

LONG-TERM SURVIVAL OF ISCHEMIC AND HEMORRHAGIC STROKE PATIENTS: AN ANALYSIS OF NATIONAL THAI DATA

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Abstract. Stroke is a leading cause of death and disability in Thailand. We conducted this study to determine any disparities in stroke due to health care in order to improve stroke survival and identify those at risk for shorter stroke survival. We retrospectively reviewed stroke survival data from the Thai National Stroke Database for 2004-2013, and found 475,571 patients with ischemic and hemorrhagic stroke. Of these, 55% were male and median age was 65 years old (age ranges 13-100 years). Twenty-nine point one percent of patients were from central Thailand, 26.9% from the northeast, 22.6% from the north, 12.8% from the south and 8.6% from Bangkok. We used the Kaplan-Meier and Cox regression methods to analyze the data. The median survival of post >30-day ischemic stroke patients (81 months) was significantly shorter ($p<0.001$) than hemorrhagic stroke patients (101 months). While the median survival time of post >30-day stroke patients was significantly longer among men (88 months) than among women (82 months) ($p<0.001$). Stroke survival decreased significantly with increasing age ($p<0.001$). Median survival time significantly differed among regions of Thailand. For ischemic stroke, patients in Bangkok had the longest median survival (95 months) followed by those from the south (91 months), the central (81 months), the northeast (79 months) and the north (76 months). The longest median survival for patients with hemorrhage stroke was those in Bangkok (119 months) followed by the northeast (105 months), the north (98 months), and the south and central (97 months). Public health strategies need to be developed and implemented to solve these disparities in stroke survival.

Keywords: survival of stroke, epidemiology, Kaplan-Meier method, regional disparities, Thailand

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INTRODUCTION

Stroke is the second leading cause of death worldwide, causing approximately 11.9% of all deaths (WHO, 2015). Stroke has a major impact on public health (Di

Carlo, 2009). Ischemic stroke (IS) and hemorrhagic stroke (HS) are the main types of stroke, but IS comprises 87% of all strokes (Sacco *et al*, 2013). Subarachnoid hemorrhage was not included in this study, since it is most often caused by cerebral aneurysms (Caplan, 2009).

The incidence of stroke worldwide has dramatically increased: in 1990 approximately 10 million stroke cases were reported; by 2010 approximately 17 million cases were reported (Feigin *et al*, 2014). In this 20-year period (1990-2010), the age-standardized incidence of stroke decreased by 12% in higher income countries while it increased by 12% in lower and middle-income countries (Feigin *et al*, 2014). Stroke is still a leading cause of mortality in many middle-income countries (Mathers, 2009). Median survival times after stroke vary globally, but usually ranging from five to ten years, depending on the stroke type, sex and age of victim and other factors (Slot *et al*, 2008; Hanchaiphiboolkul *et al*, 2011; Go *et al*, 2014). Although there are large regional variations, many regions in the world expect to face an increasing stroke incidence between 2000 and 2030 (Feigin *et al*, 2009). The largest increases are expected to occur in Southeast Asia (Feigin *et al*, 2009).

Thailand is an upper middle-income country from Southeast Asia with an estimated population of 68 million (The World Bank Group, 2016). It has a low population growth rate of 0.22% and an increasing life expectancy (65 years in 1990 to 75 years in 2012); Thailand's aging population is increasing (World Population Review, 2016). As a result, Thailand is confronted with an increase in chronic diseases, which can impact quality of life and mortality. Stroke is a leading cause of disability and death in Thailand (Makka *et al*, 2016). Previous studies of stroke in

Thailand found stroke prevalence varied by region (Viriyavejakul *et al*, 1998; Hanchaiphiboolkul *et al*, 2011).

Most stroke epidemiological reports from Thailand are limited to prevalence estimates (Viriyavejakul *et al*, 1985, 1998; Hanchaiphiboolkul *et al*, 2011), data about survival time is still lacking. Determining post-stroke survival time and detecting disparities in survival times are challenging. Estimating post-stroke survival time and disparities in survival time by various factors for IS and HS is essential to understanding the epidemiology of stroke and its burden in Thailand (Bundhamcharoen *et al*, 2011; Krishnamurthi *et al*, 2013; Viriyavejakul *et al*, 1985, 1998). The data can also inform health care programs to develop interventions to improve health outcomes. The purposes of this study are: 1) to identify post-stroke survival times among persons with IS and HS in Thailand from 2004-2013; and 2) to identify the effect of gender, age group, and region on post-stroke survival.

MATERIALS AND METHODS

Data source

The primary data source for this study was the database of the National Health Security Office (NHSO), which includes data from several departments of the Ministry of Public Health, Thailand. The NHSO is an autonomous organization acting as a coordinating office to manage and ensure universal coverage (UC) of health. Seventy-five point two percent of the Thai population is covered by the UC scheme (Hughes and Leethongdee, 2007). All diagnosed stroke patients recorded in the NHSO database had their diagnosis recorded following the International Classification of Disease 10th Revision (ICD-10). A diagnosis of stroke was con-

firmed by a physician and a computed tomography (CT) scan (The National Health Security Office, 2013). Data were encrypted to maintain confidentiality.

Subjects and follow-up period

All patients with a diagnosis of first-ever stroke [ICD-10 codes: I63 ischemic stroke and I61 (hemorrhagic stroke)] were retrieved retrospectively from the NHSO database for the time period 1 January 2004 to 31 December 2013. Mortality was confirmed by cross-referencing the patient's national identification number with the National Mortality Registry (access date 30 October 2015). Survival length was defined as the length between the diagnosis date and the mortality date. In this study we included all-causes of death.

Statistical analyses

Incomplete data files in whom a survival time could not be calculated were excluded from the study. During the study period, a total of 475,571 stroke events were registered. Survival was categorized as either short term (died within 30 days of stroke) or long term (died greater than 30 days after the stroke). Ages were classified into five groups: <25, 25-40, 41-60, 61-75 and >75 years old. Thailand is divided into five regions (northern, central, southern, northeastern and Bangkok) (Makka *et al*, 2016).

To describe the study population, continuous variables were summarized as means and standard deviations (SD); categorical data were summarized as percentages. Survival after the initial stroke was classified by sex, age group and region and was examined with the Kaplan-Meier survival analyses and log rank tests (Hosmer and Lemeshow, 2008).

Patients who survived >30-days were included in the analysis for long-term survival. Post-stroke survival was recorded

in months. Median post-stroke survival and 95% confidence intervals (CI) were calculated for sex, age group and region using Kaplan-Meier analyses and log rank tests (Hosmer and Lemeshow, 2008). We also performed multivariable survival analyses using the Cox proportional hazards method to determine predictors of mortality among stroke patients. Sex, age group and region were simultaneously included in the multivariable models to determine the hazard ratio at 30 days post-stroke and at the end of the follow-up period (31 October 2015) for stroke patients who survived >30 days post-stroke.

Ethical considerations

This study was approved by the Committee on Human Rights Related to Research Involving Human Subjects, Faculty of Medicine Ramathibodi Hospital, Mahidol University (No. MURA2015/759).

RESULTS

A total of 475,571 first stroke patients (67% with IS and 33% with HS) were eligible for survival analyses over the 10-year study period (Table 1). The mean age of patients was 63.5 years (65.2 years for patients with IS and 59.9 years for patients with HS). Males comprised 53% of those with IS and 60% of those with HS. The mean age of male patients was 61.7 years and of female patients was 65.6 years. Twenty-six percent of patients ($n=122,804$) died within 30 days and 74% ($n=352,767$) survived ≥ 30 days and were included in the long-term survival analysis. The follow-up time ranged from 1 to 132 months. The proportions of the total study population varied by region. The largest proportion of the study population (29.1%) was from central Thailand followed by northeastern Thailand (26.9%) (Table 1).

Table 1
Demographic characteristics of study population.

Characteristics	Total	IS	HS	<i>p</i> -value
No. of patients (%)	475,571 (100.0)	320,448 (67.4)	155,123 (32.6)	
Percent of subjects by region				
North	22.6	22.3	23.2	
Central	29.1	28.8	29.8	
Northeast	26.9	26.8	27.0	
South	12.8	13.4	11.5	
Bangkok	8.6	8.7	8.5	
Percent males	54.8	52.8	59.1	<0.001
Mean age in years (SD)	63.5 (14.9)	65.2 (14.1)	59.9 (16.0)	<0.001
Male	61.7 (14.8)	63.8 (13.9)	57.9 (15.6)	<0.001
Female	65.6 (14.9)	66.7 (14.3)	62.9 (16.1)	<0.001
Subjects who survived >30 days (%)	352,767 (74.2)	266,643 (75.6)	86,124 (24.4)	<0.001

SD, standard deviation; IS, ischemic stroke; HS, hemorrhagic stroke.

The Kaplan-Meier method was used to estimate the survival probability for IS and HS within 30 days of the first stroke. The short-term survival probability for HS was shorter than for IS ($p < 0.001$). Women had a poorer chance of survival than men during the first 30 days post-stroke for both IS and HS (Fig 1).

Table 2 shows the long-term survival length estimates for patients with IS and HS by sex, age and region. Among the 352,767 patients who survived the first month post-stroke, the prognosis was better for HS than IS. The median survival time was 101 months for HS and 81 months for IS ($p < 0.001$). Fig 2 shows the survival probability for stroke patients who survived >30 days. Men had a longer median survival time than women for both IS and HS ($p < 0.001$). Survival length decreased with increasing age (Fig 3). Survival time among those who lived >30 days differed significantly by region. IS patients in Bangkok had the longest median survival time (95 months) followed by those from southern Thailand

(91 months). The longest median survival time for those with HS was in Bangkok (119 months) followed by northeastern Thailand (105 months).

Variations in baseline data related to sex, age and region in the study sample influenced stroke survival. The Cox proportional hazards method was used to determine the effect of sex, age and region in terms of mortality risk in post-stroke patients. After adjusting for age and region, the risk for dying during the first 30 days after IS was significantly higher among women with a hazard ratio (HR) of 1.08 (95% CI: 1.06-1.10) and after HS was significantly higher among men (HR: 0.97; 95% CI: 0.95-0.98). The mortality risk during the first 30 days post-stroke was higher among patients from other regions than among patients from Bangkok after adjusting for age and sex (Table 3).

Among those who survived the first 30 days, women had a lower mortality risk than men (HR: 0.97 for IS and 0.92 for HS). After adjusting for sex and region, mortality risk was significantly higher

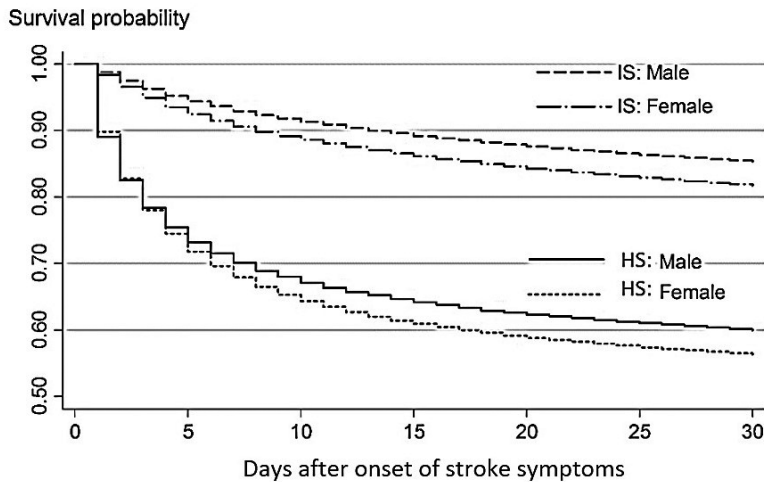


Fig 1—Survival probability (Kaplan-Meier estimates) during the first 30 days post-stroke by sex and stroke type. IS, ischemic stroke; HS, hemorrhagic stroke.

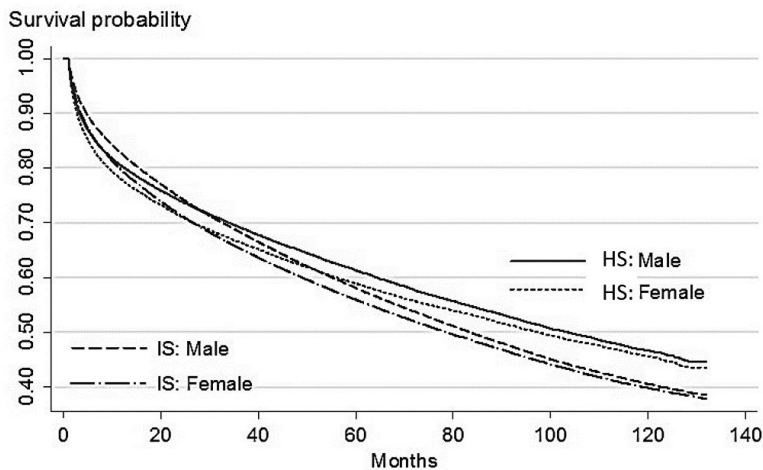


Fig 2—Survival probability (Kaplan-Meier estimates) after 30 days post-stroke by sex and stroke type. IS, ischemic stroke; HS, hemorrhagic stroke.

among the older age groups with ranges from 1.27 to 5.12 times higher compared to the youngest age group (age<25 years). Mortality risk among HS patients increased significantly with increasing age. The HR of stroke patients aged 25-40 years old was 1.30; 41-60 years old: 1.87;

61-75 years old: 4.03 and >75 years old: 7.96 compared to the youngest age group of patients (age<25 years). Only IS patients from southern Thailand had a significant lower mortality risk than those from Bangkok (HR: 0.88, $p<0.05$), while the mortality risk for other regions were not significantly different from Bangkok after adjusting for sex and age. HS patients from southern, northeastern and northern Thailand had a lower risk of dying than those with HS from Bangkok (HR: 0.88, 0.90 and 0.95, respectively) (Table 3).

DISCUSSION

In this study, the short-term survival probability was higher among IS than HS patients, similar to previous studies (Smajlovic *et al*, 2006; Rutten-Jacobs *et al*, 2013).

The long-term survival, on the other hand, was significantly higher among HS than IS patients.

In contrast to previous studies (Smajlovic *et al*, 2006; Vibo *et al*, 2012; Sun *et al*, 2013), we found that the median survival time among those who survived >30 days with HS was longer than those with IS. This could be because the mean age of study subjects with IS was 5 years older

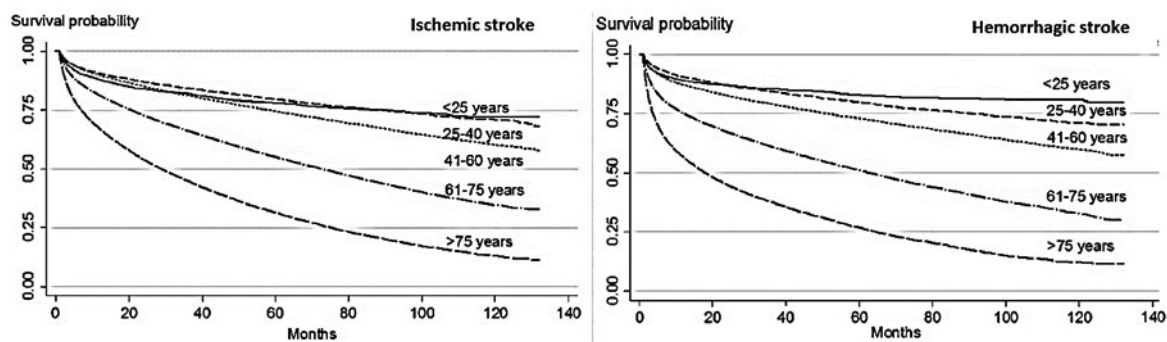


Fig 3—Survival probability (Kaplan-Meier estimates) after 30 days post-stroke by age group.

than subjects with HS. This suggests that HS may occur more often among younger people in the Thai population than IS, as reported in other studies (Rutten-Jacobs *et al*, 2013; Sun *et al*, 2013). In our study, mortality risk for IS and HS were evaluated separately.

Although our findings on Kaplan-Meier analysis revealed a shorter survival time among women than men, after controlling for age and region, women had a significantly lower mortality risk than men, similar to the findings of previous studies (Olsen *et al*, 2007; Rutten-Jacobs *et al*, 2013; Sun *et al*, 2013; Dehlendorff *et al*, 2015). In our study, men were more likely to have a stroke at a younger age than women, which might allow them to live longer after stroke than women. This finding suggests stroke prevention programs should target young men. Stroke survival depends on the quality of care. There may be disparity in care based on sex (Davis *et al*, 2006; Saposnik *et al*, 2011), but we did not study this factor since it was outside the scope of our study design. Men survived longer than women after stroke in our study, but the burden of that longer survival time in terms of quality of life or disability is unclear. Further studies

are needed regarding long-term quality of life after stroke in Thailand.

Length of post-stroke survival was shorter among older age groups in our study. This finding is consistent with similar studies (Smajlovic *et al*, 2006; Slot *et al*, 2008; Vibo *et al*, 2012; Sun *et al*, 2013).

In our study, we found a disparity in length of post-stroke survival by region. This disparity may be due to differences in stroke management programs and lack of specialists in some regions. The longer post-stroke survival in Bangkok may be due to the larger number of neurological specialists and the availability of more advanced medical technologies than in other regions. More than two-thirds of active neurologists in Thailand reside in Bangkok (Suwanwela, 2014). In our study, patients from other regions had a higher risk for mortality within 30 days of stroke than in patients from Bangkok. Stroke unit care significantly improves stroke outcomes, including mortality (Saposnik *et al*, 2011). Our findings show the need for improvement in public health strategies and equitable health resource allocation to reduce post-stroke burden.

The results from Cox' proportional hazard analyses among >30-days stroke

Table 2
Median survival time in months (95% CI) among stroke patients who survived >30-days.

	IS	<i>p</i> -value	HS	<i>p</i> -value
Overall	81 (80-82)		101 (99-103)	
Sex		<0.001		<0.001
Male	83 (82-84)		103 (101-106)	
Female	79 (78-80)		97 (94-100)	
Age group (years)		<0.001		<0.001
< 25	-		-	
25-40	-		-	
41-60	-		-	
61-75	73 (72-74)		63 (60-64)	
> 75	29 (28-29)		18 (17-19)	
Region		<0.001		<0.001
North	76 (74-77)		98 (95-102)	
Central	81 (79-82)		97 (94-100)	
Northeast	79 (77-80)		105 (104-106)	
South	91 (89-93)		97 (92-103)	
Bangkok	95 (93-99)		119 (118-120)	

IS, ischemic stroke; HS, hemorrhagic stroke.

Table 3
Multivariate analyses for hazard ratios by sex, age group and region among patients with ischemic stroke and hemorrhagic stroke.

Factors	At 30-days after stroke		After 30-days of first stroke	
	IS HR (95% CI)	HS HR (95% CI)	IS HR (95% CI)	HS HR (95% CI)
Sex (male) ^a				
Female	1.08 ^b (1.06-1.10)	0.97 ^b (0.95-0.98)	0.97 ^b (0.96-0.98)	0.92 ^b (0.90-0.94)
Age (>25 years) ^a				
25-40	1.12 ^b (1.01-1.24)	1.38 ^b (1.30-1.47)	0.96 (0.88-1.05)	1.30 ^b (1.17-1.43)
41-60	1.06 (0.96-1.15)	1.31 ^b (1.24-1.39)	1.27 ^b (1.17-1.37)	1.87 ^b (1.72-2.04)
61-75	0.89 ^b (0.82-0.98)	1.08 ^b (1.02-1.14)	2.59 ^b (2.39-2.80)	4.03 ^b (3.69-4.39)
>75	0.81 ^b (0.74-0.89)	0.98 (0.93-1.04)	5.12 ^b (4.64-5.43)	7.96 ^b (7.29-8.70)
Region (Bangkok) ^a				
North	1.16 ^b (1.12-1.20)	1.19 ^b (1.16-1.23)	1.01 (0.99-1.03)	0.95 ^b (0.91-0.98)
Central	1.12 ^b (1.08-1.16)	1.11 ^b (1.07-1.14)	0.99 (0.97-1.01)	0.98 (0.94-1.02)
Northeast	1.19 ^b (1.15-1.23)	1.16 ^b (1.12-1.20)	1.00 (0.98-1.02)	0.90 ^b (0.68-0.93)
South	1.18 ^b (1.13-1.23)	1.12 ^b (1.08-1.16)	0.88 ^b (0.86-0.90)	0.87 ^b (0.83-0.91)

^aReference group; ^b*p*-value <0.05; HR: hazard ratio; IS, ischemic stroke; HS, hemorrhagic stroke.

survivors showed HS patients from almost all other regions had a lower risk for mortality than those from Bangkok. Thailand has a referral system where persons with serious illness are referred to higher acuity level hospitals. There is a need to better understand stroke morbidity and mortality in Thailand by examining other potential contributing factors, such as variations in stroke care, diet, behavior and environment by region.

This study had the advantages of a large cohort, a 10-year study period, a broad study population representative of stroke patients in Thailand and use of the Thai national database which allowed estimation of mortality and post-stroke survival time.

A limitation of this study was that it included all-cause mortality rather than stroke associated mortality. This could have led to an underestimation of post-stroke survival rates, since patients may have died from other diseases or accidents. Using these data sources was cost efficient and provided greater coverage than traditional registries. Since this study had a long inclusion period, diagnostic ability, stroke treatment and secondary prevention may have improved over time. This could have affected long-term results. Thus, these findings should be viewed with caution. Moreover, since the sample was retrieved from hospital registries, patients who died from stroke at home were omitted. This could have led to overestimation of survival after first stroke, but not survival at follow-up. Patients who survive usually visit a hospital during the course of their disease. Therefore, we conclude the long-term survival was valid. We included all cases of first stroke under the universal coverage plan, which covers more than 70% of the Thai population. The authors presume

this study sample is representative of Thai patients with stroke.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to report for this study.

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