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# Association Between Circadian Onset Time and Clinical Outcomes in Acute Ischemic Stroke

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## ABSTRACT

**Introduction:** It has been demonstrated that the circadian rhythm influences the onset of ischemic stroke, however its impact on treatment strategies and clinical outcomes remains uncertain. The aim of this study was to investigate the association between the circadian timing of stroke onset and vascular risk profiles, stroke severity, prognosis, and treatment methods in patients with acute ischemic stroke.

**Methods:** We retrospectively reviewed acute ischemic patients with stroke admitted to our University Hospital Stroke Unit (August 2017-December 2023). Patients were grouped by stroke onset time: Group 1 (wake-up/00:00-awakening), Group 2 (awakening-12:00), Group 3 (12:00–18:00), and Group 4 (18:00–00:00). Demographic and clinical characteristics, and acute stroke treatments, including intravenous thrombolysis (IV tPA) and thrombectomy were recorded. Outcomes were assessed using the modified Rankin Scale (mRS) at the first follow-up. Following univariate analyses, multivariable binary logistic regression identified independent predictors of IV tPA administration.

**Results:** Among 1047 admissions, 751 patients met the inclusion criteria. There were 212 patients (28.2%) in Group 1, 231 patients (30.8%) in Group 2, 158 patients (21%) in Group 3, and 150 patients (20%) in Group 4. The prevalence of hypertension was significantly lower in Group 3 (p=0.0027). Multivariable analysis identified higher admission National Institutes of Health Stroke Scale scores (OR 1.202, p <0.001) and stroke onset time as independent predictors of IV tPA administration. Group 1 patients were significantly less likely to receive IV tPA (p <0.001), with no significant differences in etiology, mortality, or follow-up mRS scores.

**Conclusion:** This study shows that IV tPA is less frequently administered to patients who experienced ischemic stroke during sleep. This finding highlights the need for tools that can enable earlier detection of stroke occurring during sleep. Despite the differences in IV tPA administration rates, stroke onset time did not significantly impact overall patient prognosis, including mortality and functional outcomes.

**Keywords:** Circadian rhythm, prognosis, stroke, stroke timing, thrombolytic therapy.

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## INTRODUCTION

Stroke is the second leading cause of death worldwide and a one of the major causes of long-term disability. Ischemic stroke accounts for approximately 80% of all stroke cases (1). Circadian rhythm refers to physiological processes that follow a 24-hour cycle and plays a significant role in cardiovascular events, including ischemic stroke. Both endogenous factors (such as blood pressure fluctuations and autonomic nervous system activity) and exogenous factors (such as physical activity and stress) may contribute to temporal variations in stroke onset (2).

A meta-analysis conducted in 1998 revealed an increased risk of ischemic stroke in the morning compared with other periods of the day (3). Other studies over the past 20 years have provided additional information, particularly highlighting differences in various etiologic subtypes and indicating that ischemic strokes frequently occur in the morning (06:00–

### Highlights

- **Stroke onset shows clear circadian patterns, peaking in the morning hours.**
- **Night-time or wake-up strokes receive IV thrombolysis less often.**
- **Afternoon strokes show lower hypertension rates.**
- **Despite acute treatment differences, circadian onset did not affect outcomes.**
- **Stroke timing may reflect comorbidities, pointing to circadian influences.**

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12:00) or upon waking, while those that occur during sleep tend to be more severe and result in higher mortality rates (3–5).

This study aimed to investigate the association between the circadian timing of stroke onset and vascular risk profiles, stroke severity, prognosis, and treatment methods in patients with acute ischemic stroke.

## METHODS

The patients who were admitted with acute ischemic stroke between August 2017 and December 2023 to the stroke unit were included in the study. The hospital database was screened to identify the patients diagnosed with acute ischemic stroke who met the inclusion criteria. Patients were categorized into four groups based on the time of stroke onset: Group 1=onset from 00:00 until awakening or noticed upon awakening; Group 2=onset between awakening and 12:00; Group 3=onset between 12:00 and 18:00; and Group 4=onset between 18:00 and 00:00.

Patient records were reviewed to collect demographic data, risk factors, National Institutes of Health Stroke Scale (NIHSS) scores at admission, presence of early neurological deterioration, and modified Rankin Scale (mRS) scores at discharge. Whether thrombolytic and/or thrombectomy treatment was administered was also recorded. Stroke subtypes were classified using the automated "Causative Classification System" (CCS) (6). Stroke severity was assessed based on NIHSS scores at admission, and functional outcomes were determined by mRS scores at the first follow-up. The patients with follow-up mRS >3 were considered to have poor functional outcome.

This study was approved by the ethics committee of our institution (date: 20.08.2024, decision number: I07–552–24).

### Statistical Analysis

Statistical analysis was conducted using IBM Statistical Package for Social Sciences (SPSS) program version 27.0 (IBM Corp., Armonk, NY, USA). For categorical variables, descriptive statistics were expressed as frequencies (n) and percentages (%). For continuous variables, normally distributed parameters were summarized as mean ± standard deviation, whereas non-normally distributed parameters were summarized as median (min–max). The normality of continuous variables were assessed using visual methods (histograms and probability plots) and analytical methods (Kolmogorov-Smirnov and Shapiro-Wilk tests). Chi-square test was used to compare categorical variables. Parametric tests (Student's t-test, ANOVA) were used for continuous variables with a normal distribution, whereas non-parametric tests (Mann-Whitney U test, Kruskal-Wallis test) were used for variables that do not follow a normal distribution. The relationship between continuous variables was evaluated using Pearson's correlation test for normally distributed variables and Spearman's correlation test for non-normally distributed variables. Logistic regression analysis was used to identify independent variables in order to determine risk factors for the dependent variables with two categories, and to identify statistically significant predictors. All analyses were conducted at a 95% confidence level, and p-values <0.05 were considered statistically significant.

## RESULTS

Among 1047 patients admitted with acute ischemic stroke between August 2017 and December 2023, a total of 751 patients with documented stroke onset times were included in this retrospective analysis. According to the stroke onset time, 212 patients (28.2%) were assigned to Group 1, 231 (30.8%) to Group 2, 158 (21.0%) to Group 3, and 150 (20.0%) to Group 4. Demographic and clinical characteristics of the patients, as well as their follow-up outcomes are summarized in Table 1. The rate of tPA administration was significantly lower in Group 1 compared to the other groups (adjusted residual=–4.5, p <0.001, Bonferroni-corrected). Although tPA administration was observed more frequently in strokes occurred between awakening and 12:00 (Group 2), this difference did not reach statistical significance after Bonferroni correction (adjusted residual=2.5, p=0.01; Table 1). No significant difference was observed between the groups in terms of hospital mortality rates and mRS scores at follow-up (p>0.05, Table 1).

The prevalence of hypertension was significantly lower in Group 3 and this difference remained statistically significant after Bonferroni correction (adjusted residual=–3.0, p=0.0027). Although the prevalence of active cancer was higher in the same group (p=0.029; Table 1), no individual time interval reached statistical significance after Bonferroni correction.

Multivariable binary logistic regression analysis demonstrated that stroke onset time and admission NIHSS score (OR 1.202, 95% CI 1.149–1.258, p <0.001) were independent predictors of IV tPA administration. Compared to patients in Group 1 (00:00-awakening), the likelihood of receiving IV tPA was significantly higher in Group 2 (OR 5.427, 95% CI 2.478–11.886, p <0.001), Group 3 (OR 5.094, 95% CI 2.231–11.630, p <0.001), and Group 4 (OR 3.444, 95% CI 1.474–8.043, p=0.004) (Table 2).

## DISCUSSION

In this retrospective study, we investigated the association of stroke onset time with vascular risk profiles, stroke severity, prognosis and acute treatment modalities. We found that ischemic stroke was most frequent between waking-up and 12:00 (Group 2). Patients in Group 1 were found to receive IV tPA significantly less frequently than those in the other stroke onset groups. We also observed a lower prevalence of hypertension in patients with acute ischemic stroke that started in the afternoon (Group 3). However, no association was observed between the circadian time of stroke onset and mortality rates or functional outcomes at follow-up.

Most of the previous studies have consistently reported a morning peak in stroke incidence. In a study of 1.167 ischemic patients with stroke from four academic hospitals, stroke onset was most frequent between 10:00 and 12:00. The incidence then gradually declined throughout the afternoon and early evening, with the lowest likelihood of stroke onset occurring in the late evening, before midnight (7). Liou et al. analyzed 274 patients and found that ischemic stroke incidence was highest between 4:00 and 8:00 am (4). In a meta-analysis by Elliott et al., the highest stroke incidence was reported between 06:00 and 12:00 (3). Similarly, Fodor et al. investigated 1.083 patients with stroke and observed a peak between 06:00 and 12:00 across all subtypes of stroke (5). Raj et al. also reported a significant increase in stroke onset between 06:00 and 11:59, with the lowest incidence in the evening (8). Ripamonti et al. further confirmed the predominance of both ischemic and hemorrhagic stroke in the morning, and have suggested that risk factors such as hypertension and atrial fibrillation influenced the time of stroke onset (9). On the other hand, Menéndez Albarracín et al. reported that ischemic stroke was evenly distributed throughout different periods of the day (10). In our study, consistent with most of the previous findings, ischemic strokes were most frequently occured between waking up and 12:00.

The potential pathophysiological mechanisms underlying the circadian variation of ischemic stroke are multifactorial. The early hours of the day are characterized by increased sympathetic activity, elevated blood pressure, a higher incidence of cardiac arrhythmias, enhanced platelet aggregability, and decreased fibrinolytic activity. Together, these

**Table 1.** Demographic and clinical characteristics of patients according to ischemic stroke onset time

| | Group 1 00:00-Wake up n=212 | Group 2 Wake up-12:00 n=231 | Group 3 12:00–18:00 n=158 | Group 4 18:00–00:00 n=150 | P value |
|---|---|---|---|---|---|
| **Age, year, mean ± SD** | 69.43±13.73 | 72.19±12.76 | 70.97±13.18 | 66.99±13.67 | 0.762 |
| **Sex (Female), n (%)** | 92 (43.4) | 116 (50.2) | 67 (42.4) | 63 (42) | 0.292 |
| **TIA/Ischemic stroke, n (%)** | 9/203 (4.2/95.8) | 31/200 (13.4/86.6) | 11/147 (7/93) | 11/139 (7.3/92.7) | 0.004 |
| **Season of stroke onset** | | | | | |
| **Spring, n (%)** | 55 (25.9) | 62 (26.8) | 43 (27.2) | 36 (24) | 0.116 |
| **Summer, n (%)** | 44 (20.8) | 45 (19.5) | 45 (28.5) | 35 (23.3) | |
| **Autumn, n (%)** | 52 (24.5) | 58 (25.1) | 46 (29.1) | 44 (22) | |
| **Winter, n (%)** | 61 (28.8) | 66 (28.6) | 24 (15.2) | 35 (23.3) | |
| **Risk factors** | | | | | |
| **Hypertension, n (%)** | 160 (75.5) | 173 (74.9) | 102 (64.6)* | 119 (79.3) | **0.02** |
| **Diabetes mellitus, n (%)** | 75 (35.2) | 82 (35.5) | 60 (38) | 67 (44.7) | 0.255 |
| **Atrial fibrillation, n (%)** | 28 (13.2) | 32 (13.9) | 12 (7.6) | 21 (14) | 0.232 |
| **Hyperlipidemia, n (%)** | 59 (27.8) | 46 (19.9) | 30 (19) | 27 (18) | 0.071 |
| **CAD, n (%)** | 60 (28.3) | 73 (31.6) | 46 (29.1) | 42 (28) | 0.847 |
| **CHF, n (%)** | 21 (9.9) | 22 (9.5) | 11 (7) | 20 (13.3) | 0.313 |
| **Active cancer history, n (%)** | 4 (1.9) | 7 (3) | 11 (7) | 2 (1.3) | **0.029** |
| **Previous stroke/TIA history, n (%)** | 41 (19.3) | 59 (25.5) | 27 (17.1) | 35 (23.3) | 0.177 |
| **Smoking, n (%)** | 17 (8) | 25 (10.8) | 14 (8.9) | 9 (6) | 0.419 |
| **Admission NIHSS mean ± SD median (min-max)** | 4.99±4.07 4 (0–20) | 5.21±4.59 4 (0–21) | 5.30±4.77 4 (0–24) | 5.57±4.84 4 (0–24) | 0.687 |
| **IV tPA, n (%)** | 9 (4.2)* | 41 (17.7) | 28 (17.7) | 21 (14) | **<0.001** |
| **Mechanical thrombectomy, n (%)** | 4 (1.9) | 16 (6.9) | 7 (4.4) | 9 (6) | 0.08 |
| **Early neurological deterioration, n (%)** | 16 (7.5) | 21 (9.1) | 19 (12) | 16 (10.7) | 0.499 |
| **Hospital death, n (%)** | 16 (7.5) | 34 (14.7) | 20 (12.7) | 19 (12.7) | 0.123 |
| **Follow-up mRS mean ± SD median (min-max)** | 2.01±2.1 1 (0–6) | 2.51±2.38 1 (0–6) | 2.02±2.12 1 (0–6) | 2.37±2.25 1 (0–6) | 0.107 |
| **Follow-up mRS >3, n (%)** | 44 (20.7) | 66 (28.6) | 28 (17.7) | 33 (22) | 0.057 |
| **Follow-up mortality, n (%)** | 35 (16.5) | 49 (21.2) | 25 (15.8) | 25 (16.7) | 0.453 |
| **Follow-up time (months) mean ± SD median (Min-Max)** | 6.81±13.12 3 (0–120) | 5.34±8.61 2 (0–84) | 5.67±8.42 3 (0–90) | 5.21±7.90 2 (0–72) | 0.487 |
| **CCS classification, n (%)** | | | | | |
| **LAA** | 49 (23.1) | 62 (26.8) | 43 (27.2) | 51 (34) | 0.138 |
| **CAE** | 84 (39.6) | 67 (29) | 56 (35.4) | 46 (30.7) | |
| **SAO** | 31 (14.6) | 26 (11.3) | 13 (8.2) | 15 (10) | |
| **Other causes** | 10 (4.7) | 14 (6.1) | 10 (6.3) | 10 (6.7) | |
| **Undetermined causes** | 38 (17.9) | 62 (26.8) | 36 (22.8) | 28 (18.7) | |

*: The asterisk indicates the group responsible for the statistically significant difference after Bonferroni correction ($\alpha$=0.05/8=0.00625); CAD: coronary artery disease; CHF: congestive heart failure; NIHSS: the National Institutes of Health Stroke Scale; IV tPA: intravenous tissue plasminogen activator; mRS: modified Rankin score; CCS: Causative Classification System; LAA: Large-artery atherosclerosis; CAE: Cardio-aortic embolism; SAO: Small artery occlusion; SD: standard deviation; TIA: transient ischemic attack.

**Table 2.** Multivariable binary logistic regression analysis for factors associated with IV tPA administration

| | OR | 95% CI | p value |
|---|---|---|---|
| **Stroke onset time** | | | **<0.001** |
| **Group 1 (Reference)** | 1.000 | - | **-** |
| **Group 2** | 5.427 | 2.478–11.886 | **<0.001** |
| **Group 3** | 5.094 | 2.231–11.630 | **<0.001** |
| **Group 4** | 3.444 | 1.474–8.043 | **0.004** |
| **Admission NIHSS** | 1.202 | 1.149–1.258 | **<0.001** |
| **Age (years)** | 0.984 | 0.966–1.001 | 0.072 |
| **Hypertension** | 1.049 | 0.608–1.810 | 0.864 |
| **Active cancer history** | 1.269 | 0.418–3.857 | 0.674 |

CI: confidence interval; IV tPA: intravenous tissue plasminogen activator; NIHSS: National Institutes of Health Stroke Scale; OR: odds ratio.

physiological shifts create a prothrombotic environment that not only triggers acute thromboembolic events but may also impact overall stroke outcomes (1,3,4).

A large multicenter analysis from the SITS-ISTR (Safe Implementation of Treatments in Stroke-International Stroke Thrombolysis Register) examined potential within-day and weekly patterns in IV tPA administration and their impact on patient outcomes. Consistently, IV tPA treatments were administered significantly more during day hours, defined as 08:00–19:59, compared to night hours, 20:00–07:59 (11). In our study, the higher rate of IV tPA administration during the daytime was likely attributable to greater clarity regarding symptom onset time.

Although the landmark WAKE-UP (2018) and EXTEND (2019) trials shifted the stroke treatment paradigm from a time-based to a tissue-based approach using advanced imaging, the widespread clinical implementation of these protocols was not immediate (12,13). Consequently, continued adherence to traditional time-based guidelines for patients treated before the release of updated tissue-based recommendations likely contributed to the significantly lower rate of IV tPA administration among wake-up patients with stroke.

Previous studies show that thrombectomy procedures are most frequently performed between early morning and noon, while reaching their lowest frequency overnight (14–17). Wang et al. reported that acute ischemic patients with stroke with an onset between 00:00 and 12:00 who underwent endovascular thrombectomy had a higher proportion of favorable outcomes at 3 months (14). Similarly, other studies have demonstrated that circadian variation is associated with clinical outcomes, and that patients with stroke onset in the afternoon or late evening have worse functional outcomes after endovascular thrombectomy (15–17). In our study, no significant association was found between post-thrombectomy prognosis and stroke onset time groups. Although not statistically significant, the lower rate of thrombectomy in wake-up strokes may be related to exceeding the therapeutic window. This finding should be interpreted cautiously given the limited number of patients who underwent thrombectomy.

Liou et al. reported that stroke onset between 04:00 and 08:00 was associated with favorable functional status, whereas onset between 20:00 and 24:00 was linked to poorer functional outcomes (4). Conversely, in our study population, the proportion of patients with a follow-up mRS score >3 was higher among those with stroke onset between awakening and 12:00, albeit not statistically significant.

Hypertension is the most common modifiable risk factor for stroke and exhibits its own circadian variation, with a pronounced morning blood pressure surge linked to increased stroke risk (18,19). Interestingly, the higher incidence of active cancer among patients with afternoon-onset stroke, coupled with a lower prevalence of hypertension and atrial fibrillation in this group, suggests that stroke in cancer patients may arise from distinct pathophysiological mechanisms. Hypercoagulability, endothelial dysfunction, systemic inflammation, and altered activity-rest cycles in this population may influence the temporal patterns of thromboembolic events (20). To the best of our knowledge, the relationship between cancer-related ischemic stroke and circadian rhythm remains largely unexplored, presenting a potential area for future research.

The principal limitations of this study are its single-center setting and retrospective design. Additionally, the lower rate of IV tPA administration in wake-up strokes likely reflects both the uncertainty of symptom onset timing and the lack of routine tissue-based selection criteria during the study period.

In conclusion, our study, in line with most previous research, demonstrated that ischemic strokes most frequently occur between awakening and midday. However, in contrast to several other studies, we did not observe a significant effect of stroke onset time on mortality rates and functional outcomes. Additionally, we found that patients experiencing wake-up stroke were less likely to receive IV tPA, highlighting the need for optimized systems to overcome this barrier and the implementation of the tissue-based approach in routine practice. The timing of ischemic stroke onset may be influenced by different comorbidities and stroke etiologies. These findings should be further validated in prospective, multicenter studies with larger sample sizes.

**Ethics Committee Approval:** This study has been approved by the Ethics Committee of Ankara University Faculty of Medicine. (date: 20.08.2024, decision number: I07–552–24).

**Informed Consent:** Due to the retrospective nature of the study, the requirement for informed consent was waived.

**Peer-review:** Externally peer-reviewed.

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**Conflict of Interest:** The authors declared that there is no conflict of interest.

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