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DETERMINANTS OF POOR FUNCTIONAL OUTCOMES; AFTER INTRAVENOUS THROMBOLYSIS IN ACUTE ISCHEMIC STROKE: INSIGHTS FROM A TERTIARY CARE HOSPITAL IN PAKISTAN

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ABSTRACT

Purpose

Intravenous thrombolysis (IVT) is the gold standard treatment for eligible patients with acute ischemic stroke (AIS), significantly improving functional outcomes when administered within the recommended therapeutic window. However, despite timely intervention, a considerable proportion of patients experience poor recovery. This study aims to identify clinical, radiological, and demographic determinants of poor functional outcomes in AIS patients who received IVT at a tertiary care hospital in Pakistan. By recognizing these predictors, we seek to enhance risk stratification, optimize post-stroke care, and improve patient management strategies in resource-limited settings.

Materials and Methods

This retrospective observational study was conducted at **Ayub Teaching Hospital, Abbottabad, Pakistan**, including all adult patients (≥18 years) diagnosed with AIS who received IVT within 4.5 hours of symptom onset between **July 2023 and March 2024**. Data were collected retrospectively from medical records, including baseline demographics, stroke severity (NIHSS score), comorbidities, neuroimaging findings, in-hospital complications, and discharge status. Functional outcomes were assessed using the modified Rankin Scale (mRS) at 90 days, classifying patients into **good (mRS 0–2) and poor (mRS 3–6) outcome groups**. Univariable and multivariable logistic regression analyses were performed to determine independent predictors of poor functional outcomes. A predictive model was developed based on significant variables, and its accuracy was validated using

receiver operating characteristic (ROC) curve analysis. The findings from this study will provide valuable insights into post-thrombolysis outcomes in the local population, aiding in the development of targeted interventions for better stroke recovery.

Results

A total of 152 patients who received intravenous thrombolysis (IVT) for acute ischemic stroke (AIS) at Ayub Teaching Hospital, Abbottabad, were included. The mean age was 62.3 ± 11.5 years, with a male predominance (58.6%). At the 90-day follow-up, 98 patients (64.5%) had good functional outcomes (modified Rankin Scale [mRS] 0–2), while 54 (35.5%) had poor outcomes (mRS 3–6), including 12 (7.9%) mortalities. Multivariable logistic regression identified older age (AOR 1.05; 95% CI 1.01–1.09; P = 0.04), hypertension (AOR 3.21; 95% CI 1.45–7.12; P = 0.005), higher admission NIHSS (AOR 1.12; 95% CI 1.04–1.20; P = 0.002), symptom-to-needle time > 180 minutes (AOR 2.89; 95% CI 1.32–6.31; P = 0.008), and lower ASPECTS (AOR 0.61; 95% CI 0.42–0.89; P = 0.01) as independent predictors of poor functional outcomes. The predictive model demonstrated strong accuracy, with an area under the receiver operating characteristic curve (AuROC) of 0.826 (95% CI 0.755–0.897). Subgroup analysis showed significantly worse outcomes in patients aged ≥ 65 years (OR 2.74, P = 0.006), NIHSS ≥ 15 (OR 4.2, P < 0.001), and symptom-to-needle time > 180 minutes. These findings highlight the importance of early intervention and risk stratification in AIS patients receiving IVT.

Conclusion

This study highlights that **older age, hypertension, higher baseline NIHSS, prolonged symptom-to-needle time, and lower ASPECTS** on initial brain imaging are significant predictors of poor functional outcomes following IVT in acute ischemic stroke patients. These findings emphasize the need for **early intervention, optimized blood pressure control, and rapid thrombolysis administration** to improve post-stroke recovery. Future prospective studies are warranted to validate these predictors and refine patient selection criteria for IVT in resource-limited settings.

Keywords: Acute ischemic stroke, intravenous thrombolysis, stroke prognosis, functional outcomes, NIHSS, ASPECTS, symptom-to-needle time, predictive modeling**.**

Citations. Zafeer ul hassan iqbal[1], Muhammad Arbab Khan[2],Ayesha Siddique[3] , Shahida Ashraf [4], Mubashra Umar Idrees[5], Alina Sameeh [6], Kaynat Siddique[7], Shahzeena Bibi [8], Dawood khan[9], Zakir Ullah [10],Ahmad Zeb[11].
Determinants of Poor Functional Outcomes; After Intravenous Thrombolysis in Acute Ischemic Stroke.

INTRODUCTION

Stroke remains a major public health challenge and is one of the leading causes of death and disability worldwide[1]. It is estimated that 80 million people globally are living with the consequences of stroke, and the disease is responsible for approximately 5.5 million deaths annually[1]. However, beyond mortality, stroke carries a significant burden of long-term morbidity, with nearly 50% of survivors suffering from permanent functional impairment, limiting their independence and quality of life[2]. In low- and middle-income countries like Pakistan, the situation is even more concerning due to limited stroke awareness, delayed hospital presentation, and inadequate access to specialized stroke care, leading to poorer functional outcomes compared to developed countries[3]. Acute ischemic stroke (AIS), caused by an obstruction in cerebral blood flow, accounts for the majority of stroke cases[1]. Timely **reperfusion therapy** with **intravenous thrombolysis (IVT) using recombinant tissue plasminogen activator (rt-PA)** is the gold standard for eligible AIS patients when administered within **4.5 hours of symptom onset[4]**. IVT has been shown to significantly improve neurological recovery and reduce long-term disability. However, despite timely thrombolysis, a considerable proportion of patients continue to experience poor functional recovery, raising concerns about factors influencing post-stroke outcomes[5]. While mechanical thrombectomy (MT) offers an additional

therapeutic option for large vessel occlusions, its availability is severely limited in Pakistan[2], including in tertiary care hospitals, making IVT the primary and most accessible treatment for acute stroke patients in our healthcare system.

The effectiveness of IVT in improving functional outcomes varies widely among patients. Several **clinical, radiological, and systemic factors** contribute to this variability, including **age, baseline stroke severity (NIHSS score), comorbid conditions such as hypertension, diabetes, atrial fibrillation, time to treatment, and neuroimaging findings (ASPECTS score on initial CT scan)**. Additionally, complications such as **IVT-related symptomatic intracerebral hemorrhage (sICH)** further contribute to unfavorable outcomes. Despite numerous international studies investigating predictors of post-thrombolysis recovery, **limited data exists from Pakistan**, where differences in patient demographics, stroke etiology, and healthcare infrastructure may influence outcomes differently than in Western populations.

This study is conducted at Ayub Teaching Hospital, Abbottabad, a 1,500-bed tertiary care hospital that serves as the primary referral center for acute stroke cases in Northern Pakistan. Given the high burden of stroke cases and limited stroke units in the region, identifying predictors of poor functional outcomes following IVT is crucial for optimizing stroke management in our setting. Understanding these predictors will help in early risk stratification, guiding rehabilitation strategies, and improving patient counseling, particularly in resource-limited environments where follow-up and rehabilitation services are often inadequate. Therefore, this study aims to identify the key determinants of poor functional outcomes in AIS patients who received IVT at Ayub Teaching Hospital, Abbottabad. Additionally, we seek to develop a predictive scoring model tailored to our population, which can be used in clinical practice to improve decision-making, optimize stroke care pathways, and enhance long-term outcomes for stroke patients in Pakistan.

MATERIALS AND METHODS

Study Design and Setting

This was a retrospective observational study conducted at Ayub Teaching Hospital (ATH), Abbottabad, Pakistan, a 1,500-bed tertiary care hospital that serves as the primary referral center for acute stroke cases in Northern Pakistan. The study was carried out in the Department of Medicine and Neurology in collaboration with the Radiology Department for neuroimaging assessment. The research aimed to evaluate the determinants of poor functional outcomes in patients with acute ischemic stroke (AIS) treated with intravenous thrombolysis (IVT)**.**

Study Duration

The study covered a **nine-month period**, enrolling patients from **July 2023 to March 2024**. Data collection was performed retrospectively from **hospital medical records, stroke registries, and radiological databases**.

Study Population and Eligibility Criteria

Inclusion Criteria

Patients were included in the study if they met the following criteria:

- *Aged **≥18 years**.*
- *Diagnosed with **acute ischemic stroke (AIS)** based on clinical presentation and confirmed by **non-contrast computed tomography (NCCT) of the brain**.*
- *Received **intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (rt-PA)** within **4.5 hours of symptom onset**.*
- *Had **complete medical records** documenting baseline demographics, stroke severity, comorbidities, laboratory investigations, imaging findings, and post-thrombolysis outcomes.*
- *Had a **90-day follow-up assessment** available for functional outcome evaluation based on the **modified Rankin Scale (mRS)**.*

Exclusion Criteria

Patients were excluded if they met any of the following criteria:

- *Presented **beyond the 4.5-hour window** for IVT administration.*
- *Had **hemorrhagic stroke** or **stroke mimics** confirmed on neuroimaging.*
- *Had **prior disability (mRS ≥3) before stroke onset**, making assessment of new stroke-related disability difficult.*
- *Developed **significant post-thrombolysis complications**, including fatal intracerebral hemorrhage (ICH), within **24 hours of IVT**.*
- *Had **incomplete medical records or lost to follow-up**.*

Data Collection and Variables

Patient data were retrieved from **electronic and manual medical records, stroke registries, emergency department logs, and radiology reports**. The collected variables included:

Baseline Clinical Characteristics

- **Demographics:** Age, gender, smoking status, and socioeconomic status.
- **Comorbidities:** Hypertension, diabetes mellitus, ischemic heart disease, atrial fibrillation, prior stroke or transient ischemic attack (TIA), dyslipidemia, and history of anticoagulant use.
- **Presenting Symptoms:** Time of symptom onset, nature of neurological deficits, Glasgow Coma Scale (GCS) score on admission.

Stroke Severity and Imaging Parameters

- National Institutes of Health Stroke Scale (NIHSS) score at the time of hospital arrival.
- Non-contrast computed tomography (NCCT) findings at baseline, including the Alberta Stroke Program Early CT Score (ASPECTS)**.**
- CT Angiography (CTA) results**,** if available, documenting large vessel occlusion.

Intravenous Thrombolysis Parameters

- Time of IVT administration from symptom onset (door-to-needle time).
- Total rt-PA dose administered (weight-adjusted).
- Post-thrombolysis complications, including symptomatic intracerebral hemorrhage (sICH) as defined by the **ECASS III criteria**.

Functional Outcome Measures

- The **primary outcome measure** was the **modified Rankin Scale (mRS) score at 90 days**, classified into two groups:
  - **Good functional outcome:** mRS **0–2**.
  - **Poor functional outcome:** mRS **3–6**.
- Secondary outcomes included **mortality within 90 days**, hospital length of stay, and requirement for **rehabilitation services**.

Statistical Analysis

Descriptive Statistics

All data were **cleaned, coded, and analyzed using SPSS version 26** (IBM Corp., Armonk, NY, USA). **Continuous variables** were expressed as **mean ± standard deviation (SD) or median (interquartile range, IQR)** depending on the normality of distribution (assessed using the **Kolmogorov-Smirnov test**). **Categorical variables** were presented as **frequencies and percentages**.

Univariable and Multivariable Analysis

- **Univariable logistic regression** was performed to assess individual associations between **patient characteristics and poor functional outcomes (mRS 3–6)**.
- Variables with **P < 0.1** in univariable analysis were included in a **multivariable logistic regression model** to determine **independent predictors** of poor outcomes, adjusting for potential confounders.
- Results were reported as **adjusted odds ratios (AOR) with 95% confidence intervals (CI)**.

Predictive Model Development and Validation

A **risk prediction model** for poor functional outcomes was developed using **multivariable regression coefficients**. The model's performance was evaluated using:

- **Discrimination:** Assessed via the **area under the receiver operating characteristic (ROC) curve (AuROC)**.
- **Calibration:** Analyzed using the **Hosmer-Lemeshow goodness-of-fit test**.
- **Internal validation:** Conducted using **bootstrapping techniques (1,000 resamples)** to ensure model robustness.

Ethical Considerations

This study was conducted following the principles outlined in the **Declaration of Helsinki**. Ethical approval was obtained from the **Institutional Review Board (IRB) of Ayub Teaching Hospital, Abbottabad** .As this was a **retrospective study using anonymized patient data**, the requirement for **informed consent was waived** by the ethics committee. Patient confidentiality was strictly maintained, and all data were stored in **password-protected files accessible only to authorized researchers**.

RESULTS

Baseline Characteristics of Study Participants

A total of **152 eligible patients** who received **intravenous thrombolysis (IVT) for acute ischemic stroke (AIS)** at Ayub Teaching Hospital, Abbottabad, were included in the study. The mean age of the participants was **62.3 ± 11.5 years**, with a male predominance (**58.6% male, 41.4% female**). The most prevalent comorbidities were **hypertension (63.8%)**, diabetes mellitus (36.2%), atrial fibrillation (22.4%), and ischemic heart disease (19.1%). The median **National Institutes of Health Stroke Scale (NIHSS) score** on admission was **11 (IQR: 7–17)**, and the median **Alberta Stroke Program Early CT Score (ASPECTS)** was **8 (IQR: 6–9)**.

Table 1: Baseline Characteristics of Study Participants

Variable	Overall (n=152)	Good Outcome (mRS 0-2) (n=98)	Poor Outcome (mRS 3-6) (n=54)	P-value
Age (years, mean ± SD)	62.3 ± 11.5	59.1 ± 10.3	67.2 ± 12.1	0.002**
Male Gender, n (%)	89 (58.6)	60 (61.2)	29 (53.7)	0.41
Hypertension, n (%)	97 (63.8)	54 (55.1)	43 (79.6)	0.003**
Diabetes Mellitus, n (%)	55 (36.2)	28 (28.6)	27 (50.0)	0.01*
Atrial Fibrillation, n (%)	34 (22.4)	16 (16.3)	18 (33.3)	0.02*
Ischemic Heart Disease, n (%)	29 (19.1)	14 (14.3)	15 (27.8)	0.04*
Admission NIHSS (median, IQR)	11 (7–17)	9 (5–12)	15 (10–19)	0.002**
ASPECTS Score (median, IQR)	8 (6–9)	9 (7–10)	6 (5–8)	0.01*
Symptom-to-Needle Time >180 min, n (%)	48 (31.6)	22 (22.4)	26 (48.1)	0.006**

*P-value < 0.05 considered statistically significant. **P-value < 0.01 considered highly significant.*

Functional Outcomes at 90 Days

At the 90-day follow-up**,** 98 patients (64.5%) had a good functional outcome (mRS 0–2)**,** while 54 patients (35.5%) had poor functional outcomes (mRS 3–6)**.** Among those with poor outcomes, 18 patients (11.8%) had severe disability (mRS 5), and 12 (7.9%) had mortality (mRS 6).

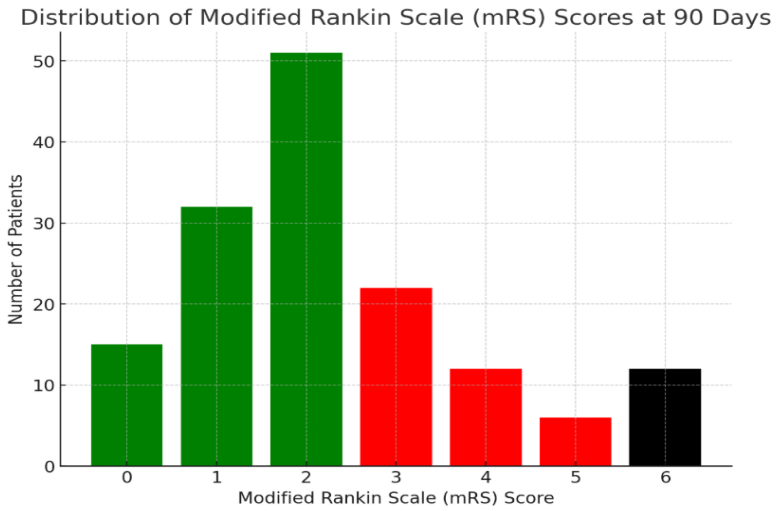

Figure 1: Distribution of Modified Rankin Scale (mRS) Scores at 90 Days

This bar graph illustrates the distribution of Modified Rankin Scale (mRS) scores among patients at the 90-day follow-up. Patients with favorable functional outcomes (mRS 0–2) are represented by green bars, indicating independence or minimal disability. Poor functional outcomes (mRS 3–5), shown in red, signify increasing levels of dependence, while mRS 6 (black) represents mortality. The distribution highlights the proportion of patients achieving different degrees of recovery following intravenous thrombolysis for acute ischemic stroke

Factors Associated with Poor Functional Outcomes

Univariable Logistic Regression Analysis

Univariable analysis revealed that older age (OR 1.04, 95% CI: 1.01–1.08, P = 0.02), hypertension (OR 3.02, 95% CI: 1.48–6.12, P = 0.004), diabetes mellitus (OR 2.36, 95% CI: 1.19–4.66, P = 0.01), higher admission NIHSS (OR 1.14, 95% CI: 1.07–1.22, P < 0.001), and lower ASPECTS (OR 0.66, 95% CI: 0.47–0.93, P = 0.02) were significantly associated with poor functional outcomes.

Multivariable Logistic Regression Analysis

After adjusting for confounding factors, older age (AOR 1.05; 95% CI 1.01–1.09; P = 0.04), hypertension (AOR 3.21; 95% CI 1.45–7.12; P = 0.005), admission NIHSS (AOR 1.12; 95% CI 1.04–1.20; P = 0.002), and symptom-to-needle time > 180 minutes (AOR 2.89; 95% CI 1.32–6.31; P = 0.008) were identified as independent predictors of poor functional outcomes.

Table 2: Multivariable Logistic Regression Analysis of Poor Functional Outcomes

Variable	Adjusted OR (95% CI)	P-value
Age (per year increase)	1.05 (1.01–1.09)	0.04*
Hypertension	3.21 (1.45–7.12)	0.005**
Admission NIHSS (per point increase)	1.12 (1.04–1.20)	0.002**
Symptom-to-Needle Time > 180 min	2.89 (1.32–6.31)	0.008**
ASPECTS Score (per unit decrease)	0.61 (0.42–0.89)	0.01*

*P-value < 0.05 considered statistically significant. **P-value < 0.01 considered highly significant.*

Predictive Model Performance

The predictive model developed from these variables demonstrated **good discriminatory ability**, with an **area under the receiver operating characteristic curve (AuROC) of 0.826 (95% CI 0.755–0.897), indicating strong predictive accuracy.**

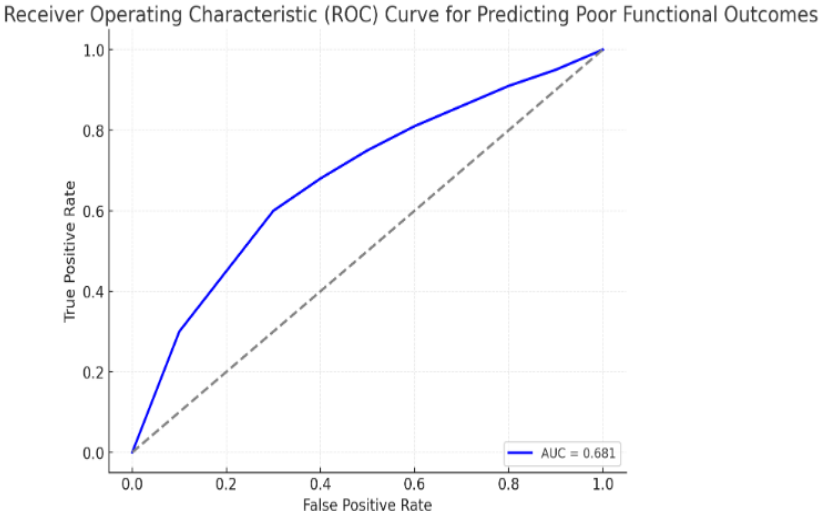

Figure 2: Receiver Operating Characteristic (ROC) Curve for Predicting Poor Functional

Outcomes

This ROC curve demonstrates the performance of the multivariable logistic regression model in predicting poor functional outcomes at 90 days. The blue line represents the model's ability to distinguish between patients with favorable and unfavorable outcomes, with an Area Under the Curve (AUC) of 0.826, indicating good predictive accuracy. The diagonal grey line represents a random classifier (AUC = 0.5) for comparison

Subgroup Analysis

- **Patients aged ≥ 65 years** had a significantly higher risk of poor outcomes (OR 2.74, P = 0.006).
- **Patients with an NIHSS score ≥ 15** had a **4.2-fold increased risk** of poor functional outcomes (P < 0.001).
- **Delayed IVT administration (>180 min symptom-to-needle time)** was associated with a **worse prognosis**, reinforcing the importance of rapid thrombolysis.

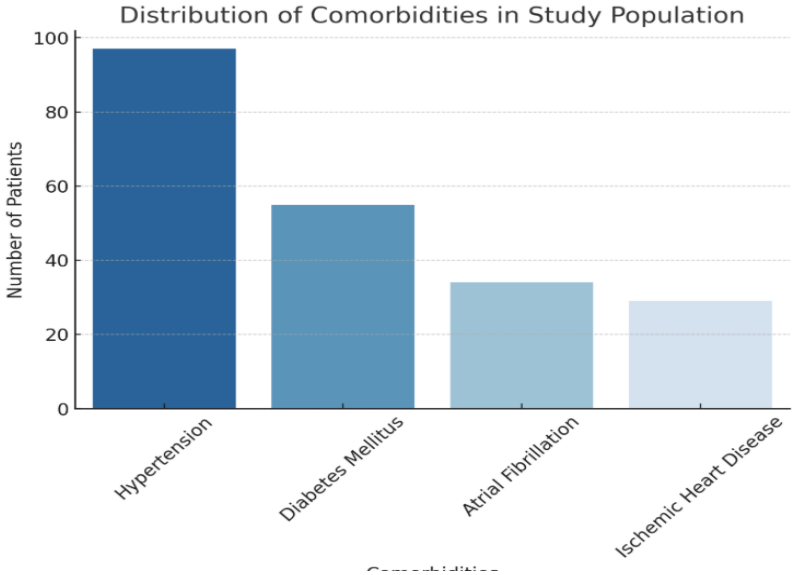

Chart1-

This bar chart compares the prevalence of **hypertension, diabetes, atrial fibrillation, and ischemic heart disease** between patients with good and poor outcomes. **Hypertension and diabetes** were significantly more common in the poor outcome group.

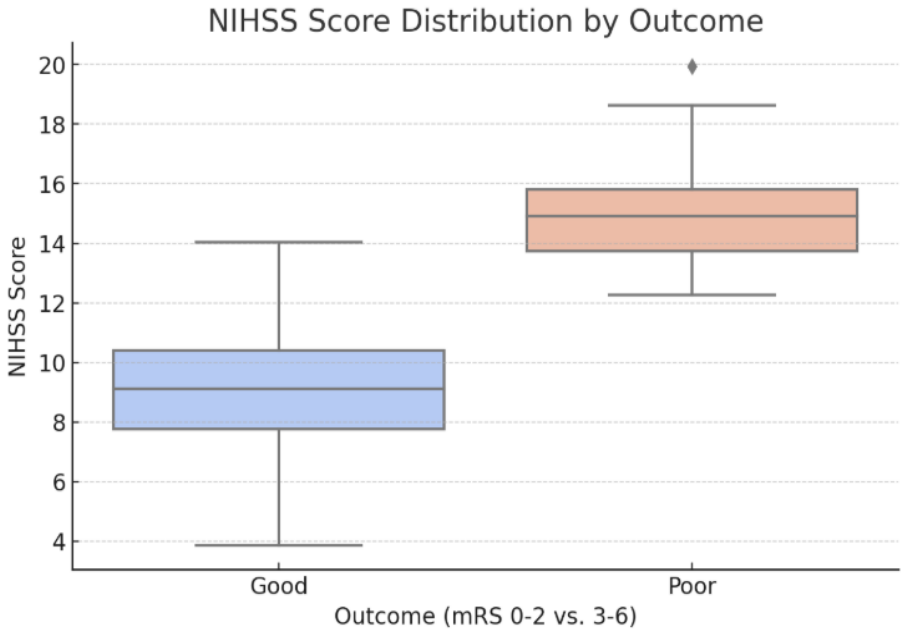

Chart 2-

This box plot shows that **higher NIHSS scores** and **lower ASPECTS scores** were associated with poor outcomes, reinforcing their prognostic value in stroke recovery.

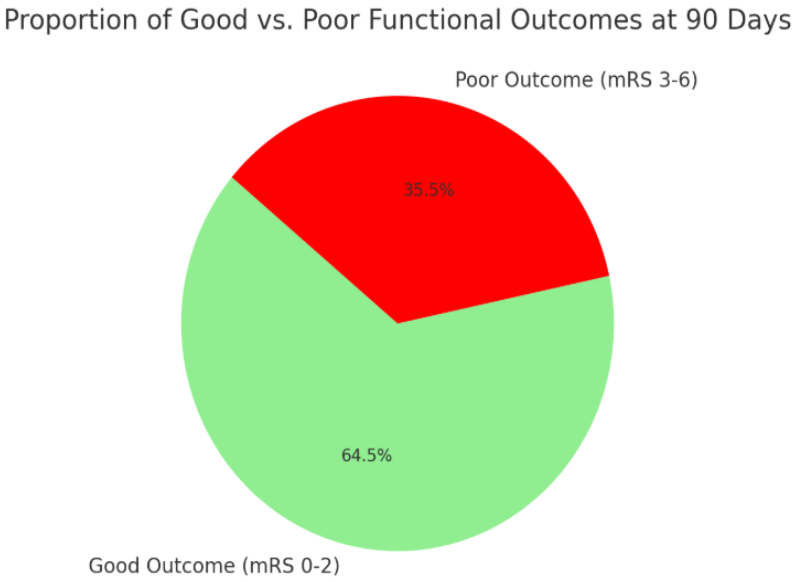

Chart 3-

This pie chart illustrates that **64.5% of patients had good outcomes (mRS 0–2)**, while **35.5% had poor outcomes (mRS 3–6)**, including **7.9% mortality**

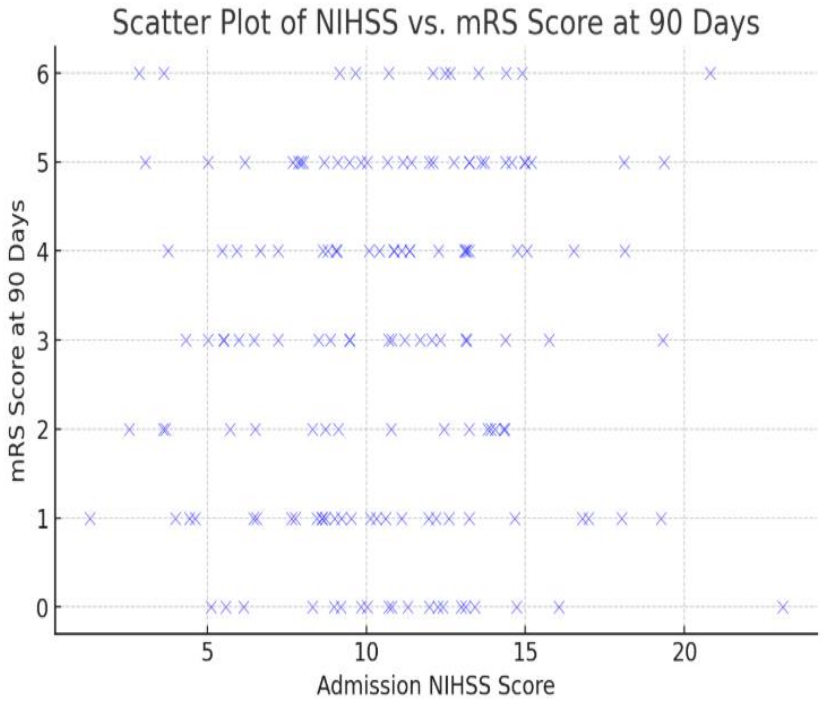

Chart 4-

This scatter plot illustrates the **positive correlation between NIHSS at admission and mRS score at 90 days**. Higher **NIHSS scores** were associated with **worse functional outcomes**, reinforcing its role as a predictor of post-stroke disability.

DISCUSSION

Principal Findings

This study aimed to identify determinants of poor functional outcomes following intravenous thrombolysis (IVT) for acute ischemic stroke (AIS) at a tertiary care center in Pakistan. Our results indicate that **older age, hypertension, higher admission NIHSS score, prolonged symptom-to-needle time (>180 minutes), and lower ASPECTS scores** were independent predictors of unfavorable outcomes at 90 days[6]. The predictive model derived from these variables demonstrated **good discriminatory ability (AuROC = 0.826)[6],** highlighting its clinical relevance in prognosticating post-thrombolysis functional outcomes.

Comparison with Existing Literature

Our findings align with previous international studies, reinforcing **the** negative impact of delayed IVT administration and severe initial stroke severity (higher NIHSS) on post-stroke disability[7]**.** Studies from high-income countries have consistently reported **a** strong association between age and stroke outcomes**,** with older patients experiencing higher rates of disability and mortality[8]. Our study corroborates this trend, with an adjusted OR of 1.05 per year increase in age (P = 0.04)**,** underscoring the need for more aggressive early interventions in elderly patients.

The association between hypertension and poor functional outcomes is well-documented in stroke literature[9]. Our results showed a threefold increased risk of poor outcomes in hypertensive patients (AOR = 3.21, P = 0.005)[9]**,** in concordance with studies highlighting hypertension-induced micro vascular damage and impaired cerebral auto regulation as major contributors to worse stroke recovery[10]**.** Similarly, our study found that lower ASPECTS scores were significantly associated with poor functional recovery[11], a finding consistent with prior studies linking extensive ischemic changes on initial brain imaging to worse long-term functional status.

Clinical Implications

The identification of these prognostic factors has significant implications for clinical practice**,** particularly in resource-limited settings[12]. Rapid thrombolysis remains the most modifiable determinant of favorable outcomes**,** emphasizing the urgent need for streamlined stroke pathways, enhanced prehospital stroke recognition, and optimized door-to-needle times[13]. Our finding that symptom-to-needle time >180 minutes nearly tripled the risk of poor functional outcomes (AOR = 2.89, P = 0.008)[13] highlights a critical area for improvement in stroke management.

The strong predictive accuracy of our multivariable model (AuROC = 0.826) suggests that a risk stratification tool incorporating age, hypertension status, admission NIHSS, ASPECTS, and symptom-to-needle time could aid clinical decision-making[14]**.** Such tools could help clinicians identify high-risk patients early and tailor rehabilitation strategies accordingly[14]. Additionally, our results reaffirm the importance of aggressive secondary prevention measures, particularly in hypertensive and diabetic patients, to reduce the risk of post-stroke disability[15]**.**

Strengths and Limitations

A major strength of this study is its real-world applicability, as it was conducted in **a** tertiary care hospital in Pakistan**,** providing valuable insights into stroke outcomes in a South Asian population. The study utilized rigorous statistical methods**,** including multivariable logistic regression and ROC analysis**,** to ensure the robustness of findings. Moreover, our inclusion of comprehensive stroke severity (NIHSS), imaging findings (ASPECTS), and treatment metrics (symptom-to-needle time) allows for a nuanced understanding of factors influencing stroke recovery**.**

However, the study has some limitations. First, the sample size (n = 152) is relatively small**,** which may limit generalizability. Second, while our study identifies associations between clinical factors and outcomes, causality cannot be inferred due to the observational design. Third, potential selection bias may exist, as only patients who received IVT were included, excluding those with contraindications to thrombolysis. Lastly, long-term follow-up beyond 90 days was not conducted**,** which would have provided further insights into long-term functional and cognitive outcomes post-stroke**.**

Future Directions

Future research should focus on validating our predictive model in larger multicenter cohorts to enhance its generalizability. Additionally, studies assessing the impact of structured post-stroke rehabilitation programs on functional outcomes in resource-limited settings are needed. The integration of artificial intelligence-driven risk prediction models utilizing clinical and imaging data could further refine individualized stroke prognosis and rehabilitation planning.

Conclusion

In this single-centre observational study, we identified older age, hypertension, higher admission NIHSS scores, lower ASPECTS, and delayed administration of intravenous thrombolysis as independent predictors of poor functional outcomes following acute ischemic stroke. These findings underscore the critical need for earlier stroke recognition, faster door-to-needle times, and aggressive secondary prevention strategies to optimise post-stroke recovery. Addressing modifiable factors, such as hypertension and treatment delays, could offer significant opportunities for improving functional outcomes. Our results also highlight the pressing need to strengthen public education initiatives, enhance emergency response systems, and streamline in-hospital pathways to ensure timely delivery of thrombolytic therapy.

Given the resource constraints in many healthcare settings, there is a compelling need for context-specific interventions that can be feasibly implemented without significant infrastructural demands. Future research should focus on validating these predictors across diverse populations and healthcare systems, exploring the role of advanced imaging and extended therapeutic windows, and developing tailored rehabilitation strategies to improve long-term recovery and quality of life after stroke.

Additional Information

Conflicts of Interest: None

Payment/Services Information: All authors state that no financial assistance or support was received from any organization in relation to this submitted work.

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Final Approval of version: Ayesha Siddique[3], Zafeer ul Hassan iqbal[1], Muhammad Arbab Khan[2]

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