

Recurrence stroke of ischemic stroke patients in Thailand: a nationwide study

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ABSTRACT

Stroke is a global health problem and a leading cause of mortality and disability. Patients who survived an initial stroke are at risk for a recurrence stroke of the same type or another. However, few studies have documented at a national level. This research aimed to investigate the magnitude of recurrence stroke among ischemic stroke patients. This descriptive study used the data from neurology database collected between 2006 to 2020 in hospitals under the National Health Security System (NHSO) of Thailand. Among 511,322 ischemic stroke patients, recurrence of all types of strokes occurred in 85,968 patients or 16.81% (95% CI: 16.71-16.92). The prevalence was highest among patients with hypertension and diabetes mellitus at 18.89% (95% CI: 18.54-19.26), atrial fibrillation at 18.79% (95% CI: 18.42-19.15), and ischemic heart disease at 18.59% (95% CI: 18.05-19.15). Furthermore, patients who received recombinant tissue plasminogen activator (rt-PA) treatment (12.15% %, 95%CI: 11.75-12.55) and rehabilitation (14.39%, 95% CI: 14.25-14.54) had a lower prevalence. Comorbidities were an important factor had a high recurrence and treatment factors that patients receive had a low recurrence. Therefore, policymakers and health institutions could use these findings to implement treatment and monitoring policies for recurrence stroke.

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1. INTRODUCTION

Stroke causes severe effects due to obstruction of the blood supply to the brain, which can result in brain damage. Stroke has two major types consisting ischemic stroke and hemorrhagic stroke. Ischemic stroke is the most common type of stroke, accounting for more than 80% of cases. Globally, stroke is a significant health problem, with over 13 million new cases each year and more than 6 million deaths. Moreover, stroke is the second-leading cause of death in the world. Over 100 million individuals worldwide have experienced and live with the effects of stroke, creating a substantial burden of disease estimated to cause a loss of 120 million healthy life-years [1], [2].

For the prevention and treatment of stroke, treatment guidelines have been continuously developed that making treatment more effective can reduce mortality and disability. Nevertheless, stroke is still a massive health problem in many countries and it is expected that will be more patients and leading to burdens on the health system in each country, especially in low-income and middle-income countries [3]. Furthermore, in Thailand stroke is a massive health problem leading cause of death below cancer with an increased mortality rate from 48.7 per 100,000 population in 2016 to 52.8 per 100,000 population in 2020

[4], [5]. With the increased occurrence of strokes and the number of patients vulnerable to stroke recurrence increasing substantially, recurrence stroke can occur as the same type of initial stroke or another stroke subtype, and several factors can affect the recurrence rate may be different. Although, over the past two decades have several studies found the factors that can reduce the risk of secondary strokes such as controlling blood pressure, statin, and changing the health behavior of patients [6]–[9]. That finding lead to improve treatment guidelines to better the efficiency of treatment and decrease the burden of stroke patients. However, the result of recurrence after initial ischemic stroke is unclear and there have been few studies on the magnitude of recurrence ischemic stroke in the long-term more than 10 years and relevant factors remain limited, particularly in emerging economies. Therefore, this research aimed to describe the magnitude of recurrence stroke among ischemic stroke patients in Thailand.

2. RESEARCH METHOD

This research used secondary data from the neurological disease database of Thailand that administered by the National Health Security Office (NHSO). The database included admitted patients who were aged 18 years or older with a principal diagnosis of ischemic stroke determined by brain CT scan and there was no an outcome of death during the first ischemic stroke hospitalization Figure 1, covering a time period of January 2006 to September 2020 in hospitals under the NHSO system

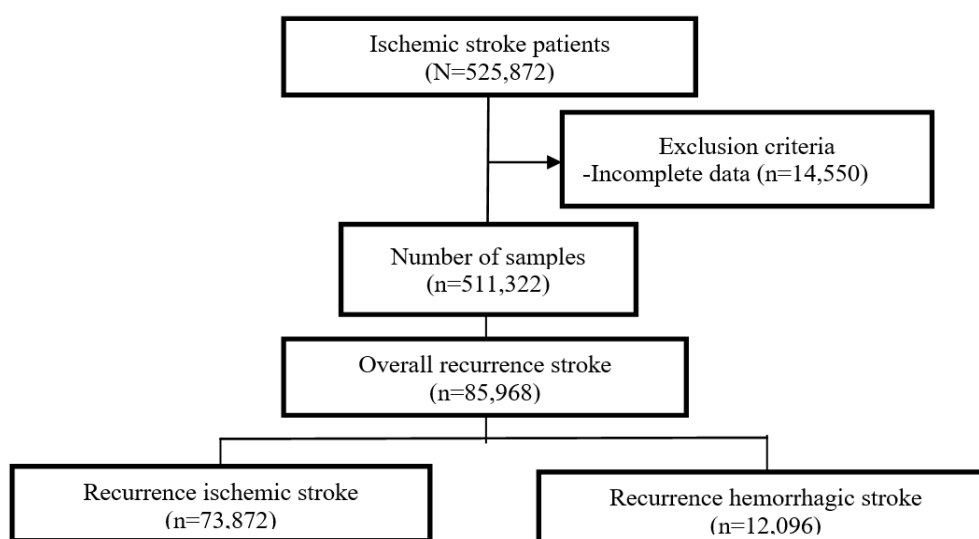


Figure 1. Study flow

The database was searched to identify ischemic stroke patients using the International Statistic Classification of Diseases and Related Health Problems-10th Revision (ICD-10) codes I63, I65 and I66. Recurrence stroke patients were defined by brain CT scan and principal diagnosis with ICD 10 codes I60-I69. However, few patients who were diagnosed with first ischemic stroke were excluded because of the intermediate hospital referral system. The stroke recurrence type was classified according to ICD 10 codes I63, I65 and I66 for ischemic stroke, and I60, I61 and I62 for hemorrhagic stroke. Comorbidities of the patients at the first ischemic stroke were classified by the relevant ICD-10 codes and ICD-9 CM Diagnosis and Procedure Codes for classifying the procedure that patients received during admission. Statistical analysis was completed using descriptive statistics to describe the characteristics, comorbidity, and treatments in the first ischemic stroke, reported as number, percentage, mean, standard deviation (S.D.), median, minimum and maximum. The prevalence analysis of recurrence stroke was classified by characteristics, comorbidity, and treatment and reported the results using 95% confidence interval (95%CI) of overall prevalence and prevalence separated by recurrence stroke types. The study protocol was approved by the Ethics Committee for Human Research of Khon Kaen University reference number HE651122 and data acquisition was authorized by the NHSO as part of the Epidemiology of Neurological Disease in Thailand Project conducted by the Department of Medicine in the Faculty of Medicine at Khon Kaen University.

3. RESULTS AND DISCUSSION

3.1. Characteristics of the patients with ischemic stroke

A total of 511,322 patients with ischemic stroke were included in the analysis Table 1. The sample included a higher proportion of males (54.56%) The mean age of the patients was 65.07 ± 13.12 SD years with a median age of 66 years, minimum 18 and maximum of 114 years. A combination effect of comorbidities consisting of hypertension (HT), diabetes mellitus (DM), and hyperlipidemia (HLD) found a large proportion of patients (31.48%) were classified as having no comorbidities followed by hyperlipidemia (HLD) and hypertension (HT) being the most common comorbidities (23.16%). Other comorbidities included atrial fibrillation (AF) 8.66%, chronic kidney disease (CKD) 6.76%, and ischemic heart disease (IHD) 3.80%. In terms of prescribed treatment, it was found that 42.1% of patients were treated with rehabilitation during admission, with a smaller percentage (5.16%) receiving recombinant tissue plasminogen activator (rt-PA).

Table 1. Characteristics of the patients with ischemic stroke

Variable	Number (%)
Gender	
Male	278,962 (54.56)
Female	232,360 (45.44)
Age group(year)	
<45	33,640 (6.58)
45-59	133,379 (26.09)
60-69	142,395 (27.85)
70-79	130,838 (25.59)
≥80	71,070 (13.90)
Mean 65.07: S.D.±13.12	
Median 66, Min 18: Max 114	
Main co-morbid	
No	160,977 (31.48)
HLD	69,654 (13.62)
HT	89,289 (17.46)
DM	19,069 (3.73)
HLD and HT	118,407 (23.16)
HLD and DM	1,594 (0.31)
HT and DM	45,697 (8.94)
HLD, HT and DM	6,635 (1.30)
Atrial fibrillation (AF)	
No	467,059 (91.34)
Yes	44,263 (8.66)
Chronic kidney disease (CKD)	
No	476,759 (93.24)
Yes	34,563 (6.76)
Ischemic heart disease (IHD)	
No	491,913 (96.20)
Yes	19,409 (3.80)
rt-PA treatment	
No	484,936 (94.84)
Yes	26,386 (5.16)
Rehabilitation	
No	296,053 (57.90)
Yes	215,269 (42.10)

3.2. Recurrence stroke by year at first ischemic stroke

According to this research, patients who have longer follow-up periods are more likely to encounter a greater rate of recurrence strokes, according to the total follow-up time of ischemic stroke patients from 2006 to 2020. The overall recurrence, percentage of patients who had recurrence strokes peaked in 2006 at 37.07% and lowest in 2020 at 5.26%. Table 2. Considering types of recurrence, ischemic strokes accounted for the majority of recurrent strokes, with hemorrhagic strokes accounting for the remainder Figure 2.

3.3. Recurrence stroke classifies by factors

Overall recurrence stroke: The total recurrence rate was 16.81% (95% CI: 16.71-16.92) Table 3. The recurrence was slightly higher in males (16.90%, 95% CI: 16.76-17.04). The age group with the highest rate of recurrence stroke was patients in their 60s (18.16%, 95% CI: 17.96-18.36). The combination of HT and DM was the comorbidity factor that had the higher prevalence (18.89%, 95% CI: 18.54-19.26) relative to other comorbid diseases, on the other hand, patients with HLD had lower prevalence (15.63, 95% CI: 15.36-15.90). Interestingly, an increased prevalence was found in those with AF (18.79%, 95% CI: 18.42-19.15)

and IHD (18.59%, 95% CI: 18.05-19.15). However, recurrence stroke was less common in patients with CKD (14.80%, 95% CI: 14.43-15.18) compared with patients without CKD. Recurrence stroke was also less common among patients that received rt-PA treatment (12.15%, 95% CI: 11.75-12.55) and rehabilitation (14.39 %, 95% CI: 14.25-14.54).

Recurrence Ischemic Stroke: The prevalence of total recurrence ischemic stroke was 14.45% (95% CI: 14.35-14.54). There was no significant difference in the prevalence of recurrence ischemic stroke among females (14.57%, 95% CI: 14.43-14.71) and males. Similar to over recurrence stroke, recurrence ischemic stroke was most common among patients aged in their 60s (15.62%, 95% CI: 15.43-15.81) and among patients with a combination of HT and DM (16.44%, 95% CI: 16.10-16.79). In addition, patients who had AF (15.97%, 95% CI: 15.62-16.31) and IHD (16.45%, 95% CI: 15.93-16.97) had a higher prevalence recurrence ischemic stroke. However, recurrence ischemic stroke was less common among patients with CKD (12.40%, 95% CI: 12.05-12.75). In addition, the factors associated with less recurrence ischemic stroke were recombinant tissue plasminogen activator (rt-PA) treatment with 11.03% recurrence (95% CI: 10.65-11.41) and rehabilitation treatment with 12.44% recurrence (95% CI: 12.30-12.58).

Table 2. Prevalence of recurrence stroke classified by years at first ischemic stroke

Years at first ischemic stroke	Number of patients each year	Overall recurrence		Recurrence Ischemic stroke		Recurrence Hemorrhagic stroke	
		Number	%	Number	%	Number	%
2006	9,649	3,577	37.07	2,952	30.59	625	6.48
2007	12,788	4,164	32.56	3,472	27.15	692	5.41
2008	16,404	4,721	28.78	3,987	24.31	734	4.47
2009	19,931	5,280	26.49	4,465	22.40	815	4.09
2010	24,493	5,911	24.13	5,033	20.55	878	3.58
2011	29,456	6,342	21.53	5,425	18.42	917	3.11
2012	32,982	6,874	20.84	5,844	17.72	1,030	3.12
2013	36,693	7,035	19.17	6,046	16.48	989	2.70
2014	40,182	7,325	18.23	6,364	15.84	961	2.39
2015	43,961	7,373	16.77	6,358	14.46	1,015	2.31
2016	46,459	7,273	15.65	6,330	13.62	943	2.03
2017	51,871	6,978	13.45	6,050	11.66	928	1.79
2018	56,744	6,411	11.30	5,598	9.87	813	1.43
2019	60,847	5,187	8.52	4,574	7.52	613	1.01
2020	28,862	1,517	5.26	1,374	4.76	143	0.50
Overall	511,322	85,968	16.81	73,872	14.45	12,096	2.37

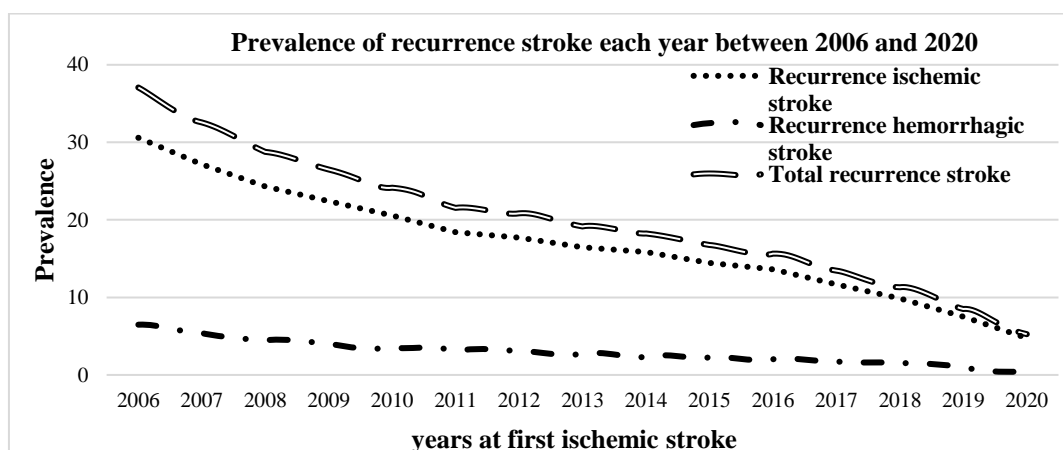


Figure 2. Prevalence of recurrence stroke each year between 2006 and 2020

Recurrence hemorrhagic stroke: The total recurrence hemorrhagic stroke prevalence was 2.37% (95% CI: 2.32-2.41). Recurrence hemorrhagic stroke was more common in males (2.55%, 95% CI: 2.49-2.61) and those aged 45-59 (2.68%, 95% CI: 2.59-2.76). HT seemed to be associated with a higher prevalence, with patients classified as having HT comorbidity having the highest prevalence (2.94%, 95% CI: 2.83-3.05) and with other classifications that included HT also having a higher prevalence. Patients who had AF (2.82%, 95% CI: 2.67-2.98) and CKD (2.40%, 95% CI: 2.24-2.57) had a higher prevalence of recurrence ischemic stroke. However, recurrence hemorrhagic stroke was less common among those with

IHD (2.15%, 95% CI: 1.95-2.36). The two treatments, rt-PA (1.12%, 95% CI: 0.99-1.25) and rehabilitation (1.96%, 95% CI: 1.90-2.01), were also associated with a lower prevalence of recurrence hemorrhagic stroke.

3.4. Discussion

The research aimed to describe the magnitude of recurrence strokes among ischemic stroke patients between 2006 and 2020 using a national neurology database. The overall prevalence of ischemic stroke (16.81%) reported here was higher than results reported in northern Sweden [10] and Finland (13.6%) [11]. On the other hand, the prevalence in this study was less than the recurrence rate among small artery occlusion patients in northern China, which had a three year recurrence rate of 36.5% [12] and less than the five year recurrence rate reported in Singapore (18.6%) [13]. When classified by type of recurrence found, recurrence ischemic stroke (14.45%) was more common than recurrence hemorrhagic stroke (2.37%), which is similar to previous findings [1], [14].

Table 3. Prevalence of recurrence stroke in ischemic stroke patients classified by factors

Factors	Total recurrence stroke			Recurrence Ischemic stroke			Recurrence Hemorrhagic stroke		
	Number	%	95%CI	Number	%	95%CI	Number	%	95%CI
Overall	85,968	16.81	16.71-16.92	73,872	14.45	14.35-14.54	12,096	2.37	2.32-2.41
Gender									
Male	47,139	16.90	16.76-17.04	40,016	14.34	14.21-14.47	7,123	2.55	2.49-2.61
Female	38,829	16.71	16.56-16.86	33,856	14.57	14.43-14.71	4,973	2.14	2.08-2.20
Age (year)									
<45	5,653	16.80	16.41-17.21	4,878	14.50	14.13-14.88	775	2.30	2.15-2.47
45-59	23,628	17.71	17.51-17.92	20,059	15.04	14.85-15.23	3,569	2.68	2.59-2.76
60-69	25,854	18.16	17.96-18.36	22,236	15.62	15.43-15.81	3,618	2.54	2.46-2.62
70-79	22,133	16.91	16.71-17.12	19,157	14.64	14.45-14.83	2,976	2.27	2.19-2.36
>80	8,700	12.24	12.00-12.48	7,542	10.61	10.39-10.84	1,158	1.63	1.54-1.73
Main co-morbid									
No	26,047	16.18	16.00-16.36	22,409	13.92	13.75-14.09	3,638	2.26	2.19-2.33
HLD	10,887	15.63	15.36-15.90	9,561	13.73	13.47-13.98	1,326	1.90	1.80-2.01
HT	15,141	16.95	16.71-17.20	12,514	14.02	13.79-14.24	2,627	2.94	2.83-3.05
DM	3,308	17.34	16.81-17.89	2,945	15.44	14.93-15.96	363	1.90	1.71-2.11
HLD and HT	20,530	17.33	17.12-17.56	17,667	14.92	14.72-15.12	2,863	2.42	2.33-2.51
HLD and DM	264	16.56	14.77-18.47	240	15.06	13.34-16.91	24	1.51	0.97-2.23
HT and DM	8,636	18.89	18.54-19.26	7,514	16.44	16.10-16.79	1,122	2.46	2.31-2.60
HLD, HT and DM	1,155	17.41	16.51-18.34	1,022	15.40	14.54-16.29	133	2.00	1.68-2.37
Atrial fibrillation (AF)									
No	77,652	16.63	16.52-16.73	66,804	14.30	14.20-14.40	10,848	2.32	2.28-2.37
Yes	8,316	18.79	18.42-19.15	7,068	15.97	15.62-16.31	1,248	2.82	2.67-2.98
Chronic kidney disease (CKD)									
No	80,852	16.96	16.85-17.06	69,586	14.60	14.50-14.70	11,266	2.36	2.32-2.41
Yes	5,116	14.80	14.43-15.18	4,286	12.40	12.05-12.75	830	2.40	2.24-2.57
Ischemic heart disease (IHD)									
No	82,359	16.74	16.64-16.85	70,680	14.37	14.27-14.47	11,679	2.37	2.33-2.42
Yes	3,609	18.59	18.05-19.15	3,192	16.45	15.93-16.97	417	2.15	1.95-2.36
rt-PA treatment									
No	82,763	17.07	16.96-17.17	70,962	14.63	14.53-14.73	11,801	2.43	2.39-2.47
Yes	3,205	12.15	11.75-12.55	2,910	11.03	10.65-11.41	295	1.12	0.99-1.25
Rehabilitation									
No	54,982	18.57	18.43-18.71	47,095	15.91	15.78-16.04	7,887	2.66	2.61-2.72
Yes	30,986	14.39	14.25-14.54	26,777	12.44	12.30-12.58	4,209	1.96	1.90-2.01

The subset of patients with comorbid HT and DM had the highest recurrence at 18.89%. This result was likely because patients with co-morbid DM had a high proportion of ischemic stroke [15], the finding has been confirmed by meta-analysis [16], and several studies which found DM associated with ischemic stroke and increased especially recurrence of ischemic stroke [17], [18]. In addition, several studies have found HT also has a significant association with stroke and recurrence stroke [19]–[22]. Thus, in this found stroke patients who have DM and HT to have the highest proportion of recurrence. On the other hand, patients with HLD had a prevalence 15.63% which less than patients without comorbidity. This result may explain by the effect of statin that patients who have HLD will receive to decrease lipid [23], consistent with the previous study that found a low prevalence and reduce risk of recurrence stroke [7], [24], [25].

Another key comorbidity in this study, AF remains a high-risk condition for a second ischemic stroke [17], [26]–[28]. Accordingly, this study found a high prevalence of recurrence stroke (18.79%) among patients with AF. Recurrence stroke was also common among patients with ischemic heart disease (18.59%). In other studies, ischemic heart disease was often associated with stroke recurrence [22], [27], [28]. On the

other hand, it was found the recurrence in patients with CKD was lower than the non-CKD group, which may be because CKD is a severe disease that leads to death before a recurrence occurs.

Two treatment factors were considered in this study, recombinant tissue plasminogen activator (rt-PA) and rehabilitation during hospitalization. The patients who received rt-PA following acute ischemic stroke and who had no medication contraindication were found to have a significantly decreased prevalence of recurrence stroke (12.15%). This result may be explained by the mechanism of the rt-PA, which dissolves the blood clots in the vessels and increases blood circulation [29], [30], possibly helping to reduce stroke recurrence. Rehabilitation patients also had a lower prevalence of recurrence at 14.39%, consistent with another study that found good outcomes from rehabilitation [31]. The database of this study recorded only the inpatient data among the Universal coverage scheme under National Health Security System (NHSO) which covered Thailand citizens with around 75% and recurrence stroke patients who died before being hospitalized might not be recorded in this database.

4. CONCLUSION

This study found a high prevalence of recurrence stroke in patients with DM and HT, AF and IHD. In addition, the prevalence was low in patients receiving rt-PA and rehabilitation. Therefore, policymakers could use this finding to develop implementation policies for monitoring and evaluating recurrence stroke. Thailand's Ministry of Public Health should develop a standard treatment system and the hospitals should implement a well-organized patient care based on the appropriate guideline especially for ischemic stroke patients under treatment.

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