stroke risk in patients awaiting bilateral revascularization. Fifth, to detect new cerebrovascular events, we excluded individuals with stroke-related hospitalizations in the 5 years preceding enrollment. While this approach reduces misclassification, it limits generalizability to those initially presenting with stroke. Finally, distinguishing MMD from moyamoya syndrome was limited by the absence of separate diagnostic codes. Although we attempted to mitigate this through a comorbidity analysis, residual misclassification is likely. Nevertheless, our study took advantage of the characteristic health insurance system and evaluated the epidemiology and outcome trends of pediatric MMD in the country with the highest incidence of MMD. Given the inherent limitations of claim data–based studies and the ethical concerns of RCTs, a multi-institutional clinical network of MMD needs to be established for future research.

Conclusion

In this nationwide cohort of 4323 pediatric MMD patients, the prevalence of pediatric MMD increased from 9.3 to 24.8 per 100,000 individuals between 2006 and 2021. This phenomenon occurred despite a decline in the absolute number of prevalent cases. The incidence rate, which gradually decreased, fluctuated around 2.0 per 100,000 children from 2010 onward, even as the absolute number of incident cases declined. The mortality rate in pediatric MMD patients remained unchanged; however, the incidence of hemorrhagic stroke showed a decreasing trend. A multi-institution-based cohort study is needed to more accurately assess the cerebrovascular outcomes of MMD more accurately.

Table 3. Mortality and morbidity of pediatric moyamoya disease among newly diagnosed patients from 2006–2021.

Outcome	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	Beta (β)[a]	P-value[a]
Prevalent MMD case (N)	1083	1398	1654	1863	2027	2132	2219	2232	2243	2249	2247	2203	2167	2160	2069	2002		
Mortality case (N)	-	5	1	2	2	1	3	2	2	6	3	-	1	2	-	3	–0.00	0.9950
Mortality rate[c]	-	3.6	0.6	1.1	1.0	0.5	1.4	0.9	0.9	2.7	1.3	-	0.5	0.9	-	1.5	–0.04	0.5084
Prevalent MMD case without prior stroke (N)[b]	909	1148	1337	1499	1590	1675	1711	1735	1741	1736	1707	1693	1675	1626	1572	1539	30.42	0.0114
Stroke case (N)	10	18	11	20	17	13	25	15	25	18	28	13	9	11	10	14	–0.16	0.6400
Ischemic stroke case (N)	7	12	8	12	11	11	17	11	17	14	21	11	6	7	7	11	0.03	0.8873
Hemorrhagic stroke case (N)	3	6	3	8	7	2	8	4	8	4	7	2	3	4	3	3	–0.13	0.2862
Stroke rate[c]	11.0	15.7	8.2	13.3	10.7	7.8	14.6	8.6	14.4	10.4	16.4	7.7	5.4	6.8	6.4	9.1	–0.32	0.0875
Ischemic stroke rate	7.7	10.5	6.0	8.0	6.9	6.6	9.9	6.3	9.8	8.1	12.3	6.5	3.6	4.3	4.5	7.2	–0.18	0.1730
Hemorrhagic stroke rate	3.3	5.2	2.2	5.3	4.4	1.2	4.7	2.3	4.6	2.3	4.1	1.2	1.8	2.5	1.9	2.0	–0.16	0.0419

MMD: Moyamoya disease.
[a]The reported Beta (β) and p-value are indicative of the observed trend and its statistical significance.
[b]For cerebrovascular outcomes, we defined prevalent patients as those who did not have an event within the past 5 years.
[c]The rate is expressed as the value per 1000 person-years.

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Data availability statement

Researchers can access the NHIS database by submitting a request to the National Health Insurance Service Big Data Platforms (https://nhiss.nhis.or.kr).

Supplemental material

Supplemental material for this article is available online.

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