SAINT PAUL'S HOSPITAL MILLENNIUM MEDICAL COLLEGE

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St. Paul's Hospital Millennium Medical College

PREDICTOR OF HEMORRHAGIC TRANSFORMATION OF ACUTE ISCHEMIC STROKE LESION AMONG INPATIENTS AT THREE HOSPITALS IN ADDIS ABEBA, ETHIOPIA

INVESTIGATOR: BETELHEM MOLLA

February, 2024

SPHMMC, ADDIS ABABA, ETHIOPIA

St. Paul's Hospital Millennium Medical College

Graduate Study Program

Department of Public Health

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INVESTIGATOR: BETELHEM MOLLA

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A RESEARCH THESIS SUBMITTED TO THE DEPARTMENT OF INTERNAL MEDICINE AND PUBLIC HEALTH, ST. PAUL'S HOSPITAL MILLENIUM MEDICAL COLLEGE IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR SPECIALITY CERTIFICATE IN INTERNAL MEDICINE.

February, 2024

SPHMMC, ADDIS ABEBA, ETHIOPIA

St. Paul's Hospital Millennium Medical College

Graduate study program

Name of investigator	Dr Betelhem Molla
Full title of the research project	Predictor of hemorrhagic transformation of acute ischemic stroke lesion among inpatient at three hospital in Addis Ababa, Ethiopia
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February 2023

Addis Ababa. Ethiopia

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Abstract

Background: Ischemic stroke is a major cause of increased morbidity and mortality. Stroke incidence, prevalence, and mortality rates have all grown globally, with low- and middle-income countries bearing the most of the burden.(1) The World Health Organization reports that between 2002 and 2012, stroke was the second leading cause of mortality.(2) Hemorrhagic transformation occurs frequently in patients with acute ischemic stroke. It increases morbidity and mortality of acute ischemic stroke. Following ischemic stroke, the occurrence of spontaneous hemorrhagic transformation ranges from 3.2% to 43.3% and is fatal in around 3% of patients.(2)

Objective: The study aims to assess the predictor of hemorrhagic transformation in acute ischemic stroke lesion among inpatients at three hospitals in Addis Ababa, Ethiopia.

Methodology: A retrospective case control study was carried out among patients with acute ischemic stroke at Saint Paul Hospital Millennium Medical College, Zewditu Memorial Hospital and Tikur Anbessa Specialized Hospital admitted to inpatient care from June 2019 to July 2022 in order to determine the predictor of hemorrhagic transformation in acute ischemic stroke patients. The study was carried out from a sample size of 270. Data was collected from medical chart of the patient and was first checked manually for completeness and later coded and analyzed using SPSS version 26.0. Bivariate and multivariate logistic regression analysis was performed to determine the association between dependent and independent variables.The cut off point used to include variables in multivariate regression was 0.25. All tests with P-Value <0.05 were considered statistically significant.

Result: In this study 37.8% of the study participants were in the age group of 61-70 years with mean and SD of 61.2±12.51 years respectively. Research participants with a history of diabetes mellitus had an increase in hemorrhagic transformation of 5.4 folds, while those with stress hyperglycemia had an increase in hemorrhagic transformation of 12.2 folds compared to the opposite compartment. Patients with previous history of stroke/ transient ischemic attack increased risk by 3.7 folds. Those who took warfarin had 13.1 increased risk and in 5.6 folds in those who took heparin. The hemorrhagic transformation risk of study participants taking one or more anticoagulant medications was 3.8 fold higher than that of research participants taking just one prescription.

Conclusion: Study participants with diabetes mellitus, stress hyperglycemia, previous history of stroke/ transient ischemic attack, taking one and above anticoagulant medication, heparin and warfarin had a significant association.

Recommendations: Guideline based acute ischemic stroke management; targeted interventions should focus on reducing modifiable risk factors like diabetes mellitus,dyslipedemia, further studies should be conducted to better understand factors associated with increased risk of hemorrhagic transformation.

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Abbreviations and Acronyms

AIS: Acute ischemic stroke
BBB: Blood brain barrier
CHF: Congestive heart failure
CT: Computerized tomography
DM: Diabetes mellitus
ECASS: European Cooperative Acute Stroke Study
ECG: Electrocardiogram
EGFR: Estimated glomerular filtration rate
GBD: Global burden of disease
GCS: Glasgow Coma Scale
HI: Hemorrhagic infarct
HMIS: Health Management Information System
HT: Hemorrhagic transformation
ICP: Intracranial pressure
ICU: Intensive care unit
LDL: Low density lipoprotein
MRI: Magnetic Resonance Imaging
mRS: Modified Rankin Scale
NCD: Non communicable disease
NIHSS: National Institutes of Health Stroke Scale
NOACS: Novel oral anticoagulants
PACS: Partial anterior circulation stroke
PH: Parenchymal hematoma
RBS: Random blood sugar
RtPA: Recombinant tissue plasminogen activator
SPHMMC: Saint Paul Hospital Millennium medical college
SPSS: Statistical Package for the Social Sciences
TACS: Total anterior circulation stroke
TASH: Tikur anbessa specialized hospital
TIA: Transient ischemic attack
TOAST: Trial of ORG 10172 in acute stroke treatment
TNF: Tumor necrosis factor
ZMH: Zewditu memorial hospital

1. Introduction

1.1. Background

Ischemic stroke is a condition that occurs when blood flow to part or all of the brain is reduced, resulting in tissue damage. The brain contains little or no energy stores of its own, and therefore relies on the blood for their delivery. Even brief deprivation can lead to death of the affected brain tissue. (3) Acute ischemic stroke sub-types are often classified in clinical studies using a system developed by investigators of the TOAST trial, based upon the underlying cause.(4) It is a major cause of increased morbidity and mortality. Ischemic stroke has been found to be the sixth leading cause of death in Ethiopia.(5)

Stroke incidence, prevalence, and mortality rates have all grown globally, with low- and middle-income countries bearing the most of the burden.(1) The World Health Organization reports that between 2002 and 2012, stroke was the second leading cause of mortality. In addition to the significant mortality associated with stroke, the substantial morbidity also leaves up to 50% of survivors with long-term disabilities. Additionally, it is projected that in 2004, 5.7 million deaths—or 9.7% of all deaths—were caused by stroke, with middle-income and low-income nations accounting for more than 85% of these deaths.(6) According to earlier studies that predicted the future trend of stroke in the Sub Saharan Africa, poor healthcare seeking behavior and poor neurologic therapies will cause the burden of stroke to rise over the next few years.(7)

There are several complications in acute ischemic stroke. They occur frequently and influence outcome after ischemic stroke.(8) Serious complications include pneumonia, urinary tract infection, gastrointestinal bleeding, myocardial infarction, deep vein thrombosis, and pulmonary embolism. It has been demonstrated that early complications including pneumonia and elevated intracranial pressure are independently related to higher mortality and poor functional outcome.(9) The most frequent neurological problems within the first week of hospitalization were elevated intracranial pressure (7.6%) and recurrent cerebral ischemia (5.1%). The three most frequent medical consequences were pneumonia (7.4%), severe arterial hypertension (7.5%), and fever >38°C (13.2%) within the first week of stroke.(10)

With some exceptions, both medical and neurologic complications usually occurred within the first 3 days. Deep venous thromboembolism, pulmonary embolism and urinary tract infection can occur late (up to 30 months) since they are consequences of immobilization.(11)

Hemorrhagic transformation (HT) is one of the complications of acute ischemic stroke. It occurs frequently in patients with acute ischemic stroke, which defined as a spectrum of ischemia-related brain hemorrhage. It increases morbidity and mortality of acute ischemic stroke. Following ischemic stroke, the occurrence of spontaneous HT ranges from 3.2% to 43.3% and is fatal in around 3% of patients.(2)

The timing of HT can be variable in patients with ischemic stroke. HT hardly ever happens in the first 6 hours in untreated patients. Most often occurs within 4 days following infarction, it typically emerges in the first few days.(12) In one review of stroke clinical trial, it was shown that majority of symptomatic HT occurred within 24 hours and 10-15% occurs after 24 hours.(13) Even though HT can occur up to 7 days or later, the majority of symptomatic HT occurs within 36 hours.(14)

HT includes symptomatic hemorrhages that are associated with clinical worsening and those that are asymptomatic which are only evident on radiologic images.(15) The radiologic definition of HT is generally classified by European Cooperative Acute Stroke Study (ECASS). On CT scans, HT is divided into two types which are hemorrhagic infarct (HI) and parenchymal hemorrhage (PH) with or without mass effect. Each type is divided in to two subtypes.(16)

HT is one of the most feared complications of acute ischemic stroke with the consequence ranging from possible worse neurologic outcome to higher mortality rate. It results in blood accumulation with in the intracranial space, which in turn leads to potentially deadly increase of intracranial pressure (ICP).(17)

The mechanism resulting in HT is likely related to the disruption of the blood brain barrier (BBB) or ischemia reperfusion.(2) There are several factors associated with increased risk of HT in acute ischemic stroke. Although it might occur spontaneously as the natural course of ischemic brain injury, it usually occurs as a result of the use anticoagulant (18) or thrombolytic therapy (19). Other factors such as advanced age(20), severity of stroke(20), atrial fibrillation, cardio emboli, CHF, high NIHSS score, hyperglycemia, history of diabetes, hypertension(21), low total cholesterol and LDL, low platelet count, albuminuria, low eGFR and early ischemic changes on the cranial CT on admission(20) have been related to HT after the ischemic event.(22)

1.2. Statement of the problem

Stroke is a major public health problem in third world countries affecting millions of people with higher mortality than in developed countries and occurrence at a younger age.(23) The burden of non-communicable diseases is becoming a major concern for Africa, driven by Sociodemographic and lifestyle changes. According to Global Burden of Disease (GBD) study in 2010, more than 11 million ischemic strokes occurred while 63% of them were in low and middle-income countries.(24)

Ethiopia is no exception to the threat of a triple burden of disease: infectious diseases, Non-Communicable Diseases (NCDs), and injuries.(25) The magnitude of stroke-related deaths in Ethiopia is 6.23% out of total deaths, and the age-adjusted death rate of stroke in the country is 89.82 per 100 000 of the population.(26)

HT is a common complication of ischemic stroke associated with even worse outcome and increased mortality. Symptomatic ICH is a major predictor of death and disability in patients with HT. (27) Hemorrhagic infarction type 2 and parenchymal hematoma type 2 were found to have a significant association with a worse functional outcome. Hemorrhagic infarction type 1 and parenchymal hematoma type 1 do not have as such significant association, but they are thought to be associated with worse long term functional outcome.(28) It frequently occurs as a complication of with the use of anticoagulation or thrombolytic which are the main management components of acute ischemic stroke. This leads to tough treatment decisions to minimize the risk of early ischemic stroke recurrence.

Identification of factors that can increase the probability of HT is very crucial part of acute ischemic stroke management, because HT accounts for a major cause of early hazard in acute-stroke patients. It is important to stratify patients with hemorrhagic risk and decide on the management of the hyperacute stroke phase. Recognition of risk factors for HT and PH may reduce their incidence and severity.(29)

This study aims to evaluate the prevalence of HT in acute ischemic stroke. It also aims to identify the predictor of HT in acute ischemic stroke patients. In our setup there is limitation in the use of thrombolytic as the management of acute ischemic stroke due to availability and cost issues although there are few centers which are using thrombolytic. As mentioned earlier thrombolytic are one of the major causes of HT. In other hand anticoagulations are widely used in our setup and are the major component of management in acute setting of ischemic stroke in most of hospitals in our country. Depending on the number of antiplatelet used, the risk of HT might also be increased. (30) This study will identify other predictors of HT in patients not treated with thrombolytics.

1.3. Significance of study

In our country there is limited study done on the predictor of HT in acute stroke patients. The hospitals could use the study result as a base line for future studies and for academic purpose. It can also be used for the pretreatment evaluation of patients with acute ischemic stroke for predicting the risk of hemorrhagic transformation and anticipate any upcoming complications. A prediction model for HT after acute ischemic stroke maybe an important clinical tool to understand the impact of therapeutic regimen selections on patient's prognosis.(31)

As the higher mortality of ischemic stroke and HT is a concern, finding of this study will be important to have precautionary measures to prevent and treat HT in the future, thereby improving the quality of the treatment for our patients. The study results could also be used as baseline information for locally based organizations and researchers working similar issue.

2. Literature review

A retrospective cohort study done at Gondar University Hospital from April 1 2017 to May 15 2017 assessing in hospital mortality among ischemic stroke patients enrolled 208 patients. Of those 208 patients with ischemic stroke 12 (5.77%) patients experienced hemorrhagic transformation.(32) A prospective study was done on patients with a primary diagnosis of stroke admitted between June 2008 and February 2009 to three hospitals in Addis Ababa (i.e. Tikur Anbesa Specialized Hospital, Bethel Teaching Hospital and Zewditu Memorial Hospital in order to assess medical and neurological complication. 71 patients was included in the study and there were a total of 28 (39.4%) patients with hemorrhagic stroke and 43 (60.5%) with ischemic stroke. There was one patient who was found to have ischemic stroke with hemorrhagic transformation.(33)

A retrospective analysis of 527 consecutive stroke rehabilitation patients at Changi General Hospital, Singapore was done between June 2008 and May 2017. Of the 527 patients who were diagnosed with ischemic stroke on admission, 102 (19.4%) experienced HT. Of these 102, 88 (86.3%) were classified as 'early HT' (within 48 hours), and 14 (13.7%) were classified as 'late HT' (beyond 48 hours). Those with large artery ischemic strokes had a higher risk of HT [(94) 25.2% vs. (8) 5.2%, p = 0.001) than those with small artery strokes. Of the 527 patients with ischemic stroke, 102 (19.4%) had underlying AF, and 55 (53.9%) of these patients developed HT (p = 0.001). Of all the subjects, 23 (4.4%) were taking vitamin k antagonists, and 14 (60.9%) of these developed HT (p = 0.001). 41 (7.8%) of the 527 patients with ischemic stroke received recombinant tissue plasminogen activator (rtPA), of which 15 (36.6%) developed HT (p = 0.004). Those who received rtPA had a higher risk of HT. Patients with large artery strokes and a

high risk of cardio embolism were also significantly more likely to have HT. Using the stroke territory classification, patients with TACS (35.7%) and PACS (35.6%) had a higher risk of HT. There were 129 (24.5%) patients taking aspirin and, of these, 39 (30.2%) developed HT ($p = 0.001$). Those on dipyridamole, clopidogrel, statins, or fibrate did not appear to have a significantly increased risk of HT. Patients with HT had a significantly lower total cholesterol (4.96 vs. 5.34, $p = 0.018$) and lower LDL cholesterol (3.20 vs. 3.5, $p = 0.023$). Altered kidney function, full blood count and liver function tests did not show any relationship with HT. Mean survival was 7.5 years in the HT group as compared to 11.1 years in the stroke patients without HT.(34)

According to a prospective study of 122 acute stroke patients, the overall prevalence of any HT on T 2 * -MRI was 20.5% (25/122 patients). HT was significantly more frequent after rtPA treatment (15/31, 48.4%, vs. 10/91, 11.0%; OR 7.59, 95% CI 2.9–19.6; $p < 0.001$). Patients who developed HT had higher NIHSS (mean 9.9 vs. 5.9; OR 1.08, 95% CI 1.0–1.17; $p = 0.003$) and mRS scores (mean 3.8 vs. 3.1; OR 1.31, 95% CI 0.96–1.76; $p = 0.035$) on admission.(35)

Another retrospective study analyzed the clinical, radiographic, and laboratory data of patients with acute ischemic stroke consecutively admitted to a Stroke Unit along 2 years and compared patients with HT with those without HT. The study population consisted of 564 patients and 52 patients (9.2%) showed HT on brain CT at 24 hours (4.9% symptomatic). NIHSS score ≥8 at Stroke Unit admission (3 points), cardio embolic etiology (2 points), acute revascularization by systemic thrombolysis and/or mechanical thrombectomy (1 point), history of previous TIA/stroke (1 point), and major vessel occlusion (1 point) were found independent risk factors of HT.(36)

Some studies reported that kidney dysfunction is a risk factor for ischemic stroke; (37) (38). There are some controversies whether there was an association between kidney dysfunction and HT in acute ischemic stroke patients. There are studies that show association between low eGFR and HT in acute ischemic stroke. In a study done at Soonchunhyang University Hospital, South Korea from September 2007 to February 2012 enrolling a total of 770 patients within 7 days of stroke onset in the prospective outcome registry of acute stroke assessed whether GFR level is associated with HT in acute ischemic stroke. Among 770 consecutive patients (mean age: 70.34 ± 13.08 years, males: 56.1%) included in the analysis, 131 (17.0%, mean age: 71.43 ± 13.20 years, males: 58.8%) had HTs on follow-up imaging; 77 (58.8%) HI and 54 (41.2%) PH and 63 patients (8.2%) had symptomatic HTs (35.0% in the patients with HI and 66.7% in those with PH).(39)

In another hospital based prospective study done from January 2014 to December 2016 in China 74 had HT (mean age: 65 ± 12 years, number of male patients: 47) from a total of 426 patients on follow-up scans while 352 had no HT (mean age: 64 ± 11 years, male: 211). In univariate

analysis, HT was apparently associated with the presence of hypertension disease (odds ratio [OR] = 0.463, CI= 0.276–0.774, P = 0.003), atrial fibrillation (OR = 3.814, CI = 1.870–7.775, P < 0.001), large cerebral infarction (OR = 2.883, CI= 1.506–5.520, P = 0.001), serum albumin level (OR = 4.971, CI= 1.214–20.353, P < 0.001), and low GFR (a low calculated GFR with a value <60 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$ was defined low GFR) based on the value of estimated GFR (OR = 1.993, CI = 0.994–3.995, P = 0.048. In multivariate regression analysis, low GFR (OR = 3.708, CI = 1.326–10.693, P = 0.013) independently predicted higher risk of HT for AIS patients who did not receive thrombolysis therapy; moreover, HT was also significantly associated with atrial fibrillation (OR = 2.444, CI= 1.087–5.356, P = 0.027), large cerebral infarction (OR = 2.583, CI = 1.236–5.262, P = 0.010), and hypoalbuminemia (OR = 4.814, CI = 1.054–22.153, P = 0.037).(40)

A retrospective study done in Saudi Arabia HT was detected in 38 patients accounting for 8% of all 504 ischemic stroke patients. Patients who developed HT median 66.5 (54.3–77.5) years of age and 24 (63%) were male. The median NIHSS stroke at admission was 10 (5.0–14.2), and the median GCS was 14.5 (13.0–15.0). Hypertension (73.7%), DM (65.8%), hyperlipidemia (63.2%), and atrial fibrillation (36.8%) were the most frequent comorbidities.(41)

A retrospectively study done in Italy assessed the association of the level of LDL and total cholesterol level with HT in acute ischemic stroke. 204 patients were included and the risk of HT significantly increased with decreasing levels of total cholesterol (p for trend = 0.03) and LDL level (p for trend = 0.01). In multivariate analysis, the risk of HT was significantly higher in the groups of patients with the lowest total cholesterol (OR 2.8, 95% CI 1.0–8.9, p = 0.05) and LDLC (OR 5.0, 95% CI 1.2–20.1, p = 0.002) values compared to those with the highest ones.(42)

3. Objective

3.1. General objective

- ✓ To assess the clinical characteristics and predicting factors in patients with HT in acute ischemic stroke lesion among inpatients SPHMMC, ZMH and TASH , Addis Ababa, Ethiopia from June 2019 to July 2022

3.2. Specific objectives

- ✓ To assess Sociodemographic characteristics of patients with HT with acute ischemic stroke lesion among inpatients SPHMMC, ZMH and TASH, Addis Ababa, Ethiopia from June 2019 to July 2022
- ✓ To assess clinical characteristics of patients with HT with acute ischemic stroke lesion among inpatients SPHMMC, ZMH and TASH, Addis Ababa, Ethiopia from June 2019 to July 2022
- ✓ To identify predictors of HT in acute ischemic stroke lesion among inpatients care at SPHMMC, ZMH and TASH, Addis Ababa, Ethiopia

4. Method

4.1. Study area

This study was conducted in three hospitals in Addis Ababa, SPHMMC, ZMH and TASH inpatient care. St Paul hospital millennium medical college is one of the two biggest specialized referral hospitals in Addis Ababa and in the country. It was established in 1968. It is a rapidly expanding hospital especially after it started working as a medical college since 2000 E.C/2007G.C. Currently it runs residency and sub-specialty programs in many fields. While the inpatient capacity is more than 700 beds, with an annual average of 200,000 patients and a catchment population of more than 5 million.(43) The College sees an average of 1200 emergency and outpatient clients daily. (44) There is a total of 18 bed in the neurology unit. It is a hospital that provides neurology services in addition to an outpatient department and specialized care for neurologic issues. There are a total of 18 beds in the neurology/Gastroenterology unit.

ZMH is located in the capital city, Addis Ababa. It was built ,owned and operated by seventh-day Adventists church, but was nationalized during the Derg regime in about 1976.The hospital

is named after empress Zewditu the cousin and predecessor on the throne of emperor Haile Selassie. Today, Zewditu Hospital is operated by the Ministry of Health.(45) It is a hospital that offers specialist care for neurologic and neurosurgical problems as well as an outpatient department and other neurology services. It currently has 10 ICU beds, 15 emergency beds and 56 beds in medical ward.

TASH is the teaching hospital of the College of Health Sciences, Addis Ababa University which was established in 1972. The Federal Ministry of Health entrusted TASH, the nation's largest referral hospital, to the School in 1998, and it has subsequently evolved into a university teaching hospital. Committed to delivering healthcare services, the TASH staff comprises 115 additional health professionals, 379 nurses, and 200 doctors and with over 700 beds serves as a training center for undergraduate and postgraduate medical students.Today, TASH serves as the primary teaching hospital for the majority of specialties' preclinical and clinical training. Additionally, the entire country receives specialized therapeutic treatments from this facility that are not provided by other public or private facilities.

4.2. Study period

The study was conducted from June to August 2023.

4.3. Study design

A retrospective case control study was carried out among patients with acute ischemic stroke at SPHMMC, ZMH and TASH admitted to inpatient care, to the medical ward, ICU and medical emergency.

4.4. Population

4.4.1. Source population

- ✓ All patients with ischemic stroke at SPHMMC, ZMH and TASH

4.4.2. Study population

- ✓ All patients admitted to inpatient care (medical ward, ICU and medical emergency) of both SPHMMC, ZMH and TASH with acute ischemic stroke June 2019 to July 2022.

4.5. Inclusion and Exclusion criteria

4.5.1. Inclusion criteria

- ✓ All patients admitted to inpatient care (ICU, medical ward and medical emergency) of SPHMMC, ZMH and TASH with a diagnosis of acute ischemic stroke

4.5.2. Exclusion criteria

- ✓ Patients with transient ischemic attack
- ✓ Patients with traumatic intracerebral hemorrhage
- ✓ Patients with insufficient data records

❖ Insufficient data records: Patients data records with no laboratory results for serum creatinine, RBS, lipid profile, no ECG or no physical examinations and no brain imaging

4.6. Sample size determination

Sample size is calculated by using the double population proportion formula. The sample size was determined in advance based on the assumption of 95% confidence interval and a 5% margin of error.

$$N \text{ cases} = \frac{(Z_{a/2} + Z_B)^2 \; p\,(1-p)\,(r+1)}{r(po-p1)^2}$$

$Z_{a/2} = 1.96$ for 95% confidence

$Z_B = 0.84$ for 80% power

P= Proportion of the exposure in the population

	DM (P-65.8%)	HTN (P-73.7%)	Dyslipedemia(P-63.2%)
Case	49	29	60
Control	98	58	120
Total	147	87	180

Two-sided confidence level(1-alpha)		95
Z_B	Power(% chance of detecting)	80
r	Ratio of Controls to Cases	2
p0	Hypothetical proportion of controls with exposure	40
p1	Hypothetical proportion of cases with exposure:	22.6(46)
	Least extreme Odds Ratio to be detected:	0.00

	Kelsey	**Fleiss**	**Fleiss with CC**
Sample Size - Cases	88	85	93
Sample Size - Controls	176	169	186
Total sample size:	264	254	279

4.7. Sampling method

From a total of patients admitted to SPMMC, ZMH and TASH inpatient care during the study period fulfilling the inclusion criteria and with no exclusion criteria. A total of 270 participants were included in the research. From this 80 patients with HT and 190 patients without HT were selected with simple randomized sampling method.

4.8. List of variable

4.8.1 Dependent variable

- ✓ Hemorrhagic transformation

4.8.2 Independent variables

- ✓ Age
- ✓ Sex
- ✓ Type of ischemic stroke
- ✓ History of diabetes
- ✓ Hypertension
- ✓ Stress hyperglycemia

- ✓ Atrial fibrillation
- ✓ Serum creatinine
- ✓ Total cholesterol
- ✓ LDL level
- ✓ Types of anti-thrombotic used
- ✓ Number of anti-coagulation used
- ✓ Thrombolytic use
- ✓ GCS during presentation
- ✓ Previous history of stroke/TIA
- ✓ Heart failure
- ✓ Early CT scan change
- ✓ Infarct size

4.9. Data collection

Data was obtained from HMIS and manual registration book for patients diagnosed as acute ischemic stroke. The charts of patients with acute ischemic stroke was reviewed to identify whether the patients had hemorrhagic transformation or not. Data was collected by trained data collectors (general practitioners) after being trained ahead of data collection. Data was checked manually for completeness and was collected by using self-prepared checklist which contains the variable. The information was extracted from patient charts.

4.10. Data processing and analysis

Data was collected and checked manually for completeness and later coded and analyzed using SPSS version 26.0. Categorical variables was recorded as percentages and frequencies and was compared by chi square chart. Multinomial logistic regression analysis performed to determine predictor of association between dependent and independent variables. Bivariate logistic regression analysis was used to check variables association with dependent variable individually. In bivariate in dependent variable of p-value< 0.25 were entered in to multiple logistic regression models for further analysis and variables having P- value of < 0.05 were considered as significantly associated with the dependent variable. The degree of association between dependent and independent variables was expressed by using odds ratio with 95% confidence interval. The data is summarized and presented by use of tables and texts.

4.11. Operational definition

- ✓ Case- patients with acute ischemic stroke and hemorrhagic transformation
- ✓ Control- Patients with acute ischemic stroke but no hemorrhagic transformation
- ✓ Acute ischemic stroke- an abrupt onset of a neurologic deficit with no acute hemorrhage in brain imaging
- ✓ Diabetes mellitus- fasting blood sugar >125 mg/dL, or HgA1c >6.5 % or symptoms of hyperglycemia and random blood sugar >200mg/dL Or two hour oral glucose tolerance test > 200mg/dL
- ✓ Early CT scan change- the loss of differentiation of the lentiform nucleus and insular ribbon, and effacement of the sulci, either alone or with a hyperdense middle cerebral artery sign
- ✓ Heart failure- identified by presence of current or prior characteristic symptoms, such as dyspnea and fatigue, and evidence of cardiac dysfunction as a cause of these symptoms (eg. abnormal left ventricular and/or right ventricular filling and elevated filling pressures)
- ✓ Hemorrhagic transformation- an abrupt and profound deterioration of clinical state in patients with acute ischemic stroke with determination of ischemic infarct with superimposed cerebral hemorrhage on brain imaging
- ✓ Hypertension- blood pressure ≥140/ 90 mmHg which is measured more than one time
- ✓ Large hemispheric infarction- ischemic stroke affecting the majority of or complete middle cerebral artery
- ✓ Stress hyperglycemia- blood glucose level above 180mg/dl in patients without preexisting diabetes
- ✓ Transient ischemic attack- a transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction

4.12. Ethical consideration

Ethical clearance was obtained from Research Ethics committee of St Paul's Hospital Millennium Medical College, Zewditu memorial hospital and Tikur Anbessa Specialized Hospital. The procedure was confidential.

4.13. Dissemination of the result

The result of this study will be submitted and presented as one of the partial fulfillment of residency program in internal medicine department, SPHMMC. The finding of the result will be submitted to the study areas.

5.Result

5.1 Sociodemographic and clinical characteristics of the study participants

In this study 270 participants were involved with 90 cases (HT) and 180 control (without HT) making a response rate of 94.7%. In this study 37.8% of the study participants were in the age group of 61-70 years with mean and SD of 61.2±12.51 years respectively. Half of the participants were male with 65.9% control and 34.1% case and 80% of the study participants had a GCS of 12-15 with 67.1% control and 32.9% case.

Eighty percent of the study participants had thrombotic, from this 70.8% were control group (without HT) and 29.2%were case group (HT) and 54.8% control and 45.2% case had DM history. Seven percent of the study participants had stress hyperglycemia

Table 3. Sociodemographic and clinical characteristics of the study participants among inpatients at three in hospitals in Addis Ababa, Ethiopia, from June 2019 to July 2022

Variable	Case	Control	Total (%)
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%)
GCS			
<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%)
Types 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%)

5.2 Co-morbid disease related characteristics of the study participants

Thirty-six percent of control & 63.2% cases had arterial fibrillation and 40.4% control and 59.6% case had previous history of stroke. Sixty-nine percent of the control group and 30.2% case of the study participants had heart failure and 69.2% control and 30.8% case had a history of hypertension.

Table 4. Co-morbid disease related characteristics of the study participants among inpatients at three in hospitals in Addis Ababa, Ethiopia, from June 2019 to July 2022

Variable	Case	Control	Total (%)
DM history			
Yes	47(45.2%)	57(54.8%)	104(38.5%)
no	43(25.9%)	123(74.1%)	166(61.5%)
History of hypertension			
Yes	56(30.8%)	126(69.2%)	182(67.4%)
No	34(38.6%)	54(61.4%)	88(32.6%)
Arterial fibrillation			
Yes	24(63.2%)	14(36.8%)	38(14.1%)
no	66(28.4%%)	166(71.6)	232(85.9%)
Previous history of stroke/ TIA			
Yes	31(59.6%)	21(40.4%)	52(19.3%)
No	59(27.1%)	159(72.9%)	218(80.7%)
History of heart failure			
Yes	16(30.2%)	37(69.8%)	53(19.6%)
No	74(34.1%)	143(65.9%)	217(80.4%)

5.3 Medication related characteristics of the study participants

Almost eighty-two percent of the study participants were taking aspirin (73.6% control & 26.4% case) and 20% (46.3% control &53.6% case) of the study participants took clopidogrel. Almost fourteen percent of the study participants took warfarin and 24.4% took two and above

medication.

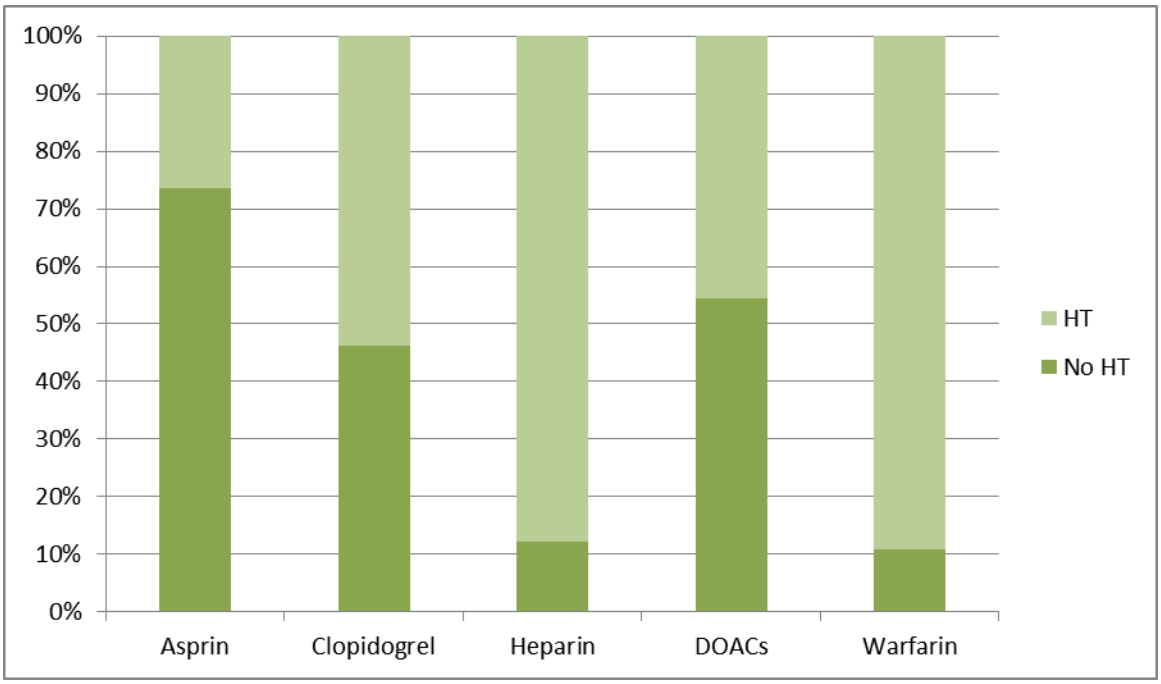

Figure 1. Medication related characteristics of the study participants among inpatients at three in hospitals in Addis Ababa, Ethiopia, from June 2019 to July 2022

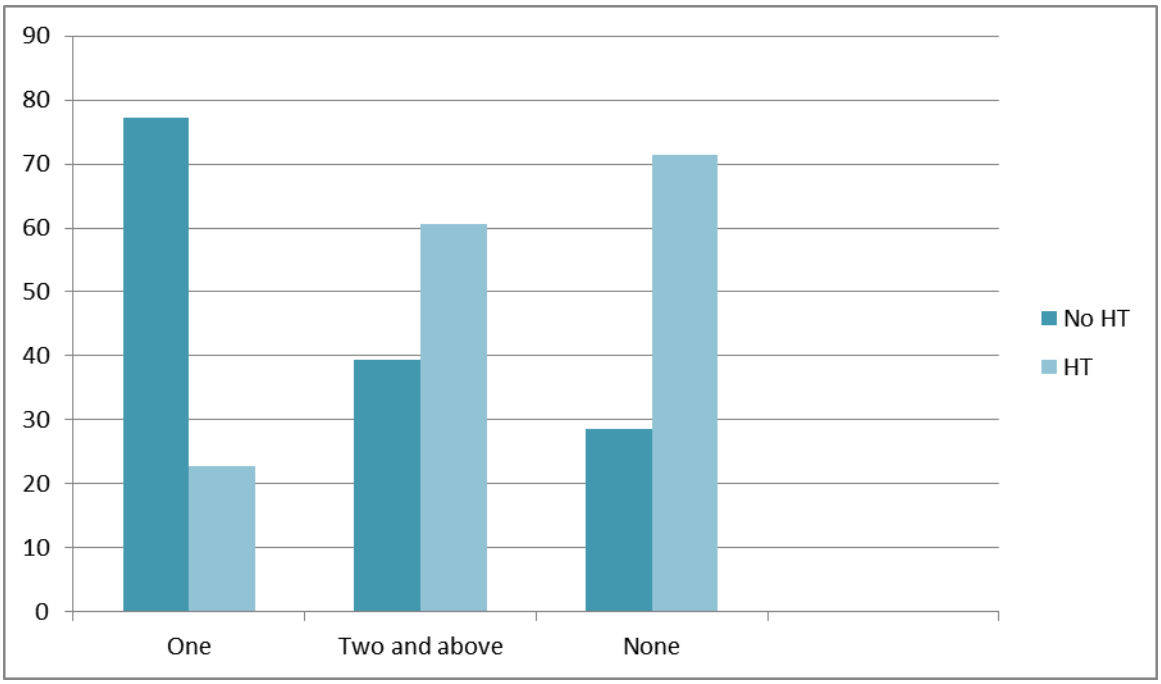

Figure 2. Number of anticoagulation used among inpatients at three in hospitals in Addis Ababa, Ethiopia, from June 2019 to July 2022

5.4 Investigation related characteristics of the study participants

Sixty-nine percent of the control group & 30.6% of case had a creatinine level of <1.2 and 66.5% control & 33.5% case had a total cholesterol level of <200. Only 2.6% of the participants had early CT scan change and 37.4% had a large infarct.

Table 3. Investigation related characteristics of the study participants among inpatients at three in hospitals in Addis Ababa, Ethiopia, from June 2019 to July 2022

Variable	Case	Control	Total (%)
Creatinine			
<1.2	71(30.6%)	161(69.4%)	232(85.9%)
>=1.2`	19(50%)	19(50%)	38(14.1%)
Total cholesterol			
<200	72(33.5%)	143(66.5%)	215(79.6%)
>=200	18(32.7%)	37(67.3%)	55(20.4%)
LDL level			
<100	62(32.6%)	128(67.4%)	190(70.4%)
>=100	28(35%)	52(65%)	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(62.6%)
yes	3(42.9%)	4(57.1%)	7(2.6%)
A large infarct			
Yes	31(30.7%)	70(69.3%)	101(37.4%)
no	59(34.9%)	110(65.1%)	169(62.6%)

5.5 The mean value of continues value and significance with hemorrhagic transformation

This chi-square result showed that age, GCS, Serum creatinine level, total cholesterol and LDL level were an association with Hemorrhagic transformation as shown in the table below.

Table 4. The mean value of continues value and significance with hemorrhagic transformation among inpatients at three in hospitals in Addis Ababa, Ethiopia, from June 2019 to July 2022

Variable	Case		Control		X2-value	p-value
	mean	SD	mean	SD		
Age	61.36	12.47	61.16	12.57	126.1	0.000
GCS	13.20	2.22	13.21	2.71	25.15	0.003
Serum creatinine	0.89	0.41	0.97	0.18	148.78	0.000
Total	150.5	52.11	159.5	47.25	155.53	0.000

cholesterol						
LDL level	90.59	43.64	92.8	31.88	180.99	0.000

5.6 The determinants predictors of hemorrhagic transformation

Odd ratio and 95% CI were used to measure the association between predictor variable and HT. Accordingly DM history, stress hyperglycemia, arterial fibrillation, previous history of stroke, heparin use, warfarin use, use of more than one anticoagulant, creatinine level had an association with HT bivariate logistic regression.

Research participants with a history of diabetes mellitus (DM) had an increase in HT of 5.4 folds compared to their opposite compartment (AOR=5.4, 95%CI=2.35, 12.31), while those with stress hyperglycemia had an increase in HT of 12.2 folds compared to non-stress hyperglycemia (AOR=12.2, 95%CI=2.30, 65.12). These findings were obtained from multivariate logistic regression analysis. The HT of research participants with a history of stroke increased by 3.7 folds when compared to the opposite compartment (AOR=3.7, 95%CI=1.57, 8.86), while the HT of study participants taking heparin increased by 5.6 folds when compared to the opposite compartment (AOR=5.6, 95%CI=1.41, 22.66). The HT risk of study participants taking warfarin was 13.1 fold higher than that of study participants in the opposite compartment (AOR=13.1, 95%CI=16.91, 131.62), while the HT risk of study participants taking one or more anticoagulant medications was 3.8 fold higher than that of research participants taking just one prescription.

Table 5. The bivariate and multivariate logistic regression of association between predicting variable and hemorrhage transformation among acute ischemic stroke lesion among patients

Variable	Case	P-Value	COR with 95%CI	P-value	AOR with 95%CI
DM history					
Yes	47(45.2%)	0.001	2.4(1.40, 3.97)	0.000	**5.4(2.35, 12.31)**
no	43(25.9%)	1			
Stress Hyperglycemia					
Yes	15(78.9%)	0.000	8.8(2.83, 27.39)	0.003	**12.2(2.30, 65.12)**
No	75(29.9%)	1			
Arterial fibrillation					
Yes	24(63.2%)	0.000	4.3(2.10, 8.84)	0.145	3.1(0.67, 14.54)

no	66(28.4%%)	1			
Previous history of stroke/ TIA					
Yes	31(59.6%)	0.000	3.9(2.12, 7.46)	0.003	**3.7(1.57, 8.86)**
No	59(27.1%)	1		1	
Heparin					
Yes	29(87.9%)	0.000	20.9(7.07, 61.92)	0.015	**5.6(1.41, 22.66)**
No	67(25.7%)	1		1	
Warfarin					
Yes	33(89.2%)	0.000	25.5(8.65, 74.99)	0.000	**13.1(6.91, 131.62)**
No	57(24.5%)	1			
Number of anti-coagulation used					
One	45(22.8%)	1		1	
Two and above	40(60.6%)	0.000	5.2(2.87, 9.43)	0.004	**3.8(1.55, 9.57)**
None	5(21.4%)	0.062	8.4(0.58, 45.00)	0.059	7.2(3.01, 50.88)
Creatinine					
<1.2	71(30.6%)	1		1	
>=1.2	19(50%)	0.021	2.3(1.13, 4.54)	0.089	2.5(0.87, 7.13)

6. Discussion

Age was a statistically significant with hemorrhage transformation at p-value 0.001), this finding was supported by the study done in China (40). This may be due to the fact that HT occurs with any age group but aged patients often have an increased risk. The reasons why growing older raises the risk of HT are complex and include increased BBB permeability and systemic inflammation. Elderly individuals also have higher rates of cerebrovascular illness, are more likely to be on anti-thrombotic therapy, and have a higher likelihood of coexisting conditions including diabetes and hypertension. These conditions, which include hypertension, diabetes, atherosclerosis, and hyperlipidemia, are known to exacerbate inflammation. This age-related inflammation may be a contributing factor to BBB disruption following a stroke, which raises the risk of HT. (47)

GCS status was a statistically significant with hemorrhage transformation at p-value 0.001). The finding was congruent with the study done in Saudi Arabia (41). This was may be due to patients

with reduced consciousness, as indicated by a lower GCS score, may have impaired cerebral autoregulation. Dysfunction in autoregulation can lead to fluctuations in cerebral perfusion pressure, increasing the risk of hemorrhagic transformation. (47)

Study participant having DM history had 5.4 folds increase its HT compared to its opposite compartment (AOR=5.4, 95%CI=2.35, 12.31). The finding was congruent with the study done in Saudi Arabia (41). This was may be due to diabetes mellitus is associated with micro-vascular complications, including damage to small blood vessels throughout the body which lead to changes in vessel structure, increased permeability, and impaired autoregulation, predisposing to hemorrhagic transformation. Increases in plasma levels of TNF, intereukin-1β, intereukin-6, interferon-g together with changes in immune cell responsiveness, are linked to diabetes and chronic low-grade inflammation. This could lead to a higher chance of HT. (48)

Study participant having stress hyperglycemia had 12.2 folds increase its HT compared to non-stress hyperglycemia (AOR=12.2, 95%CI=2.30, 65.12). The possible reason for its significance were acute hyperglycemia, particularly in the context of critical illness or acute stress, can exacerbate blood-brain barrier dysfunction. Disruption of the blood-brain barrier increases the permeability of cerebral blood vessels, making them more susceptible to rupture and hemorrhagic transformation.

Study participant having previous history stroke had 3.7 folds increase its HT compared to its opposite compartment (AOR=3.7, 95%CI=1.57, 8.86). the finding was in line with the study done in Saudi Arabia (41). This was may be due to patients with a history of stroke often have underlying vascular damage. These vascular pathologies weaken blood vessel walls, increase vascular fragility, and predispose to hemorrhagic transformation.

Study participant who took heparin had 5.6 folds increase its HT compared to its opposite compartment (AOR=5.6, 95%CI=1.41, 22.66). This finding was supported by the study done in Changi general hospital in Singapore (34) Study participant who took warfarin were 13.1 folds increase its HT compared to its opposite compartment (AOR=13.1, 95%CI=16.91, 131.62). This finding was supported by the study done in Changi general hospital in Singapore (34). Study participant who took more than one anticoagulant were 3.8 folds increase its HT compared to took one anticoagulant. No study was correlated in the literature. The reason for this event was

may be due to Anticoagulant therapy disrupts the normal hemostatic process, prolonging the bleeding time and increasing the risk of hemorrhage. Patients receiving heparin or warfarin therapy are at higher risk of bleeding complications, including intracerebral hemorrhage (ICH), subdural hematoma, and hemorrhagic transformation of ischemic stroke. The dosage of anticoagulant therapy may influence the risk of bleeding complications. Prolonged therapy with higher doses of anticoagulants increases the cumulative exposure to bleeding risk, particularly in patients with additional risk factors for hemorrhagic transformation. (18)

6. Conclusion

The finding of the study revealed that, the predicting factor of HT were older age, low GCS, high LDL and study participant with DM, stress hyperglycemia, previous history stroke/TIA had 3.7 folds increase its HT compared to its opposite compartment, Those who took warfarin and took one and above anticoagulant medication were a significant association.

7. Recommendation

- Further studies should be conducted to better understand factors associated with increased risk of HT
- Targeted interventions should focus on reducing modifiable risk factors like DM, dyslipedemia

8. Limitations

- Relying only on clinical documentation might make the study inaccurate
- Incomplete or ambiguous information was common due to retrospective reliance on existing medical records and inconsistent documentation was common

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Annexes

1. Information list

Research title: Predictor of hemorrhagic transformation of acute ischemic stroke lesion among inpatient at two tertiary hospitals, Addis Ababa, Ethiopia

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: Mrs. Fatimetu Mohammed (MPH, RH)

Sponsor: St. Paul's Hospital Millennium Medical Collage

2. Data collection check list

S. N	Questions	Response category
1	Age (in years)	
2	Sex	1. Male 2. Female
3	Hemorrhagic transformation	1. Yes 2. No
4	Type of ischemic stroke	3. Thrombotic 4. Embolic
5	History of DM	1. Yes 2. No
6	Hypertension	1. Yes 2. No
7	Stress hyperglycemia	1. Yes 2. No
8	Atrial fibrillation	1. Yes 2. No
9	Previous history of stroke/TIA	1. Yes 2. No
10	Heart failure	1. Yes 2. No

11	GCS during presentation	1. Yes 2. No

12	Types of antithrombotic used	1. Warfarin 2. NOACs 3. Aspirin 4. Heparin 5. Clopidogrel
13	Number of anticoagulation used	6. None 7. 1 8. ≥2
14	Thrombolytics	1. Yes 2. No
15	Serum creatinine	
16	Total cholesterol level	
17	LDL level	
18	Early CT scan change	1. Yes 2. No
19	Large infarct area	1. Yes 2. No

3. Assurance of investigator

I the undersigned resident agree to accept all responsibilities for the scientific, ethical and technical conduct of the research project and for provision of required progress reports as

per terms and conditions of the Research and Publication Directorate and /or Department of Public Health of St. Paul's Hospital Millennium Medical College.

Name of the Resident:__ _____

Signature:_____

Date: _____

Approval of Advisors

Name of Public Health Advisor:_____

Signature:_____

Date:_____

Approval of Advisors

Name of Clinical Advisor:_____

Signature:_____

Date:_____