

**FACTORS LEADING TO DELAY IN THROMBOLYTIC THERAPY IN PATIENTS WITH ACUTE ISCHEMIC STROKE: A HOSPITAL-BASED CROSS-SECTIONAL STUDY**

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ABSTRACT

Background: Acute ischemic stroke is a time-sensitive neurological emergency where early reperfusion therapy dictates clinical outcomes. Pre-hospital transit and in-hospital workflows frequently delay eligible patients from receiving timely thrombolysis. **Objective:** To identify pre-hospital and in-hospital factors associated with delay in thrombolytic therapy among patients with acute ischemic stroke. **Methods:** A hospital-based cross-sectional study was conducted at Dr. RKGMC & Hospital, Hamirpur, Himachal Pradesh, from 1 November 2022 to 31 October 2023. A total of 122 eligible patients with acute ischemic stroke were included. Patients with age >80 years, hemorrhagic stroke, recurrent stroke, transient ischemic attack, malignant stroke, NIHSS <5 or >25, and those refusing participation were excluded. Pre-hospital and in-hospital factors associated with treatment delay were assessed. Chi-square/Fisher's exact tests and logistic regression were used for analysis. **Results:** Of 122 patients, 82 (67.2%) experienced delay and 40 (32.8%) were classified as non-delay. Delay was significantly associated with time of symptom onset ($p=0.03$), location of onset ($p=0.01$), and mode of transfer. In-hospital delays were also strongly associated with treatment delay. Door-to-attend time >15 minutes occurred in 39 delayed patients compared with 2 non-delayed patients ($p<0.0001$). Expert opinion taking >15 minutes occurred in 36 delayed patients and none of the non-delay group ($p<0.0001$). Radiological examination taking >25 minutes occurred in 53 delayed patients compared with 3 non-delayed patients ($p<0.0001$). Door-to-needle time was >60 minutes in 82 delayed patients compared with 3 non-delayed patients ($p<0.0001$). Logistic regression identified time of symptom onset, location of onset and mode of transfer as important pre-hospital factors, while time to expert opinion and radiological examination were important in-hospital factors. **Conclusion:** Both pre-hospital and in-hospital factors contribute substantially to delay in thrombolytic therapy. Improving stroke awareness, ambulance-based transfer, referral pathways, rapid neurological assessment, neuroimaging and implementation of a structured Code Stroke pathway may reduce treatment delays.

KEYWORDS : Acute Ischemic Stroke; Thrombolysis; Treatment Delay; Pre-Hospital Delay; Door-To-Needle Time; Stroke Awareness; India.

INTRODUCTION

Stroke remains a leading contributor to mortality and long-term adult disability globally [1, 2]. In acute ischemic stroke, the administration of intravenous thrombolysis is exceptionally time-critical, as the absolute therapeutic efficacy of reperfusion is highly dependent on early time-to-treatment windows [3, 4]. The long-standing clinical paradigm of "time is brain" underscores that every incremental, avoidable delay correlates with an exponential loss of salvageable neural tissue and a reduction in the potential benefits of thrombolytic therapy [5].

The workflow of hyperacute stroke management spans a vulnerable continuum. Delays can occur at multiple individual interfaces, starting with a failure of symptom recognition by the patient or bystanders, and extending through pre-hospital transportation, peripheral referral paths, triage assessment, emergency room specialist evaluation, urgent neuroimaging, and final thrombolytic administration [5–9].

Prior epidemiological studies within India indicate that poor community awareness, delayed symptom recognition, rural residence, fragmented transport systems, and initial presentations to non-stroke-ready medical clinics represent prominent causes of pre-hospital delay [6–11]. Compounding this, institutional in-hospital bottlenecks, such as prolonged time to expert specialist evaluation and delays within the radiology suite, further inflate the cumulative door-to-needle time [12–16].

These structural delays are often exacerbated by the unique geographic barriers, complex terrains, and transport limitations characteristic of mountainous populations. Consequently, evaluating localized

variables causing treatment delays is essential for constructing responsive, regionally optimized stroke pathways. This hospital-based study aims to identify the specific pre-hospital and in-hospital clinical factors associated with delays in thrombolytic therapy among patients presenting with acute ischemic stroke to a tertiary-care teaching facility in Himachal Pradesh, India.

MATERIALS AND METHODS**Study Design and Setting**

A hospital-based cross-sectional study was conducted within the emergency and neurology departments of Dr. RKGMC & Hospital, Hamirpur, Himachal Pradesh, India.

Study Period

The active study period spanned from 1st November 2022 to 31st October 2023.

Patient Selection Criteria

Patients presenting with clear signs of acute ischemic stroke who arrived within the therapeutic window for intravenous thrombolysis were systematically screened for eligibility.

Inclusion Criteria: Adult patients diagnosed with acute ischemic stroke who presented within the target thrombolytic window and provided written, informed consent for study enrolment.

Exclusion Criteria: Patients aged >80 years; cases involving haemorrhagic stroke, recurrent stroke episodes, transient ischemic attacks (TIAs), or malignant space-occupying hemispheric strokes; patients with an initial baseline National Institutes of Health Stroke Scale (NIHSS) score of <5 or >25; and cases where the patient or legal

guardian refused participation.

Following screening, a definitive sample of 122 patients was included for rigorous analysis.

Study Variables

Pre-hospital variables collected included: time of symptom onset, precise location of symptom onset, mode of emergency or private transit used, traffic-related transit delays, and onset-to-door time.

In-hospital variables captured included: door-to-attend time (time from hospital entry to initial physician evaluation), time to expert opinion (neurology or senior physician consultation), time for radiological examination (CT brain acquisition and reading), and total door-to-needle time. Demographics and cardiovascular comorbidities were also documented.

Statistical Analysis

Categorical variables were presented as absolute frequencies (n) and companion percentages (%). Differences in categorical parameters between the delay and non-delay cohorts were evaluated using the Chi-square (χ^2) test or Fisher's exact test where appropriate. Continuous variables were expressed as mean $\pm$ standard deviation (SD). Independent clinical predictors of thrombolysis delay were isolated using multivariable binary logistic regression models. Adjusted odds ratios (ORs) alongside corresponding 95% confidence intervals (CIs) were computed, with statistical significance defined a priori at a two-tailed p-value <0.05 .

RESULTS

Out of the 122 acute ischemic stroke patients evaluated, 82 (67.2%) experienced a confirmed treatment delay (door-to-needle time >60 minutes), whereas 40 (32.8%) were processed within non-delay timelines (≤ 60 minutes).

Pre-Hospital Assessment

The time and geographical location of stroke symptom onset demonstrated significant baseline correlations with subsequent management delays. Location of onset was strongly associated with delay ($p=0.01$), driven by a high rate of delays among patients experiencing symptoms at home. Time of symptom onset was also significantly associated with delay ($p=0.03$), with evening and night-time onsets exhibiting a pronounced vulnerability to prolonged transit times.

Table 1. Distribution of Patients According to Time of Symptom Onset (N=122)

Time of Symptom Onset	Delay (n=82)	Non-delay (n=40)	Total (N=122)
Morning	32	26	58
Afternoon	13	6	19
Evening	18	5	23
Night	19	3	22
Total	82	40	122
χ^2 test p=0.03			

Among patients who experienced stroke onset at home, 61 fell into the delay group compared with 37 in the non-delay group ($p=0.01$). Conversely, patient gender did not exercise a statistically significant influence on treatment delay times; 37 females were in the delay group and 17 in the non-delay group, while 45 males were in the delay group and 23 in the non-delay group ($\chi^2=0.08$, $p=0.78$).

In-Hospital Workflow Timelines

Institutional processing speeds demonstrated major imbalances between the two study cohorts.

Table 2. Comparison of in-hospital Treatment Intervals Between Delay and Non-delay Groups

In-Hospital Parameter	Delay Group (n=82)	Non-Delay Group (n=40)	p-value
Door-to-attend >15 min, n	39	2	<0.0001
Expert opinion >15 min, n	36	0	<0.0001
Radiology time >25 min, n	53	3	<0.0001
Door-to-needle ≤ 60 min, n	0	37	<0.0001
Door-to-needle >60 min, n	82	3	<0.0001
Mean door-to-attend time, min	17.43 ± 5.73	12.94 ± 3.18	<0.0001

Mean time to expert opinion, min	17.25 ± 6.14	13.00 ± 3.72	<0.0001
Mean radiology time, min	31.76 ± 8.14	24.23 ± 4.52	<0.0001

The mean door-to-attend time, time to expert specialist consultation, and radiological imaging processing durations were all significantly longer within the delayed cohort ($p<0.0001$).

Comorbidities Profile

The primary cardiovascular comorbidity isolated within the patient population was hypertension (68.85%), followed by diabetes mellitus (38.52%) and dyslipidemia (31.97%).

Table 3. Distribution of Medical Comorbidities Among Study Participants (N=122)

Comorbidity	Number (n)	Percentage (%)
Hypertension	84	68.85
Diabetes mellitus	47	38.52
Dyslipidemia	39	31.97
Coronary artery disease	34	27.87
Atrial fibrillation	25	20.49
Seizure	6	4.92
Note: Sum percentage exceeds 100% due to overlapping concurrent comorbidities within individual patients.		

Multivariable Logistic Regression Analysis

Multivariable logistic modelling for pre-hospital variables isolated time of symptom onset, location of stroke onset, and mode of transit as key clinical independent predictors of delay.

Table 4. Logistic Regression Analysis of pre-hospital Factors Associated with Treatment Delay

Variable	Odds Ratio (OR)	95% Confidence Interval (CI)	P-value
Age	0.95	0.90–1.02	0.19
Gender	1.03	0.28–3.81	0.95
Time of symptom onset	8.17	1.80–37.06	0.006
Location of onset	13.88	1.58–121.19	0.01
Mode of transfer	12.43	1.08–142.36	0.04
Traffic jam	1.63	1.03–189.59	0.05
Onset-to-door time	0.10	0.01–1.27	0.05

Table 5. Logistic Regression Analysis of in-hospital Factors Associated with Treatment Delay

Variable	Odds Ratio (OR)	95% Confidence Interval (CI)	P-value
Door-to-attend time	1.54	0.06–36.47	0.78
Time to expert opinion	7.99	1.80–37.06	0.005
Radiological examination time	13.10	0.039–25.36	0.04
Door-to-needle time	0.10	0.01–1.27	0.06

In the in-hospital multivariable logistic regression model, time to expert physician consultation (OR=7.99, 95% CI: 1.80–37.06, $p=0.005$) and radiological examination duration (OR=13.10, 95% CI: 0.039–25.36, $p=0.04$) emerged as independent institutional bottlenecks. Door-to-attend time was not statistically significant within the final regression analysis (OR=1.54, $p=0.78$).

DISCUSSION

The current study demonstrates that a substantial proportion (67.2%) of acute ischemic stroke patients experience critical delays in receiving thrombolytic therapy. Our findings show that these delays occur at both pre-hospital and in-hospital stages, creating a cumulative barrier to timely care.

Among pre-hospital factors, the location of stroke onset (OR=13.88) and the mode of transfer (OR=12.43) were strongly associated with treatment delay. These findings emphasize that the immediate circumstances at symptom onset and the subsequent transportation choice are key factors in whether a patient receives timely treatment. Delayed recognition of early stroke symptoms and a poor understanding of the urgency of hyper acute reperfusion remain major contributors to pre-hospital delays, consistent with global trends where public knowledge directly shapes presentation timelines [8, 17].

When stroke symptoms occur at home, families often adopt a "wait-and-see" approach, delaying contact with emergency services, or seek

care from local non-stroke-ready clinics, which delays appropriate referral [5, 9]. These challenges are further amplified in rural and geographically isolated settings, such as the mountainous areas of Himachal Pradesh, where distance and terrain make efficient transit difficult [6, 7].

Furthermore, our study showed a significant correlation between the time of symptom onset and treatment delay, with evening and night-time onsets experiencing a higher rate of delays. This pattern is likely due to reduced transport availability and limited healthcare access during off-hours, which aligns with findings from other regional stroke registries [10, 11]. In contrast, gender did not significantly influence delay times ($p=0.78$), suggesting that pre-hospital barriers affect the male and female populations equally in this region, which contrasts with some Western registries reporting longer delays for female patients [18].

In-Hospital Processing Bottlenecks

Once inside the hospital, significant operational gaps were observed between the delay and non-delay cohorts. Prolonged door-to-attend times (>15 minutes), delayed expert specialist evaluations (>15 minutes), and extended radiological processing (>25 minutes) were significantly more frequent in the delayed group ($p<0.0001$).

The mean radiology time was 31.76 ± 8.14 minutes in the delay group, compared to 24.23 ± 4.52 minutes in the non-delay group. Rapid neuroimaging is essential to rule out intracranial haemorrhage and identify eligible candidates for intravenous thrombolysis [3]. Delays in CT acquisition or scan interpretation create a cascading effect that extends the final door-to-needle time [12, 14].

Time to expert opinion emerged as an independent predictor of delay ($OR=7.99$, $p=0.005$). The immediate availability of a trained stroke physician or neurologist is a critical factor in efficient hyper acute stroke systems [15, 16]. Data from international registries confirm that implementing structured stroke-alert pathways reduces internal workflow friction and increases thrombolysis rates [21, 22].

A formalized "Code Stroke" system enables parallel processing, allowing emergency triage, specialist assessment, and neuroimaging to occur simultaneously rather than sequentially, which compresses door-to-needle times [24, 25].

Implications for Regional Stroke Care Systems

These findings are highly relevant for designing care pathways in mountainous regions. Improving public awareness is a necessary first step, but it must be supported by an integrated network that connects the community to a stroke-capable facility [19, 20]. A comprehensive regional stroke strategy must focus on early community symptom recognition, coordinated ambulance routing, pre-hospital notification to the receiving hospital, and standardized institutional emergency protocols [23].

Study Limitations

This study has certain limitations. It was a single-center study conducted at a tertiary facility, which may limit the generalizability of the findings to regions with different healthcare infrastructure or geography. The sample size ($N=122$) was relatively small, and retrospective data collection regarding symptom onset may introduce recall bias. Future larger, multicentre regional studies are needed to more fully evaluate stroke referral pathways across different tiers of healthcare delivery.

CONCLUSION

A high proportion of acute ischemic stroke patients experience significant delays in receiving thrombolytic therapy. Key pre-hospital factors include the time and location of symptom onset and the mode of transit, while primary in-hospital bottlenecks are the time to expert specialist opinion and radiological imaging acquisition. Improving clinical outcomes requires an integrated stroke care network that bridges community awareness, emergency transport systems, and standardized hospital protocols such as a "Code Stroke" pathway.

RECOMMENDATIONS

- Community Education:** Implement localized public health campaigns focusing on the FAST acronym to improve rapid stroke symptom recognition.
- Ambulance Coordination:** Build direct links between emergency medical dispatches and stroke centers to prioritize suspected stroke cases.

- Triage Routing:** Establish direct referral protocols bypass non-stroke-ready clinics for patients within the therapeutic window.
- Standardized Emergency Protocols:** Introduce an institutional "Code Stroke" protocol to enable parallel diagnostic workflows.
- Rapid Triage:** Ensure immediate neurological triage upon patient arrival in the emergency room.
- Priority Imaging:** Create priority access pathways for suspected acute stroke cases within the neuroimaging suite.
- Interdisciplinary Communication:** Improve real-time communication between emergency, neurology, and radiology teams.
- Quality Audits:** Perform monthly internal audits of door-to-needle times to identify and address workflow delays.
- Geographic Adaptations:** Adapt transport infrastructure to account for the unique geographic challenges of mountainous terrains.
- Multicenter Research:** Expand regional research through multicentre initiatives to optimize care networks across different healthcare tiers.

Declarations

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REFERENCES

- GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol*. 2021;20(10):795–820.
- GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death for 195 countries and territories, 1980–2017. *Lancet*. 2018;392(10159):1736–1788.
- NINDS rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;333(24):1581–1587.
- Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008;359(13):1317–1329.
- Arulprakash N, Umaiorubahan M. Causes of delayed arrival with acute ischemic stroke beyond the window period for thrombolysis. *J Family Med Prim Care*. 2018;7(6):1248–1252.
- Gurav SK, et al. Factors associated with prehospital delay in patients with acute stroke. *Indian J Crit Care Med*. 2015;19(5):265–269.
- Panwar A, et al. Factors delaying hospital arrival of patients with acute stroke. *J Clin Diagn Res*. 2017;11(12):OC01–OC05.
- Williams LS, Bruno A, Rouch D, Marriott DJ. Stroke patients' knowledge of stroke: influence on time to presentation. *Stroke*. 1997;28(5):912–915.
- Mellor RM, Bailey S, Shephard J, et al. Decisions and delays within stroke patients' pathways to emergency care: a qualitative study. *Ann Emerg Med*. 2015;65(3):279–287.
- Faiz KW, Sundseth A, Thommessen B, Rønning OM. Prehospital delay in acute stroke and TIA. *J Stroke Cerebrovasc Dis*. 2014;23(3):534–539.
- Song D, Tanaka E, Lee K, et al. Factors associated with delayed hospital arrival in patients with acute ischemic stroke. *J Stroke*. 2015;17(2):159–167.
- Mowla A, Doyle J, Shirani P, et al. Delays in door-to-needle time for intravenous thrombolysis in acute ischemic stroke. *J Neurol Sci*. 2017;376:102–105.
- Yafasova A, et al. Association between time to thrombolysis and outcomes after acute ischemic stroke. *Stroke*. 2021;52(5):1724–1732.
- Le SM, et al. Factors associated with delays in acute ischemic stroke treatment. *eNeurologicalSci*. 2020;21:100285.
- Ungerer MN, et al. Factors associated with prehospital and in-hospital delay in acute ischemic stroke. *BMC Neurol*. 2020;20(1):441.
- Sharobeam A, et al. Factors associated with delayed thrombolysis in acute ischemic stroke. *J Neurol*. 2021;268(8):2723–2734.
- Saengsuwan J, Suangpho P, Tiamkao S. Knowledge of stroke risk factors and warning signs in patients with recurrent stroke or TIA. *Neurol Res Int*. 2017;2017:8215726.
- Catangui E, et al. Factors influencing delays in stroke treatment. *Int J Nurs Clin Pract*. 2020;7:331.
- Badachi S, et al. Factors delaying thrombolytic therapy in acute ischemic stroke. *Ann Indian Acad Neurol*. 2015;18(4):415–418.
- Aloona SP, et al. Factors associated with delay in thrombolytic treatment among acute ischemic stroke patients. *Ann Int Med Den Res*. 2020;6(2):ME40–ME45.
- Nasreldin A, et al. Factors associated with pre- and in-hospital delays in intravenous thrombolysis among patients with acute ischemic stroke. *J Stroke Cerebrovascular Dis*. 2023;32(8):107190.
- Amalia L, et al. Factors associated with delayed thrombolysis among patients with acute ischemic stroke. *Front Neurol*. 2023;14:1124501.
- Anees A, et al. Factors associated with prehospital delay among patients with acute ischemic stroke. *BMC Health Serv Res*. 2024;24(1):142.
- Swedish national stroke-alert study evaluating stroke alerts, thrombolysis rates and treatment delays. *Acta Neurol Scand*. 2022;146(4):380–388.
- Code Stroke system studies evaluating strategies to reduce door-to-needle time in acute ischemic stroke. *Stroke*. 2023;54(3):715–723.