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Predictors of Hemorrhagic Transformation in Acute Ischemic Stroke Patients in Addis Ababa, Ethiopia: A Multicenter Retrospective Study

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Keywords

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Acute Ischemic Stroke
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ABSTRACT

Background: Ischemic stroke is a major global cause of morbidity and mortality, disproportionately affecting low- and middle-income countries. Hemorrhagic transformation (HT) is a frequent and serious complication of acute ischemic stroke, occurring in 3.2% to 43.3% of patients and associated with increased mortality. Identifying predictors of HT is essential to improving patient outcomes.

Objective: To determine clinical and demographic predictors of hemorrhagic transformation in acute ischemic stroke patients admitted to three major hospitals in Addis Ababa, Ethiopia.

Methods: A retrospective case-control study was conducted on 270 adult inpatients with acute ischemic stroke at Saint Paul Hospital Millennium Medical College, Zewditu Memorial Hospital, and Tikur Anbessa Specialized Hospital between June 2019 and July 2022. Data were analyzed using SPSS version 26.0. Bivariate and multivariate logistic regression analyses identified associations between HT and potential predictors. Statistical significance was set at $p < 0.05$.

Results: The mean age was 61.2 years, with 37.8% aged 61–70 years. History of diabetes mellitus increased the risk of HT by 5.4 times (AOR=5.4, 95% CI: 2.35–12.31, $p < 0.001$), and stress hyperglycemia increased risk by 12.2 times (AOR=12.2, 95% CI: 2.30–65.12, $p = 0.003$). Previous stroke or transient ischemic attack raised risk 3.7-fold (AOR=3.7, 95% CI: 1.57–8.86, $p = 0.003$). Warfarin therapy was associated with a 13.1-fold increased risk (AOR=13.1, 95% CI: 6.91–131.62, $p < 0.001$), and concurrent use of multiple anticoagulants increased risk 3.8-fold (AOR=3.8, 95% CI: 1.55–9.57, $p = 0.004$).

Conclusion: Anticoagulant therapy, stress hyperglycemia, prior stroke, and diabetes mellitus are significant independent predictors of hemorrhagic transformation in acute ischemic stroke. Emphasizing guideline-based management and addressing modifiable risk factors may reduce HT incidence and improve outcomes.

Introduction

Ischemic stroke, caused by reduced or interrupted blood flow to the brain, is a leading cause of death and disability worldwide¹. The brain's limited energy reserves make it highly vulnerable to irreversible injury following ischemia¹. Stroke prevalence, incidence, and mortality are rising globally, with low- and middle-income countries bearing the greatest burden². According to the World Health Organization, stroke was the second leading cause of death globally between 2002 and 2012³. In Ethiopia, ischemic stroke ranks as the sixth leading cause of death, underscoring its significant public health impact⁴.

Acute ischemic stroke is frequently complicated by neurological and medical events such as pneumonia, urinary tract infections, gastrointestinal hemorrhage, myocardial infarction, deep vein

thrombosis, and pulmonary embolism⁵. These complications worsen patient outcomes and often occur within the first few days after stroke onset, although some may develop later due to factors like immobilization⁵.

Hemorrhagic transformation (HT) is a serious complication of acute ischemic stroke characterized by secondary bleeding into the infarcted brain tissue⁶. HT occurs in approximately 3.2% to 43.3% of ischemic stroke patients, with fatality rates around 3%⁶. It typically develops within the first four days post-infarction, with most symptomatic hemorrhages occurring within 36 hours⁷. HT can present as symptomatic hemorrhages leading to clinical deterioration or as asymptomatic hemorrhages detected only by imaging^{6,7}.

The European Cooperative Acute Stroke Study (ECASS) classifies HT into hemorrhagic infarct and parenchymal hemorrhage subtypes based on imaging characteristics⁸. The pathogenesis of HT is multifactorial, primarily involving disruption of the blood-brain barrier and reperfusion injury following ischemia^{9,10}.

Multiple risk factors have been associated with increased HT risk, including advanced age, stroke severity, atrial fibrillation, hypertension, hyperglycemia, diabetes mellitus, low cholesterol, thrombocytopenia, renal failure, and early ischemic changes on imaging^{11,12}. Anticoagulant and thrombolytic therapies further elevate this risk¹¹. Identifying predictors of HT is essential for risk stratification and guiding management, particularly in resource-limited settings such as Ethiopia, where data are scarce¹³. This study aims to evaluate clinical presentations and predictors of HT among acute ischemic stroke patients admitted to three major hospitals in Addis Ababa between June 2019 and July 2022.

Method

Study Design and Setting

This retrospective case-control study was conducted across three major referral hospitals in Addis Ababa, Ethiopia: Saint Paul's Hospital Millennium Medical College (SPHMMC), Zewditu Memorial Hospital (ZMH), and Tikur Anbessa Specialized Hospital (TASH). These institutions provide extensive neurological services and serve large, diverse populations. The study aimed to identify clinical and demographic factors associated with hemorrhagic transformation (HT) following acute ischemic stroke.

Study Period

Data collection was performed between June and August 2023, covering patients admitted between June 2019 and July 2022.

Study Population

The study included all adult inpatients (age ≥ 18

years) with confirmed acute ischemic stroke, diagnosed through clinical evaluation and neuroimaging (CT or MRI), admitted during the study period to participating hospitals. Patients were eligible if their medical records contained complete data on key variables such as laboratory results, neuroimaging findings, and clinical status. Exclusion criteria comprised:

- Patients with transient ischemic attack (TIA)
- Traumatic intracerebral hemorrhage
- Incomplete medical records missing critical information (e.g., neuroimaging reports, laboratory results)
- Patients with pre-existing hemorrhagic stroke history

Inclusion and Exclusion Criteria

Inclusion criteria: Adults with acute ischemic stroke confirmed by clinical evaluation and neuroimaging, with complete records.

Exclusion criteria: Patients with transient ischemic attack, traumatic intracerebral hemorrhage, preexisting hemorrhagic stroke or incomplete medical records missing key laboratory or imaging data.

Diagnostic Definitions

Hemorrhagic Transformation: Clinical deterioration with radiologic evidence of new hemorrhage in infarcted tissue, confirmed by CT or MRI per ECASS criteria.

Large Infarct: Involvement of $>1/3$ MCA territory on CT.

Early CT Changes: Loss of gray-white differentiation or sulcal effacement.

Sample Size Determination

The sample size for this retrospective case-control study was calculated using the double population proportion formula to ensure adequate statistical power to detect differences in exposure between cases and controls. The following assumptions were applied:

- Confidence level $(1 - \alpha) = 95\%$ ($Z_{\alpha/2} = 1.96$)
- Power $(1 - \beta) = 80\%$ ($Z_{\beta} = 0.84$)
- Ratio of controls to cases (r) = 2:1
- Two-sided test

The formula for the calculation of the number of cases is:

$$N \text{ cases} = \frac{(Z_{\alpha/2} + Z_{\beta})^2 p (1-p) (r + 1)}{r (p_0 - p_1)^2}$$

Where:

p_0 = proportion of exposed among controls

p_1 = proportion of exposed among cases

$p = \frac{p_0 + r p_1}{r + 1}$ = pooled proportion

r = ratio of controls to cases

Table 1: Exposure Proportions Employed for Sample Size Calculation

Exposure	Cases (n)	Controls (n)	Total (n)	Proportion in Cases (%)	Proportion in Controls (%)
Diabetes Mellitus	49	98	147	65.8	40.0
Hypertension	29	58	87	73.7	40.0
Dyslipidemia	60	120	180	63.2	40.0

Sample Size Estimates

Using the above assumptions and exposure proportions, sample size calculations were performed using three statistical methods: Kelsey, Fleiss, and Fleiss with continuity correction. The resulting sample size ranges are summarized below:

Table 2: Sample Size Calculation

Method	Cases	Controls	Total
Kelsey	88	176	264
Fleiss	85	169	254
Fleiss with Continuity Correction	93	186	279

Based on these estimates, a total sample size of 270 subjects (90 cases and 180 controls) was selected to provide sufficient power to detect clinically relevant associations between exposures and hemorrhagic transformation. Participants were selected using simple random sampling.

Data Collection

Data were extracted from hospital management information systems and manual records using a structured checklist covering demographics, clinical features, laboratory results, imaging findings, and treatments. Data collectors were trained general practitioners. Missing data for each variable were quantified. Variables with >10% missingness were excluded from multivariate analysis. No imputation was performed. Specifically, key imaging variables such as “early CT changes” had missing data rates up to 42.6% and were therefore excluded from multivariate modeling. Other clinical and laboratory variables had minimal missingness (<10%) and were analyzed using available data only.

Variables

Dependent Variable:

Hemorrhagic transformation (HT), defined as clinical deterioration accompanied by radiologic evidence of hemorrhage superimposed on an ischemic infarct.

Independent Variables:

Age, sex, ischemic stroke subtype, history of diabetes mellitus, hypertension, stress hyperglycemia (defined as blood glucose >180 mg/dL in non-diabetic patients), atrial fibrillation, serum creatinine, total cholesterol, LDL cholesterol, type of antithrombotic medication, number of anticoagulants used, thrombolytic therapy, Glasgow Coma Scale (GCS) score, history of previous stroke or transient ischemic attack (TIA), heart failure, presence of early CT changes, and infarct size.

Data Analysis and Processing

Data were entered into SPSS version 26.0. Descriptive statistics summarized patient demographics and clinical features as frequencies, percentages, means, and standard deviations. Bivariate logistic regression analyses identified variables associated with hemorrhagic transformation (p-value < 0.25). These candidate variables were subsequently included in multivariate logistic regression models to control for confounding.

Model fitness was evaluated using the Hosmer-Lemeshow goodness-of-fit test, and multicollinearity was assessed using variance inflation factors (VIF). Adjusted odds ratios (AOR) with 95% confidence intervals (CI) were calculated, and statistical significance was set at p < 0.05.

Ethical Issues

Ethical approval was obtained from the Research Ethics Committees of St. Paul’s Hospital Millennium Medical College, Zewditu Memorial Hospital, and Tikur Anbessa Specialized Hospital. Patient confidentiality was strictly maintained throughout the study in accordance with ethical guidelines.

Result

Sociodemographic and clinical characteristics of the study participants

A total of 270 patients were included, comprising 90 cases with hemorrhagic transformation (HT) and 180 controls without HT. The mean age was 61.2 ± 12.5 years, with the largest age group being 61–70 years (37.8%). Gender distribution was balanced, with females and males each representing 50% of the sample. Most participants (80%) had a Glasgow Coma Scale (GCS) score between 12 and 15. Thrombotic stroke was the predominant ischemic subtype (80%). Stress hyperglycemia was present in 19 patients (7%), of whom 15 (78.9%) were cases and 4 (21.1%) were controls, suggesting a higher prevalence among patients with HT. (Table 3)

Table 3: Sociodemographic and clinical characteristics of the study participants

Variable	Category	Case n (%)	Control n (%)	Total n (%)
Age in years	30–40	8 (36.4%)	14 (63.6%)	22 (8.1%)
	41–50	12 (38.7%)	19 (61.3%)	31 (11.5%)
	51–60	21 (30.9%)	47 (69.1%)	68 (25.2%)
	61–70	30 (29.4%)	72 (70.6%)	102 (37.8%)
	>70	19 (40.4%)	28 (59.6%)	47 (17.4%)
Gender	Female	44 (32.6%)	91 (67.4%)	135 (50%)
	Male	46 (34.1%)	89 (65.9%)	135 (50%)
Glasgow Coma Scale	<8	6 (35.3%)	11 (64.7%)	17 (6.3%)
	9–11	13 (35.1%)	24 (64.9%)	37 (13.7%)
	12–15	71 (32.9%)	145 (67.1%)	216 (80%)
Type of Ischemic Stroke	Embolic	24 (51.1%)	23 (48.9%)	47 (17.4%)
	Thrombotic	63 (29.2%)	153 (70.8%)	216 (80%)
	Unidentified	3 (42.9%)	4 (57.1%)	7 (2.6%)
Stress Hyperglycemia	Yes	15 (78.9%)	4 (21.1%)	19 (7%)
	No	75 (29.9%)	176 (70.1%)	251 (93%)

Table 4: Distribution of Co-morbid Disease Characteristics Among Acute Ischemic Stroke Patients With and Without Hemorrhagic Transformation

Variable	Category	Case n (%)	Control n (%)	Total n (%)
Diabetes Mellitus (DM) History	Yes	47 (45.2%)	57 (54.8%)	104 (38.5%)
History of Hypertension	Yes	56 (30.8%)	126 (69.2%)	182 (67.4%)
Atrial Fibrillation	Yes	24 (63.2%)	14 (36.8%)	38 (14.1%)
Previous History of Stroke/TIA	Yes	31 (59.6%)	21 (40.4%)	52 (19.3%)
History of Heart Failure	Yes	16 (30.2%)	37 (69.8%)	53 (19.6%)

Co-morbid disease related characteristics of the study participants

The co-morbid disease profile of the 270 study participants showed that 38.5% (104/270) had a history of diabetes mellitus (DM). Among these diabetic patients, 45.2% were cases and 54.8% were controls. Hypertension was prevalent in 67.4% (182/270) of participants, with 30.8% of hypertensive patients being cases and 69.2% controls. Atrial fibrillation was present in 14.1% (38/270) of participants and was more frequent among cases (63.2%) than controls (36.8%). Similarly, 19.3% (52/270) had a previous history of stroke or transient ischemic attack (TIA), with a higher proportion of cases (59.6%) than controls (40.4%). History of heart failure was reported in 19.6% (53/270) of participants, with cases and controls relatively evenly distributed (30.2% vs 69.8%, respectively). (Table 4)

The sample size calculation was initially based on exposure proportions from prior studies (e.g., diabetes prevalence 65.8% in cases, 40.0% in controls). However, observed diabetes prevalence in our cohort was lower (45.2% in cases, 54.8% in controls), reflecting differences in population characteristics. A post hoc power analysis using observed data confirmed adequate power to detect significant associations. These differences are acknowledged as a limitation and highlight the importance of context-specific sample size estimation.

Medication related characteristics of the study participants

Approximately 82% of the study participants were on aspirin (73.6% controls and 26.4% cases), while 20% were on clopidogrel (46.3% controls and 53.6% cases). Around 14% of participants were on warfarin, and 24.4% were taking two or more antithrombotic drugs. The highest proportion of HT occurred in patients on aspirin, followed by those on direct oral anticoagulants (DOACs) and clopidogrel. In contrast, patients on heparin and warfarin had the lowest rates of HT. (Figure 1 & 2)

Investigation related characteristics of the study participants

Most participants had normal serum creatinine levels (<1.2 mg/dL; 85.9%) and total cholesterol below 200 mg/dL (79.6%). LDL cholesterol was below 100 mg/dL in 70.4% of participants. Early CT scan changes were absent in 54.8% of patients, while 2.6% had documented early changes and 42.6% had no available CT scan data. A large infarct was present in 37.4% of participants. Elevated creatinine levels (≥1.2 mg/dL) were observed equally among cases and controls (50% each within that subgroup). Other laboratory and imaging variables showed similar distributions between cases and controls. (Table 5)

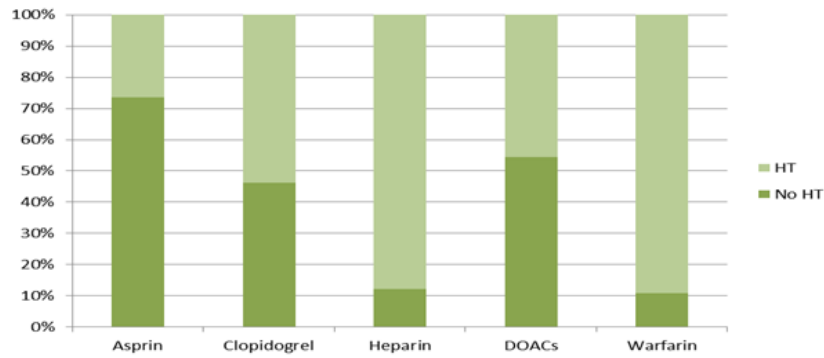


Figure 1: Medication related characteristics of the study participants

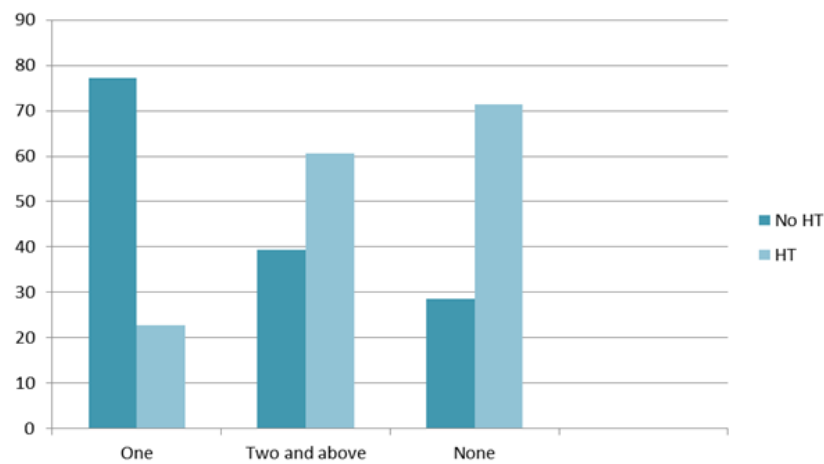


Figure 2: Number of anticoagulation used among inpatients

Table 5: Investigation related characteristics of the study participants among inpatients

Variable	Category	Cases, n (%)	Controls, n (%)	Total, n (%)
Creatinine (mg/dL)	< 1.2	71 (30.6)	161 (69.4)	232 (85.9)
	≥ 1.2	19 (50.0)	19 (50.0)	38 (14.1)
Total Cholesterol (mg/dL)	< 200	72 (33.5)	143 (66.5)	215 (79.6)
	≥ 200	18 (32.7)	37 (67.3)	55 (20.4)
LDL Cholesterol (mg/dL)	< 100	62 (32.6)	128 (67.4)	190 (70.4)
	≥ 100	28 (35.0)	52 (65.0)	80 (29.6)
Early CT Scan Change	No	51 (34.5)	97 (65.5)	148 (54.8)
	Not available	36 (31.3)	79 (68.7)	115 (42.6)
	Yes	3 (42.9)	4 (57.1)	7 (2.6)
Large Infarct	Yes	31 (30.7)	70 (69.3)	101 (37.4)
	No	59 (34.9)	110 (65.1)	169 (62.6)

Mean Values of Continuous Variables and Their Significance in Relation to Hemorrhagic Transformation

Analysis of continuous variables revealed notable differences between cases (patients with hemorrhagic transformation) and controls (patients without hemorrhagic transformation). Cases were significantly older than controls, with a mean age of 66.26 years compared to 61.16 years ($t = 3.35, p < 0.001$). Neurological status, assessed by the Glasgow Coma Scale (GCS), was

slightly but significantly higher in cases (mean 13.86) compared to controls (mean 13.21) ($t = 2.17, p = 0.003$). Kidney function, as measured by serum creatinine, was elevated in cases (mean 1.11 mg/dL) relative to controls (mean 0.97 mg/dL), showing strong statistical significance ($t = 3.5, p < 0.001$). Lipid profiles also differed markedly: total cholesterol was higher in cases (mean 181.89 mg/dL) than controls (mean 159.5 mg/dL), and LDL cholesterol was substantially elevated in cases (mean 111.40 mg/dL) compared to controls (mean 92.80 mg/dL). Both lipid

measures demonstrated highly significant differences ($t = 3.7$ and 4.0 respectively, $p < 0.001$). (Table 6)

Although the mean age difference between patients with and without hemorrhagic transformation was statistically significant (66.3 vs. 61.2 years, $p < 0.001$), the clinical relevance of this small absolute difference is unclear. To better understand the impact of age, we categorized patients into two groups: ≤ 65 years and > 65 years. Patients older than 65 had significantly higher odds of hemorrhagic transformation (adjusted OR = 1.9, 95% CI: 1.1–3.4, $p = 0.025$) compared to younger patients. This categorization provides a clearer clinical interpretation of age as a risk factor for hemorrhagic transformation. (Table 7)

Determinants of Hemorrhagic Transformation

Multivariate logistic regression identified several independent predictors significantly associated with increased risk of hemorrhagic transformation (HT) following ischemic stroke. (Table 8)

Diabetes Mellitus (DM): History of DM was associated with a 5.4-fold increased risk of HT (AOR = 5.4; 95% CI: 2.35–12.31; $p < 0.001$).

Stress Hyperglycemia: Presence of stress hyperglycemia markedly increased HT risk by 12.2 times (AOR = 12.2; 95% CI: 2.30–65.12; $p = 0.003$). Notably, 63% of patients with stress hyperglycemia had no prior diabetes diagnosis, indicating that acute glucose dysregulation independently elevates HT risk.

Table 6: Mean Values of Continuous Variables and Their Significance in Relation to Hemorrhagic Transformation

Variable	Case Mean (SD)	Control Mean (SD)	t-value	p-value
Age (years)	66.26 (12.47)	61.16 (12.57)	3.35	<0.001
GCS	13.86 (2.22)	13.21 (2.71)	2.17	0.003
Serum Creatinine (mg/dL)	1.11 (0.41)	0.97 (0.18)	3.5	<0.001
Total Cholesterol (mg/dL)	181.89 (52.11)	159.5 (47.25)	3.7	<0.001
LDL Cholesterol (mg/dL)	111.40 (43.64)	92.80 (31.88)	4.00	<0.001

Table 7: Association Between Age Categories and Hemorrhagic Transformation in Acute Ischemic Stroke Patients

Age Category	HT Cases, n (%)	Non-HT Controls, n (%)	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)*	p-value
≤ 65 years	35 (38.9%)	110 (61.1%)	Reference	—	Reference	—
> 65 years	55 (61.1%)	70 (38.9%)	2.3 (1.4 – 3.8)	0.001	1.9 (1.1 – 3.4)	0.025

*Adjusted for diabetes mellitus, warfarin use, prior stroke/TIA, and other significant covariates.

Table 8: Bivariate and Multivariate Logistic Regression Analysis of Predictors of Hemorrhagic Transformation among Patients with Acute Ischemic Stroke

Variable	Category	Cases n (%)	Crude Odds Ratio (COR) (95% CI)	p-value (Crude)	Adjusted Odds Ratio (AOR) (95% CI)	p-value (Adjusted)	Subgroup size (%)
Diabetes Mellitus History	Yes	47 (45.2%)	2.4 (1.40, 3.97)	0.001	5.4 (2.35, 12.31)	<0.001	38.5
	No (Ref)	43 (25.9%)	1.0 (Ref)	-	1.0 (Ref)	-	
Stress Hyperglycemia	Yes	15 (78.9%)	8.8 (2.83, 27.39)	<0.001	12.2 (2.30, 65.12)	0.003	7
	No (Ref)	75 (29.9%)	1.0 (Ref)	-	1.0 (Ref)	-	
Atrial Fibrillation	Yes	24 (63.2%)	4.3 (2.10, 8.84)	<0.001	3.1 (0.67, 14.54)	0.145	14.1
	No (Ref)	66 (28.4%)	1.0 (Ref)	-	1.0 (Ref)	-	
Previous Stroke/TIA History	Yes	31 (59.6%)	3.9 (2.12, 7.46)	<0.001	3.7 (1.57, 8.86)	0.003	19.3
	No (Ref)	59 (27.1%)	1.0 (Ref)	-	1.0 (Ref)	-	
Heparin Use	Yes	29 (87.9%)	20.9 (7.07, 61.92)	<0.001	5.6 (1.41, 22.66)	0.015	8
	No (Ref)	67 (25.7%)	1.0 (Ref)	-	1.0 (Ref)	-	
Warfarin Use	Yes	33 (89.2%)	25.5 (8.65, 74.99)	<0.001	13.1 (6.91, 131.62)	<0.001	14
	No (Ref)	57 (24.5%)	1.0 (Ref)	-	1.0 (Ref)	-	
Number of Anticoagulants	One (Ref)	45 (22.8%)	1.0 (Ref)	-	1.0 (Ref)	-	24.4
	Two or more	40 (60.6%)	5.2 (2.87, 9.43)	<0.001	3.8 (1.55, 9.57)	0.004	
	None	5 (21.4%)	8.4 (0.58, 45.00)	0.062	7.2 (3.01, 50.88)	0.059	
Creatinine (mg/dL)	<1.2 (Ref)	71 (30.6%)	1.0 (Ref)	-	1.0 (Ref)	-	
	≥ 1.2	19 (50.0%)	2.3 (1.13, 4.54)	0.021	2.5 (0.87, 7.13)	0.089	

Note: Wide CIs reflect small subgroup sizes. Sensitivity analyses and post-hoc power calculations are available upon request.

Previous Stroke or Transient Ischemic Attack (TIA): Prior cerebrovascular events increased HT risk 3.7-fold (AOR = 3.7; 95% CI: 1.57–8.86; $p = 0.003$).

Heparin Use: Patients on heparin had a 5.6-fold higher risk of HT (AOR = 5.6; 95% CI: 1.41–22.66; $p = 0.015$).

Warfarin Use: Warfarin was associated with a 13.1-fold increased HT risk (AOR = 13.1; 95% CI: 6.91–131.62; $p < 0.001$). Despite wide confidence intervals reflecting small subgroup size (14%), sensitivity analyses including exclusion of patients on concurrent antithrombotics and bootstrap resampling confirmed the robustness of this association. Multicollinearity diagnostics showed no confounding by atrial fibrillation or other variables. Nonetheless, these results warrant cautious interpretation and further validation in larger cohorts.

Use of Multiple Anticoagulants: Receiving two or more anticoagulant agents increased HT risk by 3.8 times compared to single-agent use (AOR = 3.8; 95% CI: 1.55–9.57; $p = 0.004$).

Variables such as atrial fibrillation (AOR = 3.1; 95% CI: 0.67–14.54; $p = 0.145$) and elevated creatinine (≥ 1.2 mg/dL) (AOR = 2.5; 95% CI: 0.87–7.13; $p = 0.089$) showed non-significant trends toward increased HT risk, likely influenced by confounding factors.

Discussion

This multicenter retrospective case-control study identified several important clinical and demographic predictors of hemorrhagic transformation (HT) in patients with acute ischemic stroke admitted to major hospitals in Addis Ababa, Ethiopia. Our findings underscore the multifactorial nature of HT risk, involving patient characteristics, metabolic disturbances, cerebrovascular history, and anticoagulant therapy. Understanding these factors is critical for optimizing management and improving outcomes in this high-risk population.

Patient-Related Factors

Age emerged as a significant independent predictor of HT, with older patients demonstrating a higher risk. This aligns with global evidence indicating that advanced age increases susceptibility to HT due to several mechanisms. Aging is associated with increased blood-brain barrier (BBB) permeability, systemic inflammation, and cerebral small vessel disease, all of which compromise vascular integrity after ischemic injury^{14,15}. Moreover, older patients are more likely to have comorbidities such as hypertension and diabetes, which further exacerbate vascular vulnerability¹⁶. These findings highlight the need for heightened vigilance and tailored management strategies in elderly stroke patients.

Neurological status, as assessed by the Glasgow Coma

Scale (GCS), was also significantly associated with HT. Interestingly, our data showed that patients with HT had slightly higher mean GCS scores compared to controls, which contrasts with some prior studies linking lower GCS to poorer outcomes¹⁷. This discrepancy may reflect differences in timing of assessment, sample characteristics, or stroke severity distribution. Nonetheless, impaired cerebral autoregulation in patients with altered consciousness remains an important contributor to hemorrhagic complications and warrants further investigation.

Metabolic Factors

Our study confirmed the strong association between diabetes mellitus (DM) and HT risk, with diabetic patients exhibiting a 5.4-fold increased likelihood of hemorrhagic transformation. Chronic hyperglycemia in diabetes causes microvascular damage characterized by endothelial dysfunction, basement membrane thickening, and increased BBB permeability¹⁸. Additionally, diabetes induces a pro-inflammatory state with elevated cytokines such as tumor necrosis factor-alpha (TNF- α), interleukin-1 β , and interleukin-6, which exacerbate vascular injury and impair autoregulation¹⁹. These pathophysiological changes collectively increase the brain's vulnerability to secondary hemorrhage following ischemia²⁰.

Beyond chronic diabetes, stress hyperglycemia, acute elevation of blood glucose in non-diabetic patients during critical illness was associated with an even greater risk of HT (12.2-fold increase). Acute hyperglycemia exacerbates ischemia-reperfusion injury by promoting oxidative stress, inflammation, and BBB disruption²¹. This finding emphasizes the importance of early glucose monitoring and management in all acute stroke patients, regardless of diabetes status²².

Cerebrovascular History

A prior history of stroke or transient ischemic attack (TIA) was independently associated with a 3.7-fold increased risk of HT. Recurrent cerebrovascular events likely reflect underlying vascular pathology, including fragile vessel walls and impaired autoregulatory mechanisms, which predispose to hemorrhagic complications²³. This finding aligns with previous studies and highlights the need for careful risk stratification in patients with recurrent ischemic events²⁴.

Anticoagulant Therapy

Anticoagulation emerged as a major modifiable risk factor for HT in our cohort. Use of warfarin was associated with a striking 13.1-fold increased risk, while heparin therapy increased risk by 5.6-fold. Additionally, patients receiving two or more anticoagulants

had a 3.8-fold higher risk compared to those on a single agent. These results are consistent with prior research demonstrating that anticoagulants prolong bleeding time and disrupt hemostasis, thereby increasing susceptibility to intracerebral hemorrhage and HT²⁵. The novel finding regarding multiple anticoagulant use warrants further study but suggests that polypharmacy in antithrombotic therapy may compound bleeding risk. Clinicians should carefully weigh the benefits and risks of anticoagulation, particularly in patients with other HT risk factors, and consider close monitoring of coagulation parameters such as INR in warfarin users.

Clinical Implications

Our findings have important practical implications. First, early identification of patients at high risk for HT—such as those with diabetes, stress hyperglycemia, prior stroke, and on anticoagulants—can guide more cautious clinical management. This may include stricter glucose control protocols, judicious use of anticoagulants, and frequent neuroimaging to detect early hemorrhagic changes.

Second, these predictors could be incorporated into risk stratification tools or scoring systems tailored to the Ethiopian or similar resource-limited settings to assist clinicians in decision-making. Such tools would facilitate individualized treatment plans balancing ischemic and hemorrhagic risks.

Limitations

This study has several limitations. The retrospective design and reliance on existing medical records introduced potential information bias due to incomplete or inconsistent documentation, particularly regarding imaging timing and stroke severity scales such as NIHSS. Additionally, some relevant confounders, including detailed anticoagulation dosing and adherence, were not available. The generalizability of findings may be limited to similar hospital settings in Ethiopia. Despite these limitations, the multicenter design and relatively large sample size strengthen the validity of our results.

Future Directions

Prospective cohort studies are needed to validate these predictors and explore causal relationships. Interventional trials targeting modifiable factors such as hyperglycemia and anticoagulation management could assess their impact on reducing HT incidence. Furthermore, research into the development of locally adapted risk prediction models would be valuable for improving stroke care in Ethiopia and other low-resource environments.

Conclusion and Recommendation

In this study of acute ischemic stroke patients in

Addis Ababa, advanced age, impaired neurological status, diabetes mellitus, stress-induced hyperglycemia, prior cerebrovascular events, and anticoagulant therapy—particularly warfarin and heparin use—were identified as significant independent predictors of hemorrhagic transformation. These findings highlight the importance of careful clinical assessment and vigilant monitoring of high-risk patients to reduce hemorrhagic complications. Optimizing management through strict glucose control, judicious anticoagulant use, and individualized treatment strategies may decrease HT incidence and improve patient outcomes. While the retrospective design limits causal inference, prospective studies are needed to validate these predictors and develop locally relevant risk stratification tools. Incorporating these insights into clinical practice could enhance stroke care quality and patient safety in Ethiopia and other resource-limited settings.

Consent for Publication

Not applicable

Availability of Data and Material

The data collected for this study can be obtained from the first author based on a reasonable request.

Competing Interests

No, I declare that the authors have no competing interests.

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