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Association between Glycosylated Hemoglobin on Outcome of Patient with Acute Ischemic Stroke Treated with Thrombolysis

Mohammad Yousuf Ali[1], Aminur Rahman[2], Bikash Chandra Paul[3], Syed Md. Asadul Hoque[4], Kazi Ismat Zakia[5]

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Key words:
Glycosylated Hemoglobin, HbA1c, Thrombolysis, Acute Ischemic Stroke

Abstract:

Background: *Elevated glycated haemoglobin (HbA1c) levels have been associated with poor outcomes in stroke patients, but evidence of its impact on the efficacy of intravenous thrombolysis (IVT) remains conflicting. This study aimed to evaluate the impact of admission glycemic status, as reflected by HbA1c, on clinical outcomes following IVT in acute ischemic stroke.* ***Methods:*** *This single-center cohort study was conducted at National Institute of Neurosciences & Hospital (NINS) from January 2024 to December 2024 included 118 hyperacute ischemic stroke patients treated with intravenous thrombolysis using rtPA. Baseline demographics, comorbidities, NIHSS, and laboratory parameters including HbA1c were recorded. Patients were stratified into normal, prediabetic, and diabetic groups based on HbA1c. Outcomes were assessed by NIHSS at 24 hours and Day 7, and by mRS on Day 7. Statistical analyses included Chi-square tests, multinomial, and binary logistic regression to evaluate predictors of outcome.* ***Results:*** *The study was predominantly male (73.7%) with a mean baseline NIHSS of 9.43±3.905. Prediabetic and diabetic patients had significantly poorer neurological improvement compared to normal HbA1c patients, in 59.1% vs. 75% of cases (p=0.035) and 52.9% vs. 75% of cases (p=0.035), respectively. Multinomial regression analysis revealed that for every 1% increase in HbA1c, odds of stable vs. improved outcome were increased by 30% (OR=1.30, p=0.034) and worsened vs. improved outcome by 72% (OR=1.72, p=0.005). Age and baseline NIHSS were also independent predictors of outcome, while hypertension was not significantly related.* ***Conclusion:*** *Elevated HbA1c levels are independently related to poor neurological outcomes following IVT in acute ischemic stroke. HbA1c may serve as a valuable prognostic marker to identify those patients at higher risk of unfavourable response to thrombolytic therapy.*

Introduction:

Stroke remains one of the leading causes of death and irreversible disability worldwide, with ischemic stroke accounting for approximately 87% of all stroke events.[1] The introduction of intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (rtPA) has revolutionised the treatment of acute ischemic stroke, improving outcomes significantly when administered within the therapeutic window.[2] Yet, though uniform protocols are established, post-IVT outcomes show great variation, inferring the involvement of

1. Junior Consultant (Medicine), National Institute of Neuroscience Hospital, Agargaon, Dhaka, Bangladesh.
2. Professor, Department of Neurology, Sir Salimullah Medical College, Dhaka- 1100, Bangladesh.
3. Registrar, Dept of medicine, Jessore Medical college, Jessore , Bangladesh.
4. Registrar, Department of Radiotherapy, Dhaka Medical College Hospital, Dhaka , Bangladesh.
5. Medical officer, Sreenagar Health Complex, Munshiganj , , Bangladesh.

Correspondence: Dr. Mohammad Yousuf Ali, Junior Consultant (Medicine), National Institute of Neuroscience Hospital, Agargaon, Dhaka, Bangladesh. Email: yousufssmc@gmail.com

multiple modifiable and non-modifiable determinants in response to treatment. Glycemic control has emerged as a potential key determinant of stroke outcome. Acute admission hyperglycemia and even chronic dysglycemia, as reflected by elevated glycated haemoglobin (HbA1c) levels, have been associated with poorer prognosis in patients with stroke.[3] HbA1c is a good marker of mean blood glucose concentrations over the past 2-3 months, offering pre-stroke evidence on glycemic control that cannot be provided by point-of-care measurements.[4] The association between admission glycemic status and outcomes following IVT in acute ischemic stroke has been a subject of growing awareness. Bruno et al. reported that admission of hyperglycemia can lower the effectiveness of thrombolytic treatment, perhaps by mechanisms including increased blood-brain barrier disruption, enhanced inflammatory responses, and exacerbated oxidative stress.[5] Raised blood glucose has been associated with a higher risk of symptomatic intracerebral haemorrhage (sICH), a feared thrombolysis complication.[6] However, the distinction between acute stress-induced hyperglycemia and chronic hyperglycemia, as indicated by HbA1c, remains unclear. Although diabetes mellitus is a recognised risk factor for stroke and unfavourable outcomes, emerging evidence indicates that prediabetic conditions, defined by HbA1c between 5.7% and 6.4%, can also be detrimental to stroke recovery.[7] Maida et al. documented that the interaction between acute hyperglycemia and chronic glycemic control in influencing thrombolytic therapy responses is a multifaceted relationship that requires more investigation. Another study by Gray et al. reported that this correlation has yielded inconsistent findings, with some revealing that elevated HbA1c is predictive of functional disability and death following IVT[8], while Lee et al. showed that the finding has no such significant relation [9]. Such inconsistencies can be attributed to variations in study designs, the use of varying definitions of poor outcomes, and the heterogeneity of the populations studied. Our study aimed to comprehensively evaluate the association between admission glycemic status, defined by HbA1c, and clinical outcomes of patients treated with IVT for hyperacute ischemic stroke. Our goal is to try to make the prognostic value of admission HbA1c clearer in such patients by stratifying the patients based on HbA1c value and analysing functional outcome, death, and the incidence of complications. Clarification of pre-stroke glycemic control effect on IVT efficacy and safety would inform more individualised management for acute stroke care, possibly optimising patient selection for thrombolytic therapy and developing adjunct therapies to maximiseoutcomes. Moreover, confirmation of HbA1c as a prognostic factor can enable risk stratification and aid clinical decision-making in the hyperacute stroke setting, ultimately determining better patient outcomes.

Methods:

This single-center cohort study was conducted at National Institute of Neurosciences & Hospital (NINS) from January 2024 to December 2024 included 118 hyperacute ischemic stroke patients treated with intravenous thrombolysis (IVT) using recombinant tissue plasminogen activator (rtPA). All eligible patients were admitted within the therapeutic window and fulfilled the established criteria for thrombolysis. Demographic and clinical data, including age, sex, vascular risk factors, comorbidities, presenting symptoms, and baseline stroke severity, were systematically recorded. Stroke severity at admission was assessed using the National Institutes of Health Stroke Scale (NIHSS). Laboratory investigations, including random blood sugar, serum creatinine, electrolytes, lipid profile, and glycated haemoglobin (HbA1c), were performed for all participants. HbA1c levels were categorised into three groups: normal (<5.7%), prediabetic (5.7–6.4%), and diabetic (≥6.5%). Radiological evaluation with CT/MRI brain was performed to confirm the diagnosis and exclude hemorrhagic stroke or contraindications.

Short-term outcomes were evaluated at two specific time points: at Day 1 (24 hours after thrombolysis) and at Day 7 of admission. Neurological status was re-assessed with NIHSS at both intervals. Improvement was defined as a reduction of ≥4 points in NIHSS from baseline, stable outcome as a change of <4 points, and worsened outcome as any increase in NIHSS score. Functional outcome was assessed at Day 7 using the Modified Rankin Scale (mRS), with scores of 0–2 considered favourable (indicating functional independence) and scores of 3–6 classified as unfavourable outcomes.[10]

Data were analysed using SPSS version 26. Continuous variables were presented as mean ±

SD and categorical variables as frequencies and percentages. Baseline characteristics were compared across HbA1c groups using Chi-square tests. Multinomial logistic regression was performed to identify predictors of short-term neurological outcomes, with improved outcome as the reference category. Binary logistic regression was used to determine predictors of unfavourable functional outcome (mRS 3–6). Results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs), and $p<0.05$ was considered statistically significant. Forest plots were generated to illustrate regression findings.

Results:

Table I illustrates the sex and age distribution of the 118 study participants. The majority of the patients were middle-aged to elderly, with over 73% belonging to the age group 41-70 years old. The age group most represented was age 51-60 (27.1%), followed by the ages 41-50 (26.2%). Only 2.5% were young adults (18-30), but 9.3% were over the age of 70. Most of the population within the study were male (73.7%), whereas the females represented just 26.3% of the participants.

Table I : Demographic Characteristics of the Study Population (N = 118)

Characteristic	(n)	(%)
Age in years		
18–30	3	2.5%
31–40	16	13.5%
41–50	31	26.2%
51–60	32	27.1%
61–70	25	21.1%
> 70	11	9.3%
Sex		
Male	87	73.7%
Female	31	26.3%

Table II summarizes the most frequent presenting symptom was motor deficit (64.4%), followed by difficulty with speech (40.67%) and facial involvement (17.8%). In terms of comorbidities, hypertension was present in 59.3% of patients, and 30.5% had diabetes mellitus. Ischemic heart disease was less common (6.77%), and 28.8% were without comorbidities.

Table II : Clinical Presentation of the Study Population Based on The Admission (N = 118)

Characteristic	(n)	(%)
Presenting symptoms*		
Motor Deficit	76	64.40%
Speech Difficulty	48	40.67%
Facial Involvement	21	17.8%
History of comorbidities*		
Hypertension	70	59.3%
Diabetes Mellitus	36	30.5%
Ischemic Heart Disease	8	6.77%
Others	14	11.86%
None	34	28.8%

*There were multiple responses

Table 3 denotes the baseline stroke severity by NIHSS (National Institutes of Health Stroke Scale) score. NIHSS scores were a mean of 9.43 (±3.905), indicating moderate stroke severity on average. The majority of the patients (75.4%) presented with moderate stroke severity (NIHSS 6-14), followed by 13.5% with mild strokes (NIHSS 0-5), and 11% with severe strokes (NIHSS >14). This distribution suggests that the majority of patients in this study came in with moderate impairment.

Table III : Baseline Stroke Severity of the Study Population by NIHSS (N = 118)

NIHSS score	Value	
Mean ± SD	9.43±3.905	
Severity category	(n)	(%)
Mild (0–5)	16	13.5%
Moderate (6–14)	89	75.4%
Severe (> 14)	13	11%

Table 4(A) examines the relationship between HbA1c and the outcomes of the nervous system at 24 hours after thrombolysis. Patients were categorized into three groups: normal (<5.7%), prediabetes (5.7-6.4%), and diabetes (e"6.5%). The best outcomes occurred in the normal group with 65.0% improvement, compared with 50.0% for the prediabetes and diabetes groups. The worst worsening was noted in the normal group (10.0%), whereas prediabetes and diabetes had a higher

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worsening rate (15.9% and 11.8%, respectively). This was significant statistically (p=0.048). Table VII(B) takes into account day-7 responses, for which improvement trend was more robust, with 80.0% improvement of the normal group, compared to 65.9% for prediabetes and 61.8% for diabetes. Worsening was least in the normal group (2.5%), greatest in the diabetic group (14.7%), with significant p-value of 0.037. Table VII(C) indicates the opposite pattern between day 7 functional independence and HbA1c, with 75.0% of the normal group achieving functional independence against 56.8% in prediabetes and 47.1% in diabetes. Poorer outcomes with higher HbA1c were identified with a significant p-value of 0.029.

TableV(A) presents multinomial logistic regression analysis to identify independent predictors of neurological outcome, with improvement (e"4 NIHSS improvement) as the reference. HbA1c was an independent predictor with a 1% increase in HbA1c having 30% higher odds of good outcome (OR 1.30, 95% CI 1.02-1.66, p=0.034) and 72% higher odds of poor outcome (OR 1.72, 95% CI 1.18-2.52, p=0.005). Age and baseline NIHSS were independent predictors, and hypertension correlated not at all. Binary logistic regression for day 7 functional dependence against independence is presented in Table 8(B) and demonstrates that for each 1% increase in HbA1c, there are 55% increased odds of being functionally dependent (OR 1.55, 95% CI 1.12-2.14, p=0.008). Age and baseline NIHSS severity also independently forecasted functional dependence, with higher age and stroke severity correlated with worse outcomes. Hypertension did not predict.

Table IV: Association between HbA1c Levels and Outcomes After Thrombolysis (N = 118)

Table 4 (A): Assessment of severity of stroke by NIHSS in Day-1 (24 Hours)

HbA1c Group	Improved (≥4) n (%)	Stable (<4) n (%)	Worsened n (%)	p-value
Normal (<5.7%)	26 (65.0%)	10 (25.0%)	4 (10.0%)	
Prediabetes (5.7–6.4%)	22 (50.0%)	15 (34.1%)	7 (15.9%)	
Diabetes (≥6.5%)	17 (50.0%)	13 (38.2%)	4 (11.8%)	
Total	65 (55.1%)	38 (32.2%)	15 (12.7%)	0.048

Table 4 (B): Assessment of severity of stroke by NIHSS in Day-7 (24 Hours)

HbA1c Group	Improved (≥4) n (%)	Stable (<4) n (%)	Worsened n (%)	p-value
Normal (<5.7%)	32 (80.0%)	7 (17.5%)	1 (2.5%)	
Prediabetes (5.7–6.4%)	29 (65.9%)	11 (25.0%)	4 (9.1%)	
Diabetes (≥6.5%)	21 (61.8%)	8 (23.5%)	5 (14.7%)	
Total	82 (69.5%)	26 (22.0%)	10 (8.5%)	0.037

Table 4 © : Day-7 Functional Outcome by Modified Rankin Scale (mRS)

HbA1c Group	Favourable (mRS 0–2) n (%)	Unfavourable (mRS 3–6) n (%)	p-value n (%)
Normal (<5.7%)	30 (75.0%)	10 (25.0%)	
Prediabetes (5.7–6.4%)	25 (56.8%)	19 (43.2%)	
Diabetes (≥6.5%)	16 (47.1%)	18 (52.9%)	
Total	71 (60.2%)	47 (39.8%)	0.029

Table 5(A): Multinomial Logistic Regression for Predictors of Short-Term Neurological Outcome after Thrombolysis (Reference: NIHSS Improvement ≥4)

Predictor	Outcome	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
HbA1c (per 1% increase)	Stable vs Improved	1.30	1.02 – 1.66	0.034
	Worsened vs Improved	1.72	1.18 – 2.52	0.005
Age (per year)	Stable vs Improved	1.02	0.99 – 1.05	0.160
	Worsened vs Improved	1.05	1.01 – 1.09	0.014
Baseline NIHSS (per point)	Stable vs Improved	1.12	1.03 – 1.21	0.006
	Worsened vs Improved	1.28	1.12 – 1.47	0.001
Hypertension (Yes vs No)	Stable vs Improved	1.22	0.58 – 2.55	0.590
	Worsened vs Improved	1.75	0.65 – 4.72	0.260

Table 5(B): Binary Logistic Regression for Predictors of Functional Outcome (mRS 0–2 vs 3–6) at Day-7 After Thrombolysis (N = 118)

Predictor	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
HbA1c (per 1% increase)	1.55	1.12 – 2.14	0.008
Age (per year)	1.04	1.01 – 1.07	0.012
Baseline NIHSS (per point)	1.20	1.08 – 1.34	<0.001
Hypertension (Yes vs No)	1.28	0.61 – 2.69	0.510

Discussion:

This study provides strong evidence in favor of the robust correlation between elevated HbA1c and poor neurological outcome following intravenous thrombolysis in hyperacute ischemic stroke patients. Our findings show that patients with good glycemic control (HbA1c <5.7%) had significantly superior post-thrombolysis outcomes, with 75% of them experiencing worthwhile neurological improvement as opposed to just 52.9% of diabetic patients (HbA1c ≥6.5%). This association remained after adjusting for potential confounding factors, rendering HbA1c a predictor of outcome following thrombolysis independent of these factors.The pathophysiologic mechanisms underlying this correlation are multifactorial and well-illustrated in the existing literature. Hyperglycemia induces a pro-oxidative and proinflammatory state that can exert direct neuronal toxicity.[11] Furthermore, hyperglycemia-induced increase in matrix metalloproteinase-9 is capable of inducing neuronal injury by increasing cerebral edema.[12] These mechanisms collectively undermine the efficacy of thrombolytic therapy and enhance reperfusion injury. New evidence indicates that hyperglycemia aggravates ischemic stroke outcome irrespective of platelet glucose metabolism[13], pointing towards alternative pathways independent of classic vascular mechanisms.Our findings are in line with recent clinical studies investigating glycemic management in acute stroke treatment. Pre-diabetes was identified as a predictor of early poor outcome after acute ischemic stroke with the administration of IV thrombolysis|14, in agreement with our finding that even prediabetic patients (HbA1c 5.7-6.4%) exhibited worse outcomes than normoglycemic patients. Also, stress hyperglycemia has been observed to be a strong prognostic indicator of functional outcomes in intravenous thrombolysis-treated acute ischemic stroke patients[15], and this indicates the clinical utility of glycemic status in the acute stroke environment.Independent predictive validity of HbA1c in our study is of most interest. For each 1% rise in HbA1c, it independently increased the odds of stable vs improved outcome by 30% and

worsened vs improved outcome by 72%. Dose-response relation points towards an immediate pathophysiological relationship rather than mere association. HbA1c levels are an independent predictor of adverse outcome following endovascular thrombectomy[16], supporting our findings in diverse reperfusion strategies.The clinical relevance of our observation extends beyond prognostication. Presentation hyperglycemia in acute stroke increases the risk of hemorrhagic transformation with tPA treatment and is associated with poor clinical outcome, increased length of stay, increased cost, and mortality[17]. This underscores the importance of glycemic assessment in treatment decision and risk stratification in patients with acute stroke. Our demographic presentation, reflecting male predominance (73.7%) and middle-aged age at presentation, is consistent with local stroke epidemiology. The relatively younger age structure than reported in Western populations may reflect population risk and accessibility profiles for health care. The finding that hypertension did not, regardless of other variables, determine outcome, but was of high frequency (59.3%), differs from some studies but may reflect optimal regimens of blood pressure management or population effects.Increased HbA1c levels were correlated with early neurological deterioration in general[18], confirming our short-term outcome data. Diabetes mellitus and consequent chronic hyperglycemia, nonetheless, predispose to acute ischemic stroke and lead to worse clinical outcome and increased mortality[19], confirming the broader implications of chronic glycemic control.Integration of HbA1c monitoring into acute stroke pathways may enhance risk stratification and inform treatment. Targeted therapies among high-risk individuals with high HbA1c and ideal glycemic control in the setting of acute stroke need to be examined in future research. Present stroke guidelines emphasize evidence-based global care paradigms[20], further underscoring the importance of metabolic parameters in guidelines for treatment.

Limitations of the Study:

The study was limited by its single-center nature and relatively small sample size, which may impact the generalizability of the results. The study also examined only short-term outcomes and lacked long-term follow-up data to ascertain the persistence of observed associations over time.

Conclusion:

This study demonstrates that high HbA1c has a strong association with poor neurological outcome following intravenous thrombolysis in patients with hyperacute ischemic stroke. Patients with good glycemic control had considerably better recovery compared to patients with prediabetes or diabetes. Such findings confirm HbA1c as an independent prognostic factor and emphasize the supreme importance of glycemic control in acute stroke management.

Recommendations:

Multicenter trials involving larger patient numbers should determine whether interventions that attempt to optimize glycemic control pre-stroke or during stroke treatment may affectoutcomes in patients with elevated HbA1c. Additional study of the pathophysiologic mechanisms that are causative in linking hyperglycemia and adverse outcomes from stroke would be helpful for the development of targeted therapies.

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Conflict of Interest:

No author has any conflict of interest to disclose for this manuscript. The authors themselves are responsible for their ideas and views expressed in this article, which do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

Ethical Approval:

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of the National Institute of Neurosciences & Hospital. Written informed consent was taken from all the patients before taking part of the study.

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