Epidemiology of Moyamoya disease in China: A nationwide hospital-based study

Dong Zhang,[a,b,c,†] Liangran Huang,[a,b,c,†] Zheng Huang,[d] Qi Zhou,[a,b] Xin Yang,[a,b] Hongqiu Gu,[a,b] Zixiao Li,[a,b,g] Ying Shi,[e] Lanxia Gan,[e] Haibo Wang,[f] Xvdong Ma,[b] Yongjun Wang,[a,b,g,*,‡] and Jizong Zhao[a,c,*,‡]

[a]China National Clinical Research Center for Neurological Diseases, Beijing Tiantan Hospital, Capital Medical University, Beijing, China
[b]National Center for Healthcare Quality Management in Neurological Diseases, Beijing Tiantan Hospital, Capital Medical University, Beijing, China
[c]Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, China
[d]Department of Neurosurgery, Xiangya Hospital Central South University, Changsha, Hunan, China
[e]China Standard Medical Information Research Center, Shenzhen, Guangdong, China
[f]Clinical Trial Unit, Sun Yat-Sen University First Affiliated Hospital, Guangzhou, Guangdong, China
[g]Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

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Summary

Background The national epidemiologic data in mainland China is still absent for moyamoya disease (MMD).

Methods This study was a nationwide hospital-based observational retrospective study to estimate epidemiological characteristics of MMD. The data was based on the Hospital Quality Monitoring System (HQMS), a national database which covers all tertiary hospitals in mainland China. This system consistently collects medical records including demographic characteristics, diagnoses, procedures, and expenses etc. for all inpatients. MMD was identified by ICD-10 code (I67·5) in HQMS.

Findings A total of 47,443 new-onset patients with total 69,680 hospitalization records from 1312 hospitals during 2016 to 2018 were included. The annual incidence rate was 1·14 per 100,000 inhabitants (95% CI, 1·12–1·16) and approximately a 2-fold increase from 2016 to 2018. The incidence in children (0·18 per 100,000 inhabitants per year; 95% CI, 0·17–0·20) was significantly lower than that in adults (1·40 per 100,000; 95% CI, 1·38–1·42) ($P<0·001$) and the peak incidence was 45–54 years. The distribution model of incidence rate was presented as a clustered regional pattern (Moran's $I = 0·155$, $P = 0·018$, $Z = 2·375$) by global spatial correlation analysis.

Interpretation Our study reported the annual incidence of MMD was 1·14 per 100,000 inhabitants in mainland China during 2016 to 2018, and it was increasing year by year. The geographical distribution of MMD incidence presented as a clustered regional pattern, which may provide new view for future study on the etiology for MMD.

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Keywords: Moyamoya disease; Epidemiology; Incidence; Geographical distribution

Introduction

Moyamoya disease (MMD) is a chronic cerebrovascular disease characterized by progressive narrowing of the distal internal carotid arteries and their proximal branches with abnormal collateral vessels.[1] Clinical presentations included ischemic and/or hemorrhagic stroke and cognitive impairment, which can occur in both children and adults, thus resulting in high incidence of disability and deaths.[2]

MMD was more common in East Asian countries, such as Japan, Korea, and China.[2] The national

*Co-corresponding author: Yongjun Wang and Jizong Zhao, 119 South Fourth Ring West Road, Fengtai District, Beijing, China, 100070, Phone: 0086-010-59978350, 0086-13701095698.

E-mail addresses: yongjunwang@ncrcnd.org.cn (Y. Wang), zhaojz205@163.com (J. Zhao).

† Co-first author: Dong Zhang and Liangran Huang contributed equally to this work.

‡ Co-corresponding Author: Yongjun Wang and Jizong Zhao contributed equally to this work

incidence of MMD in Japan and South Korea has been well-documented. In Japan, the annual incidence was 0·35 per 100,000 inhabitants in 1994, 0·54 per 100,000 in 2003, and 0·94 per 100,000 from 2002 to 2006.[3–5] An upward trend was also observed In Korea, and the annual incidence increased from 1·7 per 100,000 inhabitants in 2007 to 4·3 per 100,000 in 2013.[6,7]. In the US, although with a much lower prevalence, an increasing trend of hospital admissions was also observed.[8,9] In Europe, a similar upward trend has also been observed in a Danish population-based study with a relatively low annual incidence of 0·07 per 100,000 inhabitants.[10]

However, the national and relatively accurate epidemiological data of MMD in China is still absent, except studies in Nanjing and Taiwan. The annual incidence was 0·43 per 100,000 inhabitants from 2000 to 2007 in Nanjing based on 15 major hospitals in local areas,[11] and it was 0·15 per 100,000 inhabitants from 2000 to 2011 in Taiwan,[12] which was lower than Japan and Korea. China has 34 provinces, municipalities, and autonomous regions with approximately one-fifteenth of the world's population. Therefore, clarification of the epidemiology features of MMD in China is of great importance.

In this study, to estimate the national epidemiological data including incidence, geographical distribution, and basic clinical features of MMD in mainland China, we used Hospital Quality Monitoring System (HQMS) maintained by the National Health Commission (NHC) from 2016 to 2018 to undertake the nationwide hospital-based observational retrospective study.

Methods

Study design and participants

It was a population-based retrospective study and a project of China National Clinical Research Center for Neurological Diseases and China National Center for Quality Control of Neurological Diseases. Our study was approved by the Institutional Review Board of Beijing Tiantan Hospital.

The data was based on a national database of the Hospital Quality Monitoring System (HQMS). It was established in 2011 which is maintained by the National Health Commission to monitor the quality of medical care in all tertiary hospitals of 31 provinces and municipalities in mainland China except for Hong Kong, Macao, and Taiwan province. The system consistently collects a dataset of medical records from all inpatient and contains 346 variables including department demographic characteristics, diagnoses, procedures, and expenses etc.[13] The HQMS was described as previous study and several papers had published based on HQMS by Chinese research groups.[14] In HQMS, every uploaded record must be reviewed the diagnosis accordance of ICD-10 code and procedures accordance of ICD-9-CM code by a "Quality Assurance Physician" or coder in local hospital to confirm the accuracy of the diagnosis from the medical records.

According to the China Health Statistics Yearbook 2018, there are 2340 tertiary hospitals in China. All tertiary hospitals were included in the survey in HQMS. In this study, a total of 1312 hospitals which covered more than a half of tertiary public hospitals, had at least one medical record of patient with MMD during 2016 to 2018, which indicated that MMD might not be a rare cerebrovascular disease in China according to the traditional epidemiological theory.[11] And geographical distribution of the 1312 hospitals was shown in Section 1 of Supplemental materials. Although we cannot accurately evaluate the patients only in outpatient clinics and other relatively low-level hospitals, this certainly will be bound to cause some deviation in our evaluation of the incidence. However, the remaining 228 private hospitals and 422 traditional Chinese medicine hospitals rarely treated MMD patients.

Procedures

A flow diagram of this study is shown in Fig. 1. The hospitalization records of MMD were reviewed from the HQMS database between 1st January 2016 to 31st December 2018. The records in patients with miss information were excluded. The variable of "The same person" was identified based on name, gender, and Citizen Identification Number (a unique, unchanging legal number in China), which was used for selecting the initial hospitalization record of patients. Patients who were initially discharged with a diagnosis of MMD were defined as "new-onset cases" of each year during the study period for estimating the incidence.

MMD was identified based on the ICD-10 code I67·5 in principle or other discharge diagnoses. The diagnosis of MMD was made according to the diagnostic guidelines proposed by the Ministry of Health and Welfare of Japan.[15]

Patients were categorized into juvenile (<20 years of age) and adult (≥20 years of age) according to WHO guidelines. Geographic information of the MMD patients was determined by the parameter of "from province" in HQMS. The geographic and demographic information of China were provided by China National Bureau of Statistics (http://www.stats.gov.cn). The initial clinical presentations included Intracranial hemorrhage, Cerebral infarction, Epilepsy, Transit ischemic attack (TIA) and others. It was worth noted that the clinical presentations of TIA and others meant that the patient with no infarction, hemorrhage, or epilepsy in diagnosis, which included the asymptomatic patients with MMD and the patients with TIA or headache.

For surgically treated patients, the surgical procedures were divided into direct cerebral revascularization

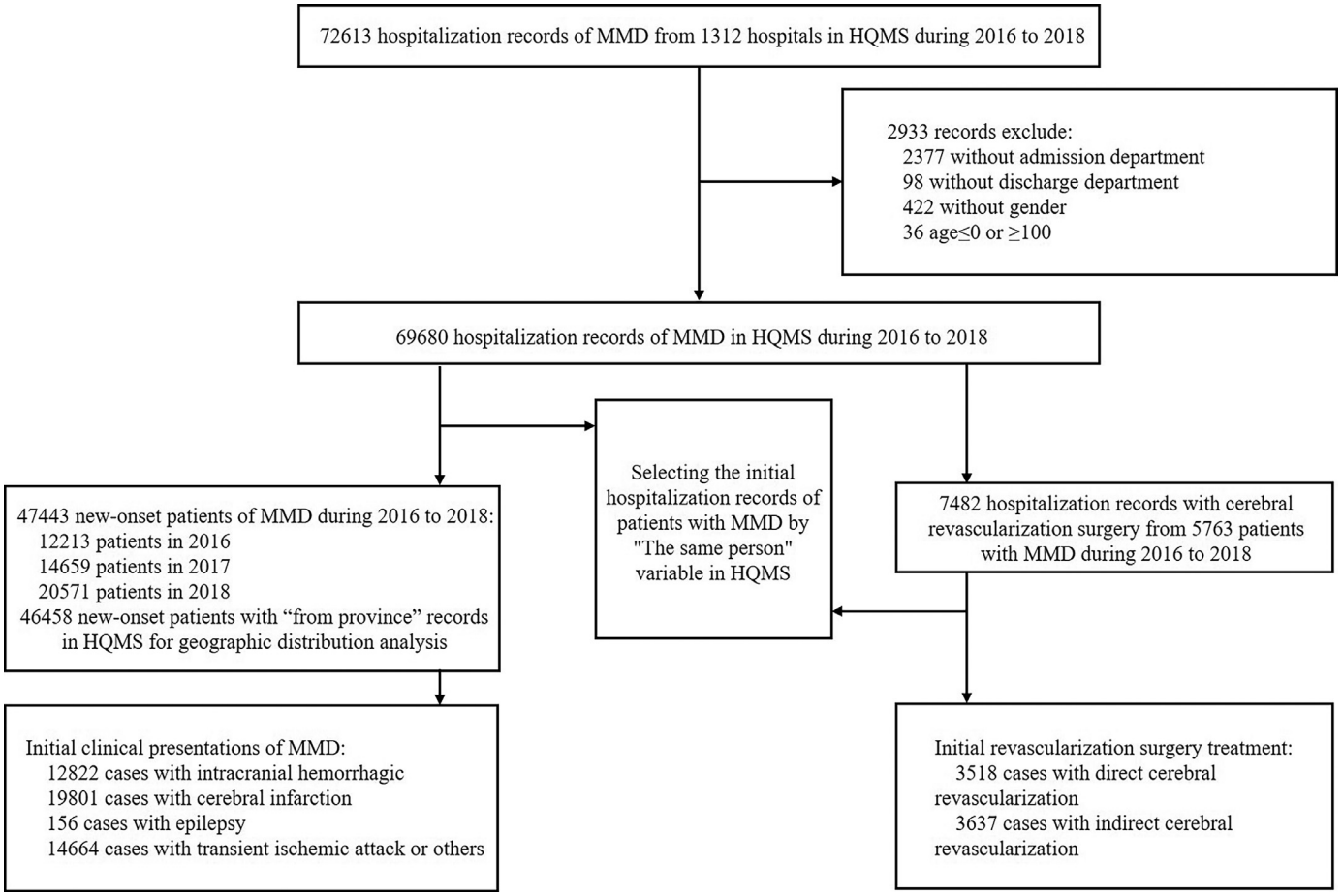

Fig. 1. Flowchart of study population selection.

included superficial temporal artery-middle cerebral artery bypass (STA-MCA bypass) and indirect cerebral revascularization included encephala-duro-arterio-synangiosis (EDAS), encephala-myo-synangiosis (EMS) and encephala-duro-arterio-myo-synangiosis (EDAMS). The surgical procedure was identified based on the ICD-9-CM3 code. The basic information of HQMS and detailed procedures of analysis protocol were shown in the Section 1 and 2 of Supplemental materials.

Statistical analysis

Statistical analyses were performed using SAS version 9·4 (SAS Institute Inc., Cary, NC, USA), and $P< 0·05$ was considered statistically significant. The annual incidence rate was defined as the number of MMD patients divided by the total population in 2016, 2017 and 2018, and the incidence was categorized by gender and analyzed across age groups by 5-year increments. We used the indirect method to standardize the incidence adjusted for age and gender between the provinces, autonomous regions and municipalities based on 2010 Chinese Census (http://www.stats.gov.cn). 95% confidence intervals (CI) of the incidences were calculated by the Poisson distribution. We used the GENMOD model in SAS fitted by Poisson regression to analyze the difference in incidence between adults and children. The significances of the trend of the annual incidence rates and the proportion of clinical presentations and fully self-funded patients were examined by Mann-Kendall trend analysis. The Spatial Statistics Tools of ArcMap 10·7 was used to analyze the spatial distributions features, moreover a spatial relationship model was established to identify clustered or dispersed pattern of MMD. We calculated the globe Moran's I index indicating spatial autocorrelation of incidence to clarify spatial distribution pattern.

Role of the funding source

The funding source had no role in study design, data collection, data analysis, data interpretation, or drafting of the manuscript. The author Ying Shi, LanXia Gan, HaiBo Wang and XvDong Ma had full access to all the data in the study and all authors had final responsibility for the decision to submit for publication.

Results

A total of 47,443 new-onset patients with total 69,680 hospitalization records from 1312 hospitals during 2016 to 2018 were identified which including 12,213 in 2016, 14,659 in 2017 and 20,571 in 2018. The annal incidence rate during 2016 to 2018 was 1·14 per 100,000 inhabitants (95% CI, 1·12–1·16). The annal incidence rate was increasing from 2016 to 2018(0·88 in 2016, 1·06 in 2017, and 1·47 in 2018 by Mann-Kendall trend analysis ($P<0·001$).

The estimated incidence in geographic distribution varied from 0·06 (95% CI, −0·03–0·14) in Tibet to 2·81 (95% CI, 2·65–2·96) in Jiangxi (Details in the Section 3 of Supplemental materials). After standardization of indirect method adjusted for age and gender, the distribution model of MMD incidence rate during the study period was presented as a clustered, rather than dispersed regional pattern (Moran's $I = 0·155$, $P = 0·018$, $Z = 2·375$) by global spatial correlation analysis. Jiangxi, Henan, Anhui, Shandong, and Hubei provinces were high incidence gathering places (standardized incidence rate>1·5 per 100,000 inhabitants per year). However, the Tianjin province and the western regions of China such as Tibet, Qinghai, Gansu, Xinjiang, Shaanxi, Ningxia, Chongqing, Sichuan, and Guizhou provinces had a lower incidence (standardized incidence rate<0·5 per 100,000) (Fig. 2).

Female accounted for 52·3%, and the sex ratio was 1:1·1. No significant difference was found in the incidence of MMD between males and females, with 1·06 per 100,000 inhabitants per year (95% CI 1·04–1·08) in male and 1·22 per 100,000 (95% CI 1·19–1·25) in female. Children (age < 20 years old) accounted for 3·52% of all patients, and the incidence of MMD in children (0·18 per 100,000 inhabitants per year; 95% CI, 0·17–0·20) was significantly lower than that in adults (1·40 per 100,000; 95% CI, 1·38–1·42) (OR=7·71; 95% CI, 7·34–8·09) ($P<0·001$). The peak incidence was 45–54 years (Fig. 3).

The initial clinical presentations included 12,822 cases (27·0%) with intracranial hemorrhage, 19,801 cases (41·7%) with cerebral infarction, 156 cases (0·3%) with epilepsy and 14,664 cases (30·9%) with transient ischemic attack (TIA) or others. Moreover, cerebral infarction (42·3%) was more common in adults, whereas transient ischemic attack and other presentations (63·3%) in children (Fig. 4).

The associated comorbidities were summarized in Table 1. Hypertension, diabetes and hyperlipidemia were respectively 41·3%, 13·6% and 9·6%. Moreover, 2·6% of patients suffered hyperthyroidism or thyroid nodules. Associated autoimmune diseases and congenital conditions were rare, with only a proportion of 0·3% and 1·4% in patients with MMD.

A total of 5763 (12·1%) patients had surgical records and 7428 cerebral revascularizations were performed. 61·0% (3518/5763) of patients were performed direct cerebral revascularization and 63·1% (3637/5763) of patients were performed indirect cerebral revascularization including EDAS and EMS.

The average expenses (presented by median with IQR) of hospitalizations were ¥16,092·2 (IQR, 8879·8–44,419·8) (Table 2). With the effort of the Chinese government, the national health insurance including the basic medical insurance for urban workers (UEBMI), the basic medical insurance for

Fig. 2. Incidence map of moyamoya disease in mainland China during 2016 to 2018.
The study was conducted in mainland China. Hong Kong, Macao, and Taiwan were not included. Major rivers in mainland China are also shown in the figure.

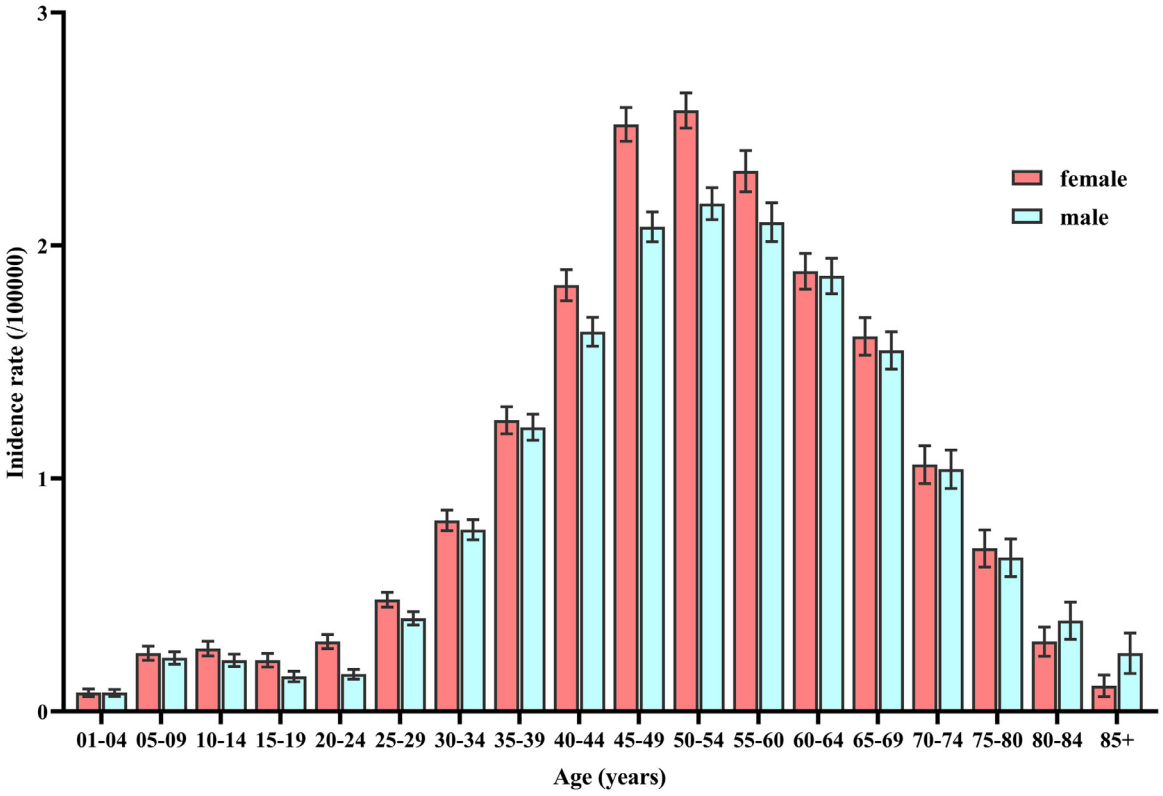

Fig. 3. The incidence of moyamoya disease in different age groups during 2016 to 2018.

urban residents (URBMI) and the new Rural Cooperative Medical Insurance (NRCMI), covered far more patients than commercial insurance (57·9% vs. 0·4%). During the study period, a slight downward trend with a proportion of 20·9% in 2016 to 19·5% in 2018, was found in the proportion of fully self-funded patients by Mann-Kendall trend analysis ($P = 0·0016$).

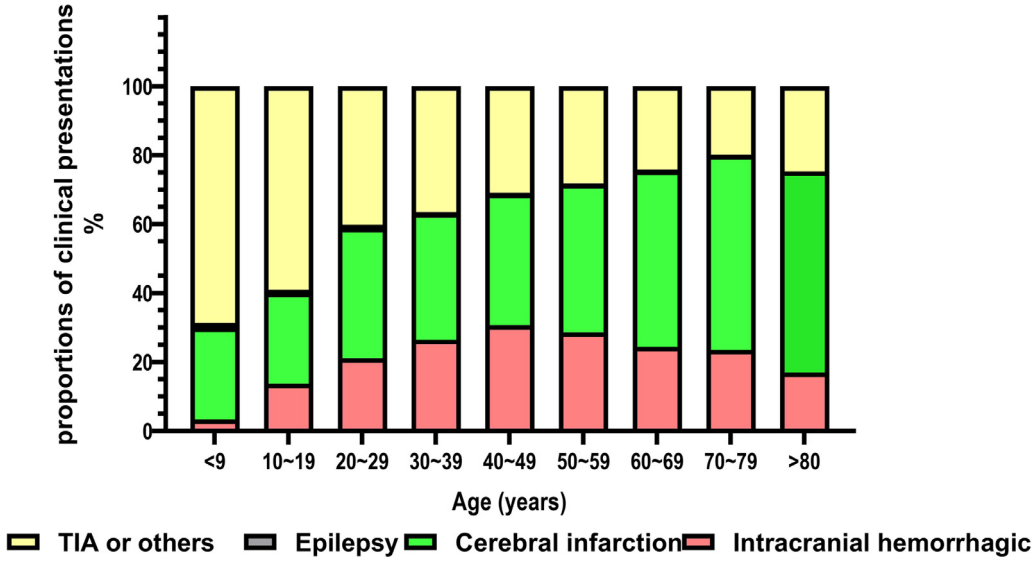

Fig. 4. Clinical presentations in patients with moyamoya disease according to age.

	Hemorrhage	Infarction	Epilepsy	TIA or others	Total
Demographics					
Number, n (%)	12,822 (27·0)	19,801 (41·7)	156 (0·3)	14,664 (30·9)	47,443
Age, mean±SD, years	49·1 ± 11·4	50·4 ± 13·3	41·7 ± 16·6	45·2 ± 14·9	48·4 ± 13·6
Children, n (%)	153 (1·2)	443 (2·2)	17 (10·9)	1057 (7·2)	1670 (3·5)
Adults, n (%)	12,669 (98·8)	19,358 (97·8)	139 (89·1)	13,607 (92·8)	45,773 (96·5)
Female, n (%)	7120 (55·5)	9539 (48·2)	69 (44·2)	8090 (55·2)	24,818 (52·3)
Comorbidities, n (%)					
Hypertension	4563 (35·6)	10,712 (54·1)	42 (26·9)	4294 (29·3)	19,611 (41·3)
Diabetes	699 (5·5)	4253 (21·5)	14 (9·0)	1505 (10·3)	6471 (13·6)
Hyperlipidemia	615 (4·8)	2951 (14·9)	14 (9·0)	961 (6·6)	4541 (9·6)
Hyperthyroidism or thyroid nodules	133 (1·0)	744 (3·8)	6 (3·8)	356 (2·4)	1239 (2·6)
Autoimmune diseases	12 (0·1)	92 (0·5)	——	48 (0·3)	152 (0·3)
Congenital diseases	162 (1·3)	282 (1·4)	3 (1·9)	231 (1·6)	678 (1·4)

***Table 1*: Characteristics and Comorbidities of the moyamoya disease patients in Tertiary Hospital of China during 2016 to 2018.**
SD: standard deviation; TIA: transient ischemic attack.

	2016 (*n* = 12,213)	2017 (*n* = 14,659)	2018 (*n* = 20,571)	Total (*n* = 47,443)
Hospitalization cost, Median (IQR), RMB (￥)	16,438·3 (8913·3—42,899·2)	15,684·7 (8678·2—42,534·5)	16,217·0 (8965·4—46,177·9)	16,092·2 (8879·8—44,419·8)
Payment methods, n (%)				
UEBMI	1581 (12·9)	2216 (15·1)	3752 (18·2)	7549 (15·9)
URBMI	3010 (24·6)	3299 (22·5)	4007 (19·5)	10,316 (21·7)
NRCMI	2551 (20·9)	3034 (20·7)	4019 (19·5)	9604 (20·2)
CHI	48 (0·4)	51 (0·3)	96 (0·5)	195 (0·4)
Fully self-funded	2812 (23·0)	3099 (21·1)	4308 (20·9)	10,219 (21·5)
Others	2211 (18·1)	2960 (20·2)	4389 (21·3)	9560 (20·2)

***Table 2*: Burden of hospitalization of the moyamoya disease patients during 2016 to 2018.**
IQR: interquartile range; UEBMI: The Urban Employee Basic Medical Insurance; URBMI: The Urban Resident Basic Medical Insurance; NRCMI: The New Rural Cooperative Medical Insurance; CHI: Commercial Health Insurance.

Discussion

This study reported the incidence of MMD based on a national database of the HQMS in mainland China, and filled in the blank of epidemiologic data for approximately 1·4 billion Chinese. Our study found the annual incidence of MMD in mainland China was 1·14 per 100,000 and approximately a 2-fold increase from 2016 to 2018. The geographical distribution of MMD incidence presented as a clustered regional pattern.

Higher prevalence of MMD was reported in East Asian countries, which included Japan, Korea, and China. In Japan and Korea, an upward trend of incidence was observed with an approximate 3-fold increase during nearly a decade.[4,6] However, national epidemiologic data in mainland China is not reported before our study. Although some recent studies had tried to estimate the incidence of MMD from a nationwide perspective, there were obvious selection bias that could not be ignored. Sun et al. used data from the national databases of Urban Basic Medical Insurance (UBMI) between 2013 and 2016 to evaluate basic epidemiological characteristics of MMD in mainland China with an incidence of 0·59 per 100,000 inhabitants per year.[16] However, in our study, among all medical records of MMD, the proportion of patients covered by UEBMI and URBMI were only 15·9% and 21·7%, which suggested it was inevitable to underestimate the incidence of MMD and cause significant selection bias based on UBMI merely. Besides, there were nine provinces including Fujian, Tibet, Sichuan, Beijing, Shanghai, Tianjin, Ningxia, Hebei, and Jiangxi were excluded in Sun's study, due to the absence or abnormality of crucial information, which also implied the deficiencies of UBMI.[16] However, in our study, Jiangxi province was the with highest incidence of MMD, which might be a significant reason for differences in incidence. Therefore, our study revealed nationwide epidemiologic data of MMD, which covered whole population and region in mainland China.

The present study revealed the incidence in mainland China was slightly lower than that in Korea and higher than that in Japan. However, it should be noted that a direct comparison may be inappropriate due to differences in the data collection method. The Japanese

study used data from a survey conducted in hospital, and the Korea study collected data from the National Health Insurance system. Therefore, it is necessary to conduct multi-region and multi-center surveys around the world.

The present study found that incidence increased annually, which increased from 0·88 per 100,000 inhabitants per year in 2016 to 1·47 per 100,000 in 2018 ($P<0·001$). This change may be explained by recent advances in noninvasive imaging methods that enable the diagnosis of MMD. Another potential explanation was the awareness of this disease is increasing for doctors and society.

The distribution of age at onset has been reported to have two peaks: children at 5 years of age and adults in their mid-40 s. Our study found the high peak of incidence was patients with 45–54 years of age, followed by a tiny peak age was 10–14 years among children. The incidence in children is far lower than that in adults (0·18 per 100,000 inhabitants per year vs. 1·40 per 100,000). The reasons that the number and incidence in children was lower than in other previous studies were as follows. First, a trend of incidence peak shifting from children to adults had been observed throughout recent years.[17] In the early studies before 2000, MMD patients mainly consist of children, and the incidence of children is higher than that of adults.[3,18,19] However, in a recent study in Taiwan, the incidence has increased in adults from 2000 to 2011, but no upward trend was observed in children.[12] Similar trends have also been reported in Japan and Korea.[5,6] One possible explanation for this trend is that some adult patients presenting with stroke or TIA are diagnosed with MMD for the popularization of routine imaging examination, which has been previously misdiagnosed as atherosclerosis.[17] Second, the age in HQMS was defined as the age in the admission. However, a patient who had been diagnosed with MMD before 2016, will be defined as a new case if he had a recent admission record during 2016–2018. Moreover, it cannot be ignored that certain patients will not be admitted to hospital immediately after the first symptom occurred. Some patients presented with symptoms in childhood, however, were diagnosed or treated until adulthood. Therefore, these may be the reason for a lower proportion of children in this study compared with other epidemiological data. Further register study will be carried to clarify the age distribution of MMD in mainland China.

Previous studies have reported the difference between pediatric patients and adults in clinical presentations. Most pediatric patients develop transit ischemic attack (TIA) or cerebral infarction, whereas adults have the similar rates of ischemic stroke and hemorrhagic stroke.[1] In our study, as the age of onset increases, the proportion of patients who present with transit ischemic attack decreased ($P<0·001$), and the proportion of patients with cerebral infarction increased ($P<0·001$). Moreover, the most patients who present with cerebral hemorrhage were around the age of 40. Although there were some age-related differences in presentations compared with previous studies which may be due to different database and data collection methods.[20] Our study revealed that as age increase, the proportion of cerebral infarction and bleeding was increasing, which suggested that the MMD patients should be further treated as soon as possible after the diagnosis, to avoid irreversible neurological dysfunction caused by infarction or hemorrhage.

Our study revealed the geographic distributions of incidence in mainland China presented as a clustered regional pattern (Details in the Section 4 of Supplemental materials). Although the potential causes for the geographical distribution were still not clear, but this epidemiologic feature may provide new view for the etiology for MMD. The *RNF213* p.R4810K was identified as a strongest susceptibility gene for MMD in east Asia[21,22] The mutation rates of p.R4810K was high in east, north, and northeast China,[23] which were inconsistent with the incidence distribution in our study. Thus, besides genetic factors, other factors may be required to induce MMD. Our study found in neighboring provinces at the same latitude, such as Jiangxi and Hunan province, the carrying rate of *RNF213* p.R4810K in MMD patients was similar (12·9% vs.13·04%)[23], however, the incidence was extremely different (3·15% vs. 0·45%; in our study).

Besides, according to previous epidemiological studies of stroke in China based on HQMS, the incidence of ischemic and hemorrhagic stroke also showed difference in geographic distribution, which presented as a relatively higher trend in the north of China, and a similar prevalence between the southern provinces of China like Hunan and Jiangxi.[24] Recent research highlighting the genetic differences in China's population showed that the Han population can be significantly divided into seven subgroups, and Hunan and Jiangxi belong to the population cluster of South Han, also including Guizhou, Sichuan, Chongqing, and Yunnan which indicate there must be other significant factors that contribute to this difference of the incidence of MMD in addition to genetic differences.[25] The majority of Chinese have similar ethnic backgrounds contributed by the extensive migration of Han nationality and the integration of multi-ethnic groups, although there were diversity and complexity of the genetic background of Chinese people across geographical regions.[25] However, China spans more than 60 longitudes and 50 latitudes with obvious environmental diversity. Similar genetic background and lifestyles yet with huge difference in incidence between Jiangxi and Hunan province, suggest environment play an important role in development of MMD, which is worthy of future study.

In our study, the common comorbidities were hypertension (41·3%), diabetes (13·6%) and dyslipidemia

(9·6%). These was consistent with the proportion of comorbidities reported in other large retrospective studies in China.[26] Compared to the recent large-scale studies in Japan, the prevalence of hyperlipidemia (11%) was similar with our study, however, we reported a relatively higher prevalence of hypertension and diabetes with a proportion of 35% and 5% in Japan.[27] Moreover, several studies indicated that preoperative hypertension was an independent risk factor for postoperative ICH after revascularization, and hypertension was associated with increased mortality in natural course of hemorrhagic MMD, which suggested more attention in preoperative blood pressure management and subsequent clinical follow-up.[28,29] MMD with abnormal thyroid function had been gradually concerned. Especially increased thyroid function (10·5%) and elevated thyroid autoantibodies (13·2%) were more associated with MMD.[30,31] In our cohort, 2·6% of the patients were combined with the diagnosis of hyperthyroidism or thyroid nodules, which needs further attention in clinical practice. The burden of hospitalization was an important weighty consideration for patients with MMD in diagnosis and treatment. With the gradual improvement of national medical insurance policy, nearly 60% of MMD hospitalizations were covered by China's basic health insurance. Although there was no obvious change in the total cost of hospitalization, we were glad to see that the proportion of fully self-funded patients had a slight downward trend. However, the proportion of patents covered by NRCMI (The New Rural Cooperative Medical Insurance) was relatively lower, more attention should be paid to the medical service of rural patients in the process of gradual optimization of medical insurance policy, consequently.

Our study has several limitations. First, patients who only visited outpatient clinics were not included in the study and it resulted in underestimation of the incidence rate. Certain patients with mild symptoms or observation treatment may be diagnosed and followed in the outpatient clinics. The actual incidence may be higher than our data. Second, we could not obtain the radiological data of every medical record. Lack of imaging diagnostic data might lead to misdiagnosis inevitably, however, as a national database for medical quality supervision, every uploaded record of the HQMS must be reviewed in local hospital to confirm the accuracy which will reduce the possibility of misdiagnosis to a considerable extent. The age onset was recorded as the age at admission, and the clinical presentations and postoperative complications were confirmed by diagnostic coding. Only by ICD-10 code, it was insufficient to confirm the diagnosis of MMD and clinical presentations, and Moyamoya syndrome could not be ruled out accurately. Besides, in order to handle the problem of overestimation caused by misclassification as new-onset cases, a period before the index date (the wash-out period is equal to the clinical observation period as usual) is essential to judge the incident cases, which requires continuous observations for more than ten years. We will continue to track the status of MMD patients for a long time in the future to obtain a more accurate incidence rate based on the HQMS. In addition, we cannot estimate the positive prediction value of the diagnosis from HQMS because the detailed hospital information was hidden for protecting the privacy of patients. Finally, we cannot estimate the prevalence in our study. Prevalence is the product of the incidence and mean duration of MMD. And we couldn't accurately track the continuous treatment and prognosis of each patient, and the observation period in this article was not enough to estimate the mean duration of such a relatively rare disease. It will be more accurate to estimate the prevalence when we get decades of incidence rate data in the future. Therefore, the inherent limitations of the HQMS database should be taken into consideration when compared with clinical registry study.

In conclusion, the present study reported the annual incidence of MMD was 1·14 per 100,000 inhabitants per year in mainland China during 2016 to 2018, and it was increasing year by year. The geographical distribution of MMD incidence presented as a clustered regional pattern, which may provide new view for further study on the etiology for MMD.

Contributors

Yongjun Wang and Jizong Zhao designed, planned, and supervised the study, and submit manuscript for publication. Dong Zhang and Liangran Huang designed the study and drafted the manuscript. Zheng Huang revised the manuscript. Ying Shi, Lanxia Gan, Haibo Wang and Xvdong Ma had full access to and provided the original data from HQMS.Qi Zhou, Xin Yang, Hongqiu Gu and Zixiao Li performed the statistical analysis and contributed to interpretation of data.

Data sharing

Dates are available upon reasonable request. The original data are not available publicly, unless it was approved and provided by the Institutional Review Board of China Standard Medical Information Research Center (Shenzhen, China) and China National Clinical Research Center for Neurological Diseases (Beijing, China). Detailed analysis protocols were shown in Section 2 of the Supplemental materials.

Declaration of Competing Interest

We declare no competing interests.

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Editor note

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lanwpc.2021.100331.

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