Circadian Variation of Stroke in a Tertiary Level Hospital

ABSTRACT

Introduction: *Stroke, a primary global health concern, is the fifth leading cause of death in Bangladesh, with a prevalence of 0.3%. While 85% of stroke cases globally are cerebral infarctions, Asian countries exhibit stroke patients on average 15 years younger than developed countries. Survival studies reveal strokes exceeding coronary events in hypertensive patients. Observational data suggests circadian, circaseptan, and circannual variations in stroke occurrence, with a morning peak. Circadian rhythm in ischemic stroke is higher in the early morning. Thrombotic strokes, influenced by platelet aggregation and fibrinolysis, often occur in the morning. Haemorrhagic strokes result from blood vessel ruptures. Population-specific circadian patterns remain unconfirmed.*

Aim of the study: *The study aims to find out the relation of circadian variation of stroke.*

Methods: *This cross-sectional study, conducted at Sylhet MAG Osmani Medical College Hospital, Bangladesh, analyzed 100 stroke patients over six months. Ethical approval was obtained, and informed consent was taken. Inclusion criteria covered patients with clinical and imaging stroke diagnoses, while exclusion criteria excluded transient ischemic attack, previous stroke, head injury history, and refusal to participate. Stroke onset time was categorized into four six-hour intervals. Demographic data, risk factors, and comorbidities were recorded, and brain CT scans were performed. Data analysis used SPSS version 22, employing descriptive statistics, Chi-square Test, and Student's t-test. Significance was set at $p<0.05$. Results were presented in tables.*

Result: *The study involves 100 participants, primarily aged 60-70 (50%), predominantly male (76%), residing 62% in urban and 38% in rural areas. Occupationally, 35% are businessmen, 24% are housewives, and 15% are service holders and laborers. Smoking status shows 58% smokers. Stroke types include 57% ischemic strokes and 39% hemorrhagic strokes. Hypertension (72%) is the significant risk factor. Stroke symptoms predominantly occur between 06:01 and 12:00 (46%). These insights comprehensively understand the study population's demographics, lifestyle, and clinical characteristics.*

Conclusion: *The study established circadian patterns in stroke onset, with the highest frequency between 06:00-12:00 and the lowest between 18:01-24:00. Ischemic stroke was the most common subtype, followed by hemorrhagic stroke and fewer subarachnoid hemorrhages. Managing blood pressure and coagulation during peak onset times could aid stroke prevention, but further extensive studies are needed for validation.*

Keywords: *Circadian Variation, Stroke, Tertiary Level Hospital*

INTRODUCTION

Stroke is a neurological disease and is a significant cause of disability and death worldwide. World Health Organization (WHO) defines *stroke* as a Rapidly developing clinical sign of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin [1]. Stroke has been ranked as the fifth leading cause of death in Bangladesh [2]. The overall prevalence of stroke in Bangladesh is 0.3% [3]. Of the overall 180-300 per 100,000 population worldwide presenting annually with a stroke, 85% sustain a cerebral infarction due to inadequate blood flow to part of the brain, and most of the remainder have an intracerebral haemorrhage [4]. In Asian countries, the average age of patients with stroke is 15 years younger than in developed countries [5]. Relatively recent studies of survival in hypertensive patients have revealed that the incidence of stroke exceeded that of coronary events [6]. Available data from observational studies suggest that cerebrovascular events are not randomly distributed over time but have a peculiar distribution along the day (circadian variation with morning peak of occurrence), week (circaseptan variation with higher frequencies in the last and first days of the week) and even months of the year (circannual or seasonal variation with predilection for the cold months) [7]. It has been observed that the frequency of circadian rhythm in ischaemic stroke is higher in the early hours of the morning [8]. Many recent studies also observed that the risk of cardiovascular events is higher in the hours around and just after awakening. In most cases, circadian variation is related to ischemic stroke rather than to haemorrhagic stroke and subarachnoid haemorrhage. However, a study of 137 cases of intracerebral haemorrhage between 1960 and 1989 noted a significant increase in the time of onset of haemorrhagic stroke between 8.00 and 16.00. Another study in different Medicine Units of Faridpur Medical College and Dhaka Medical College Hospitals from July 2012 to June

2013 showed a maximum number of patients developed hemorrhagic stroke between 4:01 am and 8:00 am. Circadian variation is reported to be related to the circadian rhythm of fibrinolysis, platelet aggregability, and mainly arterial blood pressure, with its minimum value during sleep and maximum value in the early morning hours [9-12]. Ischaemic stroke can be either thrombotic or embolic. Thrombotic strokes occur when a thrombus in one of the arteries blocks the blood supply to the brain, while an embolic stroke occurs when part of the thrombus formed at a distal part of the vasculature dislodges and is then swept through the bloodstream and subsequently lodges in narrow blood vessels in the brain [13]. Thrombotic strokes could result from increased platelet aggregation and reduced fibrinolytic activity, which both occur during the morning [14]. Changes in platelet aggregation correlate with changes in plasma catecholamine levels, which increase between 6 and 9 am. On the other hand, the fibrinolytic system represents reciprocal changes in the concentrations of tissue plasminogen activator (tPA) and its fast-acting inhibitor (PAI) during the morning, which found high PAI activity in contrast to low PAI activity during the early morning [15]. Haemorrhagic stroke occurs when a blood vessel in the brain ruptures from an aneurysm. The haemorrhage may be intracerebral or occur in the subarachnoid space [16]. Although several studies have reported circadian variation of cerebral ischemia, and meta-analysis also supports the presence of a circadian pattern in the onset of stroke, with a significantly higher risk in the morning, it has not yet been confirmed whether the same is true in the context of our population. The study aims to find out the relation of circadian variation of stroke.

METHODOLOGY & MATERIALS

This cross-sectional study was conducted at the Department of Medicine and Neurology in Sylhet MAG Osmani Medical College Hospital, Bangladesh. During six months from May 17, 2017, to November 16, 2017, 100 stroke patients were enrolled and analyzed. The ethical approval was obtained from the institution's ethics committee. All physicians of medicine units and the neurology department will be aware of the study. Informed written consent was obtained from the patients or guardians after the disease process, and the purpose of the study was fully explained to them.

Inclusion criteria:

- All patients with clinical and imaging diagnoses of stroke with definitive time of onset were included in the study.

Exclusion criteria:

- Patient with transient ischemic attack.
- History of the previous stroke.
- Patient with a history of head injury.
- Those who refused to enroll in this study.

Stroke onset was the earliest time the patient or witness noticed definite neurological symptoms or signs. The time was obtained from the history given by the patient, relative or bystander. The time of stroke onset was ascertained to the nearest possible hour. Patients who had had a stroke during sleep were assigned the time when they went to bed. The time of arrival was recorded as 24-hour time.

The classifiable onset time was divided into one of four six-hour intervals: 00.01-06.00 (night), 06.01-12.00 (morning), 12.01-18.00 (afternoon) and 18.01-24.00 (evening). Demographic data, risk factors and comorbidities (hypertension with or without previous treatment), diabetes mellitus, dyslipidemia, coronary artery disease (CAD), atrial fibrillation (AF), smoking status, history of previous transient ischemic attack (TIA) or stroke.) was recorded for each patient. A CT scan of the brain was done and reported to stratify the patient into each category of ischemic and hemorrhagic stroke. Fasting plasma glucose and lipid profile were measured, and for two h PG during an OGTT, 75 glucose was administrated orally, and plasma glucose was measured two h later.

Data analysis and interpretation:

Data processing and analysis were done using SPSS (statistical package for social sciences), version 22. The test statistics used to analyze the data are descriptive statistics, the Chi-square ($\chi 2$) Test and Student's t-test. Data presented on the categorical scale was compared between groups using the hi-square ($\chi 2$) Test. In contrast, the data presented on the continuous scale was compared between groups using the student's t-test. The significance level was set at 0.05 for all analytical tests, and $p<0.05$ was considered significant. The summarized data was presented in the form of tables.

RESULT

Table 1 delineates the age distribution of the study population, comprising 100 individuals. Notably, 50% fall within the 60-70 age range, with participants aged 50-59 and 70-75 contributing 20% each, and those aged 45-49 contributing 10%. Moving to Figure 1, which illustrates the gender distribution, a significant majority of participants are male, constituting 76%, while females represent the remaining 24%. Figure 2 provides insights into residents' distribution, revealing that 62% reside in urban areas, and 38% come from rural environments. Table 2 outlines occupational status, with businessmen constituting the largest group at 35%, followed by housewives at 24%, and service holders and laborers at 15% each. The study population's smoking status, depicted in Figure 3, indicates that 58% are smokers, and the remaining 42% are non-smokers. Table 3 details stroke types, with 57% being ischemic strokes, 39% hemorrhagic strokes, and 4% subarachnoid hemorrhages. In Table 4, hypertension is the predominant risk factor at 72%, followed by smoking at 44%, hyperlipidemia at 28%, diabetes mellitus at 26%, atrial fibrillation at 23%, and ischemic heart disease at 17%. Finally, Table 5 illustrates the distribution of stroke symptom onset times, emphasizing that 46% occur between 06:01 and 12:00, 19% from 00:00 to 06:00, 24% from 12:01 to 18:00, and 11% from 18:01 to 24:00. Collectively, these findings provide a comprehensive overview of the demographic, lifestyle, and clinical characteristics of the study population, forming a foundation for further analysis and interpretation.

Table 1: Age distribution of the study population (N=100).

Age range (year)	Frequency (n)	Percentage (%)
45-49	10	10.00
50-59	20	20.00
60-70	50	50.00
70-75	20	20.00

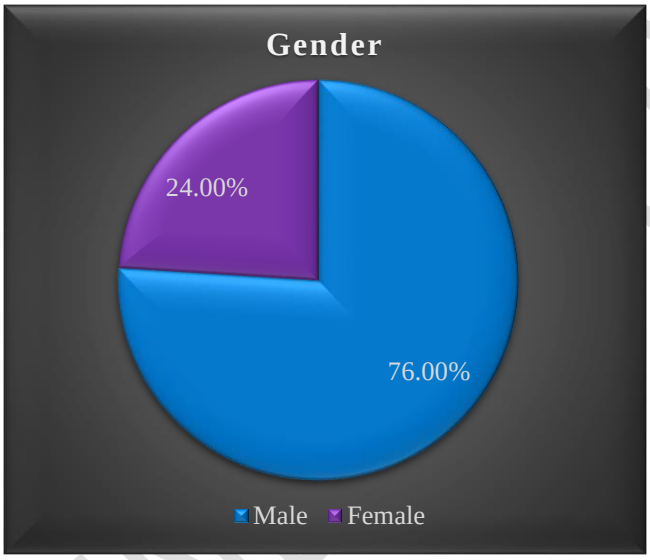

Figure 1: Gender distribution of the study population (N=100).

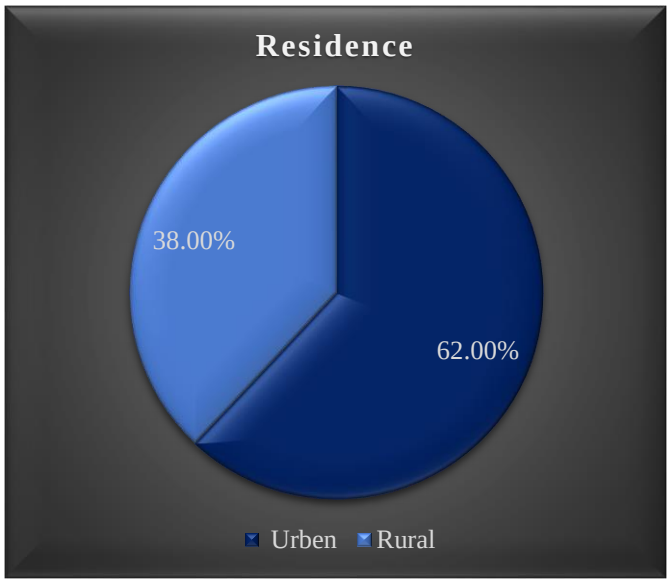

Figure 2: Study resident status.

Table 2: Occupational status of the study population (N=100).

Occupation	Frequency (n)	Percentage (%)
Businessman	40	35.00
Labor	15	15.00
Service holder	15	15.00
Farmer	1	1.00
Housewife	24	24.00
Others	5	5.00

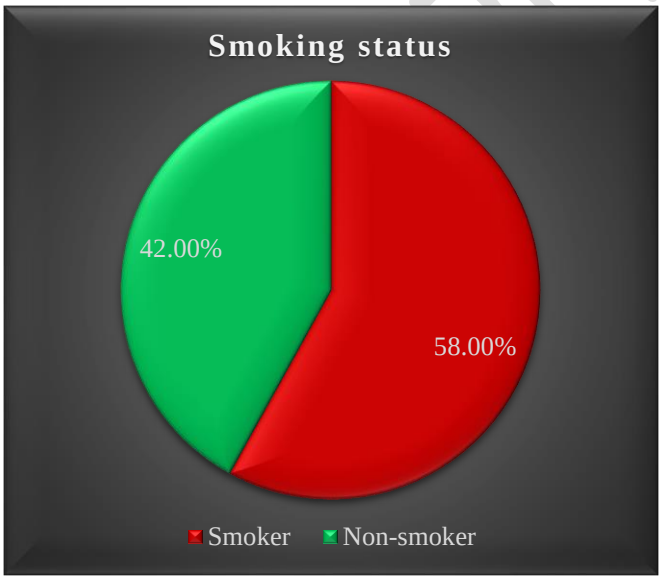

Figure 3: Smoking status of the study population (N=100).

Table 3: Type of stoke of the study population (N=100).

Type of stroke	Frequency (n)	Percentage (%)
Ischemic stroke	57	57.00
Hemorrhagic stroke	39	39.00

SAH	4	4.00

Table 4: Risk factor for stoke patients (N=100).

Risk factor	Frequency (n)	Percentage (%)
Hypertension	72	72.00
Smoking	44	44.00
Hyperlipidemia	28	28.00
Diabetes mellitus	26	26.00
Atrial fibrillation	23	23.00
Ischemic heart disease	17	17.00

Table 5: Symptom onset time of stoke.

Time	Frequency (n)	Percentage (%)
00:00-06:00	19	19.00
06:01-12:00	46	46.00
12:01-18:00	24	24.00
18:01-24:00	11	11.00

DISCUSSION

Stroke is the third leading cause of death and primary cause of adult disability worldwide. Data show that stroke onset is not random during 24 hours but has a characteristic distribution. The clinical onset of myocardial infarction and stroke occurs more frequently in the early morning [17]. In this study, we analyzed the relation of circadian variation of stroke patients. The majority of the patients in this study were above 60 years old. In the present study, the frequency of stroke increases with increasing age. A study showed that 34% of patients in the sixth decade and 27% in the seventh decade have aged 26-84 years [18]. In a study of 51 patients with cerebrovascular disease, the age range was 17 to 84 years, with the majority of the patients between 50 and 60 years [19]. In another study, the patients' highest percentage (37.51%) was in the sixth decade [20]. So, these observations conform to that of the present study. In this study, 75% of stroke patients were male, and 25% were female. The ratio is 3:1. In a study, it was found male-female ratio was 3.21:1 [21]. Another study showed different findings where the male-female ratio was 4:1 [22]. In another study, the male-female prevalence was 1.24:1. The male-female ratio is higher in our country than in Western countries. In this study, most patients (62%) came from urban areas. This does not signify the preponderance of stroke in urban areas because it may reflect the poor communication in the rural area and also superstition about the management of stroke patients in the rural area. In the present study, 58% of the patients were smokers. It is the third most typical risk factor. In a study of British doctors, a significant correlation between smoking and mortality from cerebral thrombosis was evident after 20 years of follow-up [23]. In the Medical Research Council trial (1985) placebo group, the risk of stroke was doubled among smokers [24]. Yano et al. and Donnan et al. had shown a strong association between cigarette smoking and stroke [24]. This study shows that 57% were ischemic stroke, 39% were hemorrhagic stroke, and 4% were SAH. A Pakistani study on 800 patients, where 55% of cases were of ischemic stroke, 41% were of intracranial bleeding, and 4% were of subarachnoid haemorrhage, showed a circadian variation in the onset of acute ischemic stroke [25]. This study shows that hypertension (72%) emerges as the most critical risk factor for stroke. The result correlates with other studies where hypertension was the most critical risk factor [25-27]. Smoking (44%) appears as the second most important risk factor of ischemic stroke in this study, which correlates with a study that found smoking to be a vital risk factor for SAH and cerebral infarction [28]. Another study demonstrated that cigarette smoking might modulate stroke risk through a gene-environment interaction V. M Bhat and Walker et al. [29-31]. also suggested a strong relationship between cigarette smoking and causation of acute ischemic stroke. In this study, the maximum number of acute ischemic strokes occurred between 6:01 and 12:00 hours. Two peaks of onset of symptoms were observed, first during 6:01-12:00 hours in 46% of patients and the second between 12:01- 18:00 hours in 24%. The results of this study are to the findings of the majority of previous reports available in the literature, with the highest incidence of stroke occurrence during the morning (6.01–12.00) and the minimum occurrence during the night (00.01–06.00) for all stroke types (IS, HS and SAH) [32-35]. Some authors observed a single peak [22-25] in the morning, including Elliot's meta-analysis, and others showed a double peak pattern of circadian variation for all or someone types with a second small peak in the afternoon [33,34,36]. Their methodology included the division of the 24-hour daytime in more than four intervals (six 4-hour, twelve 2-hour or

even 24 1-hour) because the patients' data from their Stroke Registries were more accurate and permitted an increased precision in the stroke onset time determination.

Limitations of the study: While this study provides valuable insights into the circadian variation of stroke in a tertiary-level hospital in Bangladesh, several limitations should be acknowledged:

1. The sample size of 100 stroke patients may only partially represent the diverse population and the prevalent risk factors in the country.
2. Reliance on patient or witness-reported onset times introduces the possibility of recall bias. The study's cross-sectional design limits the establishment of causation, and the exclusive focus on a single hospital may not capture variations in circadian patterns across different regions.
3. The study needs long-term follow-up data, hindering a comprehensive analysis of stroke outcomes and recurrence.

CONCLUSION AND RECOMMENDATIONS

This study confirmed the circadian variation of onset occurrence for all stroke subtypes. Stroke occurred most frequently at times of 06:00-12:00 and smallest amount frequently at times of 18:01-24:00. The primary common subtype was an ischemic stroke, then hemorrhagic stroke and only a few subarachnoid haemorrhages (SAH). By the circadian variation of stroke onset, strategies to control blood pressure and coagulation can positively impact stroke prevention. Future large-scale studies are required to explore these findings.

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Ethical approval: *The study was approved by the Institutional Ethics Committee.*

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