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Circadian Variation of Stroke Onset Among Thai Patients: Observational Study

Veerapun Suvannamai [1], Thunnawat Wattanaseth [2], Nuttakul Lungkorn [3] and Mart Maiprasert [4]*

[1]MD, FRCNST, Department of Anti-aging and Regenerative Medicine, College of Integrative Medicine, Dhurakij Pundit University Bangkok, Thailand.
ORCID ID: 0009-0001-8635-3653, E-mail: Veerapun.doc@gmail.com
[2]MD, PhD, Department of Anti-aging and Regenerative Medicine, College of Integrative Medicine, Dhurakij Pundit University Bangkok, Thailand.
ORCID ID: 0000-000201787-5781, E-mail: Thunnawatw@gmail.com
[3]M.D., Department of Anti-aging and Regenerative Medicine, College of Integrative Medicine, Dhurakij Pundit University Bangkok, Thailand.
ORCID ID: 0009-0003-2285-0698, E-mail: Nuttakulmd@gmail.com
[4]M.D., Department of Anti-aging and Regenerative Medicine, College of Integrative Medicine, Dhurakij Pundit University Bangkok, Thailand.
ORCID ID: 0000-0001-9320-5635, E-mail: mart.mai@dpu.ac.th

Abstract

The prevalence of stroke in Thailand presents a pressing public health concern, with a notable increase in recent years, contrary to the declining trends observed in high-income and low-income countries. Mortality rates for stroke patients admitted to hospitals in Thailand mirror those of high-income countries, with ischemic stroke patients facing a mortality rate of 7-14% and hemorrhagic stroke patients 27-35%. The manifestation of stroke symptoms among patients is commonly observed to peak between the hours of 6:01 a.m. and 6:00 p.m., notably accentuated on Mondays and Saturdays. Consequently, heightened attentiveness to stroke symptoms is imperative for both patients themselves and their familial caregivers. In the event of the emergence of any anomalous symptoms or the onset of depressive feelings in the patient, prompt hospitalization is strongly advocated, with particular emphasis on individuals aged 60 years or older presenting with comorbid diabetes mellitus, given their heightened susceptibility. Vigilant management of blood glucose levels assumes paramount importance in the preventive regimen, alongside the imperative of abstaining from both tobacco and alcohol consumption, recognized precipitating factors for stroke symptoms that demand perpetual vigilance.

***Keywords*:** *Circadian Variation of Stroke, Patterns of Stroke Occurrence, Immediate Triggering Factors*

INTRODUCTION

Stroke presents a formidable public health challenge in Thailand, demanding proactive intervention strategies and resource allocation to mitigate its deleterious effects on mortality, disability, and healthcare infrastructure. Despite global trends indicating a decline in stroke prevalence, Thailand has experienced a concerning 11% surge in age-standardized stroke prevalence, indicative of persistent hurdles in managing this condition.[1] Notably, stroke stands as a paramount contributor to worldwide disability and mortality rates, with mortality figures akin to those observed in affluent nations. However, disparities in access to thrombolytic therapy underscore the exigency for bolstering healthcare infrastructure and referral pathways to enhance patient outcomes.[2]

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Comprehending the temporal dynamics of stroke incidence holds significant potential for enhancing treatment efficacy and curtailing associated morbidity and mortality. Identifying periods of heightened risk assumes paramount importance, particularly for individuals harboring predisposing factors such as hypertension, diabetes, and cardiovascular ailments, mandating vigilant surveillance and lifestyle modifications.[3,4]

Moreover, timely identification and referral of high-risk individuals by caregivers can expedite access to life-saving interventions, including thrombolysis for ischemic strokes and emergent surgical interventions for hemorrhagic strokes.[5,6] Informed resource allocation by policymakers, informed by insights into peak stroke periods, constitutes a critical imperative for optimizing healthcare provision and ensuring the availability of requisite personnel and infrastructure to meet patient exigencies.

While antecedent research has predominantly delved into temporal stroke patterns within Western cohorts, the dearth of localized inquiries specific to Thailand underscores the urgency for indigenous investigations.[7-14]

Given inherent ethnic and behavioral divergences, findings stemming from such studies hold promise for illuminating novel perspectives on stroke etiology and triggers, thereby potentially informing targeted preventive paradigms.

Exploring putative triggers proximal to stroke onset, encompassing factors such as sleep deprivation, tobacco use, alcohol consumption, and acute psychological stress, represents a novel frontier for scholarly exploration, affording avenues for refining extant preventive frameworks and augmenting patient outcomes.[15]

This research aimed to investigate the timing of the day and the day of the week when strokes occur most frequently, and to investigate the immediate triggering factors that contribute to the occurrence of these strokes.

MATERIAL AND METHODS

Study design and setting of participants

The research methodology employed in this study adheres to a survey research format, with data collection conducted during the period spanning from September to November 2023. The study population comprises individuals aged 18 years and above who have been diagnosed with stroke through CT or M.R.I. scan, encompassing four distinct types: ischemic stroke of any etiology, hemorrhagic stroke (including intracerebral and intraventricular hemorrhage), subarachnoid hemorrhage, and transient ischemic attack. Participants were recruited from the Dr. Veeraphan Brain and Nervous System Clinic located in Phitsanulok Province, Thailand, provided they possessed proficiency in the Thai language and voluntarily consented to participate in the study.

Data collection

The research questionnaire employed in this study serves as a comprehensive data collection tool designed to gather pertinent information pertaining to participants' personal characteristics and treatment history. It encompasses various dimensions, including the time and day of symptom onset, with weekdays designated as Monday through Friday, and weekends categorized as Saturday to Sunday. Stroke type is delineated into ischemic stroke, intracerebral hemorrhage involving rupture of cerebral blood vessels within brain tissue, subarachnoid hemorrhage involving rupture of brain blood vessels beneath the meninges, and transient ischemic attack.

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Furthermore, the questionnaire captures risk behaviors and underlying medical conditions associated with an elevated risk of stroke, encompassing a history of smoking, alcohol consumption, sleep disturbances, atrial fibrillation, diabetes, hypertension, hypercholesterolemia, chronic kidney disease, cancer, and exposure to triggering events such as smoking or alcohol consumption within six hours preceding symptom onset, insufficient sleep (less than four hours), or acute stress experienced within 24 hours prior to symptom manifestation. Additionally, the questionnaire gathers data on the frequency of prior strokes, the duration from symptom onset to hospital arrival, and receipt of thrombolytic therapy.

To ascertain the precise time of symptom onset, interviews are conducted with either the patient or their family members, relying on recollections of the last known well time or documentation from medical records. Symptom onset times are subsequently categorized into four distinct groups: 0.01-6.00 hours, 6.01-12.00 hours, 12.01-18.00 hours, and 18.01-0.00 hours, facilitating systematic analysis and interpretation of temporal patterns in stroke occurrence.

Statistical analysis and sample size calculation

The determination of the sample size was informed by a power analysis of the Chi-Square test, guided by established parameters. The effect size, drawn from prior research by Hayes MK et al.10, was set at 0.14. The significance level (α) was predetermined at 0.05, with a test power (1-β) of 0.9. The sample was stratified into four study groups, culminating in an initial estimated sample size of 786 individuals. To mitigate potential discrepancies and data loss, the sample size was augmented by 10%, resulting in a final sample size of 873 participants.

The comprehensive analysis of demographic factors, proximal triggers, and temporal patterns of stroke events is integral to unraveling the complexities of stroke occurrence. Utilizing descriptive statistics, including frequencies, percentages, means, and standard deviations, facilitates a nuanced understanding of clustered data, while proportion analysis offers insights into the distribution of stroke occurrences across various timeframes and weekdays.

Subgroup analyses based on stroke type and gender, coupled with Chi-square tests and Cramer's V values, provide a detailed exploration of the relationship between temporal characteristics and stroke incidence.

This meticulous approach not only illuminates the temporal dynamics of stroke events but also sheds light on potential risk factors and triggers associated with different time intervals and days of the week. Moreover, employing univariable and multivariate analyses, such as simple and multiple logistic regression, enables the identification and assessment of factors influencing stroke symptom onset, while controlling for confounding variables. By leveraging IBM SPSS Statistics for Windows Version 25.0, these analytical techniques uphold rigorous standards, ensuring robust statistical inference and enhancing our comprehension of the multifaceted determinants of stroke occurrence.

Ultimately, this methodological rigor contributes to a comprehensive understanding of stroke epidemiology, thereby informing targeted interventions and advancing efforts to mitigate the burden of stroke on public health.

Statement of ethics

The study protocol was approved by the Human Research Ethics Committee of Dhurakij Pundit University, with Certificate of Approval: DPUHREC 001/66FB. COA No. 008/66

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RESULTS

A cohort comprising 946 stroke patients was stratified based on stroke type, revealing that 73.4% suffered from ischemic stroke, 25.4% from intramembranous hemorrhage, 0.6% from subdural hemorrhage, and 0.6% experienced transient ischemic attacks. Predominantly, the male gender constituted 64.9% of the cohort.

The mean age of the patients was calculated at 60.47±11.74 years, with the average age at the onset of the first stroke slightly lower at 60.18±11.81 years. Noteworthy comorbidities included hypertension, prevalent among 73.2% of the patients, with 30.0% reporting a history of smoking and 39.3% disclosing alcohol consumption.

Proximal triggers implicated in stroke onset encompassed behaviors such as smoking within six hours preceding symptom manifestation, reported by 15.0% of patients, and alcohol consumption within the same timeframe, noted in 10.4% of cases.

Furthermore, 10.4% of patients reported inadequate sleep (less than four hours) prior to symptom onset, while severe stress within 24 hours preceding symptom manifestation was documented in 0.4% of cases. The median duration between symptom onset and hospital presentation was 2 (1, 10.25) hours. Treatment with clot-busting injections was administered to 8.9% of patients, with the majority experiencing a single stroke episode (95.5%), while 4.5% reported multiple stroke occurrences. **(Table 1)**

Table 1: Demographic data, vascular risk factors, and stroke onset are classified by the type of strokes.

Factors	Total	Ischemic	Intracerebral hemorrhage	Subarachnoid hemorrhage	Transient ischemic attack
n (%)	946	694 (73.4)	240 (25.4)	6 (0.6)	6 (0.6)
Sex, n(%)					
Male	614 (64.9)	460 (66.3)	148 (61.7)	2 (33.3)	4 (66.7)
Female	332 (35.1)	234 (33.7)	92 (38.3)	4 (66.7)	2 (33.3)
Age (years), mean±SD	60.47±11.74	61.79±11.29	56.53±12.31	68.67±7.50	56.67±3.14
Age of first stroke onset (years), mean±SD	60.18±11.81	61.46±11.38	56.36±12.40	68.67±7.50	56.00±2.37
Comorbidities, n(%)					
Hypertension	692 (73.2)	504 (72.6)	180 (75.0)	4 (66.7)	4 (66.7)
Dyslipidemia	590 (62.4)	469 (67.6)	115 (47.9)	2 (33.3)	4 (66.7)
Diabetes mellitus	246 (26.0)	213 (30.7)	31 (12.9)	2 (33.3)	0 (0.0)
Insomnia and OSA	192 (20.3)	149 (21.5)	41 (17.1)	2 (33.3)	0 (0.0)
Chronic kidney disease	40 (4.2)	32 (4.6)	8 (3.3)	0 (0.0)	0 (0.0)
Atrial fibrillation	38 (4.0)	30 (4.3)	8 (3.3)	0 (0.0)	0 (0.0)
Malignancy	10 (1.1)	8 (1.2)	2 (0.8)	0 (0.0)	0 (0.0)
Smoking, n(%)	284 (30.0)	224 (32.3)	58 (24.2)	2 (33.3)	0 (0.0)
Alcohol, n(%)	372 (39.3)	248 (35.7)	120 (50.0)	2 (33.3)	2 (33.3)
Vascular risk factors, n(%)					
Smoking within 6 hours before the onset	142 (15.0)	113 (16.3)	27 (11.3)	2 (33.3)	0 (0.0)
Alcohol drinking within 6 hours before the onset	98 (10.4)	58 (8.4)	38 (15.8)	2 (33.3)	0 (0.0)
Sleep less than 4 hours in the night before	4 (0.4)	4 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Acute stress full situation within 24 hours before	2 (0.2)	0 (0.0)	2 (0.8)	0 (0.0)	0 (0.0)
Onset to door time (hours), median (IQR)	2 (1, 10.25)	3 (1, 12)	1 (1, 4)	0.5 (0.5, 1)	1 (0.5, 4)

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Factors	Total	Ischemic	Intracerebral hemorrhage	Subarachnoid hemorrhage	Transient ischemic attack
rt-PA, n(%)	84 (8.9)	80 (11.5)	2 (0.8)	0 (0.0)	2 (33.3)
Number of stroke onset, n(%) (n=942)					
1	900 (95.5)	656 (94.5)	232 (96.7)	6 (100.0)	6 (100.0)
2	42 (4.5)	36 (5.2)	6 (2.5)	0 (0.0)	0 (0.0)

The temporal distribution of stroke events revealed that the most prevalent timeframe was between 6:01 a.m. and 12:00 p.m., accounting for 31.3% of occurrences, followed by 12:01 p.m. to 6:00 p.m. at 27.2%, 0:01 a.m. to 6:00 a.m. at 22.7%, and 6:01 p.m. to 12:00 a.m. at 18.8%. These proportions exhibited statistically significant differences at the 0.05 level (P<0.001). **(Table 2)**

Table 2: Time of stroke onset classified by the types of strokes.

Time of stroke onset	Total	Ischemic	Intracerebral hemorrhage	Subarachnoid hemorrhage	Transient ischemic attack
0.01-6.00	212 (22.7)	156 (22.8)	56 (23.5)	0 (0.0)	0 (0.0)
6.01-12.00	292 (31.3)	222 (32.5)	62 (26.1)	4 (66.7)	4 (66.7)
12.01-18.00	254 (27.2)	198 (28.9)	52 (21.8)	2 (33.3)	2 (33.3)
18.01-0.00	176 (18.8)	108 (15.8)	68 (28.6)	0 (0.0)	0 (0.0)
χ^2	32.595	44.000	2.471	0.667	0.667
P-value	<0.001*	<0.001*	0.481	0.414	0.414

Data were analyzed with One-way goodness-of-fit chi-square test

* Statistically significant at the 0.05 level (α=0.05)

Analysis of stroke symptom occurrence by day of the week revealed that 69.5% of events transpired on weekdays, with the remaining 30.5% occurring on holidays, exhibiting a significant difference at the 0.05 level (P<0.001). Predominantly, strokes manifested on Mondays and Saturdays, each accounting for 15.9% of occurrences, followed closely by Sundays at 14.6%, Tuesdays at 14.2%, Thursdays at 13.8%, Wednesdays at 13.4%, and Fridays at 12.1%. These proportions did not display statistically significant disparities (P=0.720). **(Table 3)**

Table 3: Days of the week of stroke onset classified by the types of strokes. (**n=478**)

Days of the week	Total	Ischemic	Intracerebral hemorrhage	Subarachnoid hemorrhage	Transient ischemic attack
Weekdays	332 (69.5)	252 (70.0)	76 (69.1)	2 (33.3)	2 (100.0)
Weekends	146 (30.5)	108 (30.0)	34 (30.9)	4 (66.7)	0 (0.0)
χ^2	72.377[(a)]	57.600[(a)]	16.036[(a)]	0.667[(a)]	-
P-value	<0.001*	<0.001*	<0.001*	0.414	-
Sunday	70 (14.6)	48 (13.3)	20 (18.2)	2 (33.3)	0 (0.0)
Monday	76 (15.9)	62 (17.2)	14 (12.7)	0 (0.0)	0 (0.0)
Tuesday	68 (14.2)	56 (15.6)	12 (10.9)	0 (0.0)	0 (0.0)
Wednesday	64 (13.4)	44 (12.2)	18 (16.4)	2 (33.3)	0 (0.0)
Thursday	66 (13.8)	42 (11.7)	22 (20.0)	0 (0.0)	2 (100.0)
Friday	58 (12.1)	48 (13.3)	10 (9.1)	0 (0.0)	0 (0.0)
Saturday	76 (15.9)	60 (16.7)	14 (12.7)	2 (33.3)	0 (0.0)
χ^2	3.682	7.267	7.345	0.000	-
P-value	0.720	0.297	0.290	1.000	-

Data were analyzed with One-way goodness-of-fit chi-square test

* Statistically significant at the 0.05 level (α=0.05)

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Furthermore, an interplay between the day of the week and the timing of stroke events was observed, with a significant difference noted at the 0.05 level (P<0.001).

A notably high correlation (Cramer's V = 0.31) was identified, indicating that stroke occurrences between 0:01 a.m. and 6:00 a.m. and between 6:01 a.m. and 12:00 p.m. predominantly transpired during the weekend, whereas occurrences between 12:01 p.m. and 6:00 p.m. and between 6:01 p.m. and 12:00 a.m. were more prevalent on weekdays. **(Table 4)**

Table 4: Association between time and days of the week of stroke onset

	0.01-6.00	6.01-12.00	12.01-18.00	18.01-0.00	P-value
Sunday	12 (12.5)	24 (14.8)	20 (16.1)	14 (14.6)	<0.001* (χ^2 = 46.408, Cramer's V = 0.31)
Monday	20 (20.8)	28 (17.3)	12 (9.7)	16 (16.7)	
Tuesday	12 (12.5)	18 (11.1)	14 (11.3)	24 (25.0)	
Wednesday	10 (10.4)	18 (11.1)	18 (14.5)	18 (18.8)	
Thursday	10 (10.4)	24 (14.8)	24 (19.4)	8 (8.3)	
Friday	10 (10.4)	14 (8.6)	22 (17.7)	12 (12.5)	
Saturday	22 (22.9)	36 (22.2)	14 (11.3)	4 (4.2)	

Data were analyzed with Two-way contingency chi-square test

* Statistically significant at the 0.05 level (α=0.05)

The multivariate analysis discerned significant contributors to stroke symptom occurrence within specific time intervals, attaining statistical significance at the 0.05 level (P<0.05). Notably, during the 0.01-6.00 hrs. Timeframe, factors such as male gender (Adj. OR 1.61 [95% CI 1.13, 2.29]), age greater than or equal to 60 years (Adj. OR 0.72 [95% CI 0.52, 0.99]), and smoking within six hours preceding symptom onset (Adj. OR 0.27 [95% CI 0.14, 0.51]) emerged as significant predictors.

Similarly, in the 6.01-12.00 hrs. Interval, male gender (Adj. OR 0.56 [95% CI 0.41, 0.76]), smoking cigarettes within six hours before symptom onset (Adj. OR 1.64 [95% CI 1.03, 2.61]), and alcohol consumption within the same timeframe (Adj. OR 0.45 [95% CI 0.24, 0.82]) exhibited notable associations with stroke occurrence. Conversely, during the 12.01-18.00 hrs.

Period, diabetes mellitus (Adj. OR 1.46 [95% CI 1.02, 2.08]), smoking prior to symptom onset (Adj. OR 2.76 [95% CI 1.76, 4.33]), and alcohol consumption within six hours preceding symptoms (Adj. OR 0.51 [95% CI 0.29, 0.90]) emerged as significant predictors.

In the 18.01-0.00 hrs. Timeframe, significant predictors included diabetes mellitus (Adj. OR 0.44 [95% CI 0.28, 0.70]), smoking within six hours before symptom onset (Adj. OR 0.38 [95% CI 0.20, 0.71]), and alcohol consumption within the same timeframe (Adj. OR 5.51 [95% CI 2.85, 9.31]).

Additionally, during the daytime period (6.01-18.00 hrs.), factors such as male gender (Adj. OR 0.74 [95% CI 0.55, 0.99]), age greater than or equal to 60 years (Adj. OR 1.48 [95% CI 1.12, 1.94]), diabetes mellitus (Adj. OR 1.67 [95% CI 1.19, 2.33]), smoking within six hours before symptom onset (Adj. OR 4.83 [95% CI 2.82, 8.25]), and alcohol consumption within the same timeframe (Adj. OR 0.26 [95% CI 0.15, 0.47]) were identified as significant predictors. **(Table 5)**

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Table 5: Multivariable analysis of the association of vascular risk factors with the onset of stroke between 12.01 AM and 6.00 AM, 6.01 AM and 12.00 PM, 12.01 PM and 18.00 PM, 18.01 PM and 12.00 AM, 6.01 AM and 18.00 PM (daytime)

Factors	0.01-6.00		6.01-12.00		12.01-18.00		18.01-0.00		6.01-18.00	
	Adjusted OR (95%CI)	P-value	Adjusted OR (95%CI)	P-value	Adjusted OR (95%CI)	P-value	Adjusted OR (95%CI)	P-value	Adjusted OR (95%CI)	P-value
Sex										
Male	1.61 (1.13, 2.29)	0.008*	0.56 (0.41, 0.76)	<0.001*	1.35 (0.96, 1.90)	0.082	0.91 (0.63, 1.32)	0.617	0.74 (0.55, 0.99)	0.046*
Female	Ref.		Ref.		Ref.		Ref.		Ref.	
Age of first stroke onset (years)										
< 60	Ref.		Ref.		Ref.		Ref.		Ref.	
≥ 60	0.72 (0.52, 0.99)	0.041*	1.24 (0.93, 1.65)	0.150	1.29 (0.96, 1.74)	0.097	0.81 (0.57, 1.14)	0.228	1.48 (1.12, 1.94)	0.005*
Comorbidities										
Malignancy	2.19 (0.57, 8.33)	0.252	0.42 (0.08, 2.23)	0.307	2.13 (0.58, 7.83)	0.253			1.04 (0.27, 4.01)	0.950
Atrial fibrillation	0.84 (0.33, 2.13)	0.720	1.70 (0.83, 3.46)	0.145	0.90 (0.39, 2.10)	0.812	0.52 (0.18, 1.53)	0.234	1.64 (0.75, 3.56)	0.213
Diabetes mellitus	0.95 (0.65, 1.40)	0.809	1.23 (0.88, 1.72)	0.228	1.46 (1.02, 2.08)	0.037*	0.44 (0.28, 0.70)	0.001*	1.67 (1.19, 2.33)	0.003*
Hypertension	0.98 (0.68, 1.41)	0.914	1.04 (0.74, 1.46)	0.833	0.80 (0.57, 1.12)	0.193	1.27 (0.85, 1.91)	0.249	0.88 (0.64, 1.21)	0.415
Chronic kidney disease	0.39 (0.14, 1.15)	0.088	1.93 (0.97, 3.86)	0.062	1.00 (0.46, 2.17)	0.995	0.72 (0.25, 2.14)	0.558	2.16 (0.95, 4.90)	0.065
Dyslipidemia	0.96 (0.68, 1.36)	0.830	1.12 (0.81, 1.53)	0.492	0.77 (0.56, 1.07)	0.115	1.35 (0.93, 1.96)	0.115	0.86 (0.64, 1.16)	0.319
Insomnia and OSA	1.29 (0.88, 1.88)	0.194	0.95 (0.66, 1.36)	0.760	1.07 (0.74, 1.55)	0.721	0.67 (0.42, 1.06)	0.083	1.05 (0.75, 1.48)	0.783
Smoking within 6 hours before the onset	0.27 (0.14, 0.51)	<0.001*	1.64 (1.03, 2.61)	0.036*	2.76 (1.76, 4.33)	<0.001*	0.38 (0.20, 0.71)	0.003*	4.83 (2.82, 8.25)	<0.001*
Alcohol drinking within 6 hours before the onset	1.01 (0.53, 1.90)	0.989	0.45 (0.24, 0.82)	0.009*	0.51 (0.29, 0.90)	0.019*	5.15 (2.85, 9.31)	<0.001*	0.26 (0.15, 0.47)	<0.001*

Data were analyzed with multiple logistic regression (Enter method)

* Statistically significant at the 0.05 level (α=0.05)

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DISCUSSION

The analysis revealed distinct patterns in the timing of stroke symptoms. The most prevalent occurrence was observed between 6:01 a.m. and 12:00 p.m., accounting for 31.3% of cases, followed by 12:01 p.m. to 6:00 p.m. (27.2%), 12:01 a.m. to 6:00 a.m. (22.7%), and 6:01 p.m. to 12:00 a.m. (18.8%), with statistically significant differences noted. These findings align with previous studies by Hayes MK. et.al.[9] and Wang Elliott WJ.[11], indicating a higher relative risk of stroke during the morning hours compared to other time intervals.

The temporal distribution of stroke symptoms, particularly the morning predilection, is attributed to various physiological factors, including fluctuations in blood pressure, heart rate, hemostasis processes, and occurrences of atrial fibrillation.[16] Additionally, the sleep-wake cycle influences stroke occurrence, with increased risk during rapid eye movement (REM) sleep. The interplay between the brain's penumbra region and body temperature further modulates circadian variations.[17] Notably, while traditional risk and treatment factors may not alter the biological clock pattern of stroke symptoms uniformly[16], our study found that stimulating factors, such as smoking within six hours before symptom onset, pose a higher risk during daytime hours compared to nighttime. Regarding stroke type, both ischemic and hemorrhagic strokes exhibit similar temporal patterns, primarily occurring between 6:01 a.m. and 12:00 p.m. Despite their distinct pathophysiological mechanisms, this consistent pattern underscores the shared temporal vulnerability to cerebrovascular events.[11,19] These findings contrast with the study by Vargas FP et al.[18], where ischemic strokes peaked between 10:00 a.m. and 9:59 p.m., while hemorrhagic strokes occurred between 9:00 a.m. and 7:00 p.m.

The distribution of stroke occurrences across weekdays was examined, revealing that the majority of strokes occurred on weekdays (69.5%), with Mondays demonstrating the highest prevalence (15.9%). However, comparative analysis did not yield statistically significant differences between weekdays. Notably, among individuals under 60 years of age, a notable proportion experienced strokes on Mondays (52.6%), coinciding with the working age demographic, whereas no discernible pattern was observed among those aged 60 and above. Additionally, patients exhibited a higher frequency of smoking on weekends compared to weekdays, consistent with findings by Hayes M.K. et al.[9], which also reported a higher likelihood of stroke incidence, smoking habits, alcohol consumption, and employment status on Mondays. Furthermore, male patients who experienced strokes on Mondays were more likely to be employed, aligning with prior research by Manfredini R. et al.[19], which identified transient ischemic attacks as more prevalent on Mondays (16.1%) and least on Sundays (11.6%), albeit with a distinct frequency pattern from Monday to Sunday. However, this contradicts our study's observations, where stroke frequency declines from Monday to Friday before rising on Saturday, albeit without statistical significance.

The investigation into factors influencing stroke symptoms during sunrise (6:01 a.m. - 6:00 p.m.) revealed several significant determinants, including gender, age, and the presence of diabetes, alongside the impact of behaviors such as smoking and alcohol consumption.

Firstly, **gender** emerged as a noteworthy determinant, with male patients exhibiting a 1.61 times higher likelihood of experiencing strokes during sunset compared to sunrise (95%CI 1.13, 2.29). This observation may be attributed to socialization patterns, as men often engage in post-work activities or social gatherings during evening hours, potentially increasing exposure to risk factors such as smoking and alcohol consumption, consistent with prior research.[20] Additionally, sleep disturbances, particularly obstructive sleep apnea prevalent among elderly male stroke patients, and its association with diabetes further elevate stroke risk and post-stroke mortality rates.[21-23]

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Secondly, **advancing age**, particularly among patients aged ≥60 years, was identified as a significant factor, with this demographic being 1.48 times more likely to experience strokes during sunrise compared to sunset (95%CI 1.12, 1.94). Age-related changes in brain tissue, coupled with the heightened prevalence of chronic conditions like diabetes and hypertension, contribute to the increased stroke risk among older individuals.[24] Moreover, physiological variations such as elevated blood pressure and heart rate levels during morning hours, alongside the diurnal rhythm of cerebrovascular symptoms, which peak in the morning, further underscore the propensity for strokes among the elderly during sunrise.[25-26]

Thirdly, **diabetes**, the investigation into diabetes as a contributing factor to stroke symptoms during sunrise (6:01 a.m. - 6:00 p.m.) yielded compelling insights, with stroke patients diagnosed with diabetes exhibiting a 1.67 times higher likelihood of experiencing symptoms during sunrise compared to sunset (95%CI 1.19, 2.33). Several mechanisms may underpin this association. Firstly, fluctuations in blood sugar levels among diabetic patients have been implicated in increasing stroke risk, with higher blood sugar levels observed in stroke patients with severe neurological impairment compared to those with milder symptoms, as indicated by the National Institute of Health Stroke Scale (NIHSS).[27] Secondly, insulin resistance, characteristic of diabetes, can precipitate abnormalities in vascular function and structure, alongside fostering inflammation, endothelial dysfunction, and atherosclerosis, thereby predisposing individuals to ischemic stroke.[28] . Furthermore, the co-occurrence of diabetes and sleep apnea, which disrupts sleep patterns and oxygen levels, presents a pathway for morning strokes, with shared pathophysiological mechanisms contributing to atherosclerosis.[29] Additionally, postprandial spikes in blood sugar levels following meals pose a further risk factor for stroke during daytime hours, highlighting the multifaceted interplay between diabetes and stroke occurrence during sunrise (6:01 a.m. - 6:00 p.m.).

Fourthly, **smoking within the 6-hour window** preceding symptom onset escalates the risk of stroke during sunrise (6:01-18:00 hrs.) by a striking 4.83 times compared to sunset (95%CI 2.82, 8.25). The deleterious effects of smoking on vascular health are manifold, encompassing vasoconstriction, heightened blood pressure, and augmented blood clotting propensity.[30] this cascade of physiological responses culminates in compromised cerebral perfusion, rendering the brain susceptible to ischemic stroke. Furthermore, smoking-induced reductions in blood oxygen transport capacity via hemoglobin exacerbate cerebral hypoxia, further predisposing individuals to stroke.[30] Beyond its direct vascular effects, smoking engenders a pro-inflammatory and endothelial dysfunction milieu, which collectively heighten stroke risk. Notably, smokers exhibit a markedly elevated stroke risk, with estimates suggesting a 2-4-fold increase compared to non-smokers or individuals with a protracted smoking cessation history exceeding a decade.[30] Intriguingly, while smoking primarily augments the risk of hemorrhagic stroke, it also exerts a discernible influence on ischemic stroke occurrence, underscoring its pervasive impact on cerebrovascular health.[31,32]

Finallly, **consuming alcoholic beverages within 6 hours** preceding symptom onset magnifies the likelihood of stroke during sunset by a substantial 3.86 times (95%CI 0.2.13, 6.67) compared to sunrise (calculated back from adjusted odds ratio in 6.01-18.00 group). This pattern of alcohol consumption was notably prevalent among the majority of patients in this study, often occurring post-work hours during social engagements, dinner gatherings, or relaxation routines before bedtime. Despite the potential cardiovascular benefits associated with moderate alcohol intake for select individuals[33,34], excessive or heavy drinking precipitates a surge in blood pressure levels, fosters arrhythmias like atrial fibrillation, and disrupts sleep patterns, contributing to cardiovascular morbidity and stroke risk.[35]

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Corroborating recent research on the global impact of modifiable cardiovascular risk factors, this study underscores the pivotal role of alcohol consumption alongside hypertension, hyperlipidemia, smoking, and hyperglycemia in driving cardiovascular disease burden.[36]

Hence, advocating smoking cessation emerges as a critical public health imperative to curtail inflammation-mediated stroke and coronary artery disease escalation. Moreover, the elevated rate of clot-busting injections observed among 8.9% of patients in this study, surpassing prevailing figures in Thailand ranging from 0.18-8.14%, likely reflects enhanced healthcare accessibility and infrastructure in urban locales, facilitating expedited stroke management and treatment delivery.[37]

CONCLUSION

The comprehensive analysis of a cohort comprising 946 stroke patients delineated critical insights into the demographic profile, proximal triggers, and temporal dynamics of stroke events. Predominantly, the cohort predominantly suffered from ischemic stroke (73.4%), with notable representation from intramembranous hemorrhage, subdural hemorrhage, and transient ischemic attacks.

Male patients constituted the majority (64.9%), with an average age of 60.47 years, showcasing hypertension as the most prevalent comorbidity (73.2%), alongside smoking (30.0%) and alcohol consumption (39.3%). Proximal triggers such as smoking, alcohol consumption, inadequate sleep, and severe stress within 24 hours preceding symptom onset were identified, underscoring the multifactorial etiology of stroke.

The manifestation of stroke symptoms among patients is commonly observed to peak between the hours of 6:01 a.m. and 6:00 p.m., notably accentuated on Mondays and Saturdays. Notably, stroke events exhibited a notable association with gender, age, and comorbidities such as diabetes, with significant predictors identified across various timeframes.

Vigilant management of blood glucose levels assumes paramount importance in the preventive regimen, alongside the imperative of abstaining from both tobacco and alcohol consumption. These findings underscore the nuanced interplay between sociodemographic factors, behavioral determinants, and temporal dynamics in precipitating stroke events, necessitating tailored preventive strategies and targeted interventions to mitigate stroke risk within vulnerable populations.

Overall, the meticulous examination of stroke epidemiology and associated risk factors enhances our understanding of stroke pathogenesis, facilitating informed clinical management and public health interventions aimed at ameliorating stroke burden and improving patient outcomes.

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Conflict of interest:

The authors declare that there is no conflict of interest regarding the publication of this paper. We confirm that we have no financial or personal relationships with other people or organizations that could inappropriately influence our work. All authors have reviewed and agreed upon the content of this manuscript, and there are no competing interests to disclose.

Informed consent:

Prior to their involvement in the study, all participants provided informed consent. A detailed explanation of the research objectives, procedures, potential risks, and benefits was provided to each participant. Participants were assured of the confidentiality of their responses and were informed that their participation was voluntary.

They were also informed of their right to withdraw from the study at any time without consequence. Consent was obtained in writing from each participant. The consent form outlined the purpose of the research, the procedures involved, and the measures taken to ensure confidentiality. Participants were encouraged to ask questions and seek clarification before providing consent.

All consent procedures adhered to the ethical guidelines outlined by the Human Research Ethics Committee of Dhurakij Pundit University. And the study protocol was approved by the same organization.

Author Contributions

Suvannamai V., Maiprasert M., Lungkorn N., Jangwangkorn C. and Wattanaseth T. contributed to this research project in different capacities: Suvannamai V.: Conducted experiments, gathered data, and provided critical analysis throughout the research process. Lungkorn N. and Jangwangkorn C.

Contributed to the discussion section. Wattanaseth T: Provided valuable insights and supported the discussions with relevant literature and analysis. Maiprasert M.: Conceptualized the research idea, designed the study, supervised data collection and analysis, drafted the manuscript and corresponding author. All authors have reviewed and approved the final version of the manuscript.

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