ADDIS ABABA UNIVERSITY
COLLEGE OF HEALTH SCIENCES
SCHOOL OF PUBLIC HEALTH

SURVIVAL OF STROKE PATIENTS ACCORDING TO HYPERTENSION STATUS IN NORTHERN ETHIOPIA

BY

ZENAWI HAGOS GUFUE (BSc)

A THESIS SUBMITTED TO THE SCHOOL OF GRADUATE STUDIES OF ADDIS ABABA UNIVERSITY IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF PUBLIC HEALTH IN EPIDEMIOLOGY AND BIOSTATISTICS.

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ACRONYMS AND ABBREVIATIONS

ACSH	Ayder Comprehensive Specialized Hospital
AHR	Adjusted Hazard Ratio
AIDS	Acquired Immuno-Deficiency Syndrome
CHR	Crude Hazard Ratio
CT	Computerized Tomography
CVA	Cerebro-Vascular Accident
DALYs	Disability Adjusted Life Years
DVT	Deep Venous Thrombosis
ECG	Electrocardiogram
GBD	Global Burden of Disease
GCS	Glasgow Coma Scale
HIV	Human Immuno-Deficiency Virus
HS	Hemorrhagic Stroke
ICP	Intracranial Pressure
ICU	Intensive Care Unit
IS	Ischemic Stroke
MRI	Magnetic Resonance Imaging
NCDs	Non-Communicable Diseases
PDOs	Person Days of Observation
rtPA	recombinant tissue Plasminogen Activator
SAH	Subarachnoid Hemorrhage
SSA	Sub-Saharan Africa
STATA	Statistics and data analysis soft ware
TIA	Transient Ischemic Attack
WHO	World Health Organization

ABSTRACT

Background: Globally, stroke appears as a major cause of preventable death and disability. In Ethiopia, the intra-hospital mortality of stroke is significant and there is scarcity of epidemiologic data whether there is a difference in the overall survival time between hypertensive and non-hypertensive adult stroke patients admitted in specialized hospitals.

Objectives: To determine the survival of stroke patients according to their hypertension status admitted in Ayder Comprehensive Specialized Hospital, Northern Ethiopia from March 1, 2012 to February 28, 2019.

Methods: A facility-based retrospective cohort study conducted among all cohorts of confirmed first-ever stroke patients admitted in Ayder Comprehensive Specialized Hospital, Northern Ethiopia. Kaplan-Meier survival analysis applied to estimate the survival probability of hypertensive and non-hypertensive first ever stroke patients. Cox proportional hazards regression model used to determine the adjusted hazard ratio of death for each main baseline predictor variable, with 95% CI and P-value <0.05 was used to declare statistical significance. The assumptions of Cox proportional hazards regression model assessed by the global test, Schoenfeld residuals.

Results: There were 503 (323 were hypertensive, 180 Non-hypertensive) confirmed first, ever stroke patients, the overall median age of the patients was 65 years, IQR (53-75) years. Seventy-five (14.91%) of them were dead, with median survival time of 48 days and 428 (85.09%) of them were censored. At any particular point in time the hazard of death among hypertensive patients was two times higher than non-hypertensive patients but this was not found to be a statistically significant (adjusted HR=2.13: 95% CI 0.66-6.81). Glasgow coma scale 3-8 at admission (adjusted HR=10.12; 95% CI 2.58-40.68), presence of stroke complications (adjusted HR=7.23; 95% CI 1.86-28.26) and borderline high total cholesterol level (adjusted HR=3.57; 95% CI 1.15-11.1), were the only independent predictors of intra-hospital patient mortality.

Conclusion and recommendations: There was a non-significant difference in the overall survival time between hypertensive and non-hypertensive first-ever stroke patients. Early identification and treatment of stroke complications, co-morbidities along with strict follow up of comatose patients may improve intrahospital survival of stroke patients and we recommend community based studies using large sample size.

Key Words: Hypertension; Stroke; Cox regression; Predictors of survival; Ethiopia

1. INTRODUCTION

1.1 Background

According to the World Health Organization (WHO) clinical definition, stroke is defined as "a focal (or global) neurological deficit of sudden onset, and lasting more than 24 hours (or leading to death), and of presumed vascular origin". The WHO classifies stroke sub-types in to three major categories as; ischemic stroke, intracerebral hemorrhage and subarachnoid hemorrhage (1).

Previous literatures have identified that there are ten leading modifiable, traditional risk factors for stroke and from those the first six risk factors are; hypertension, current smoking, diabetes mellitus, abdominal obesity, poor diet and physical inactivity which account for more than 80% of the global risk factors for all types of stroke. The remaining risk factors for stroke are excessive alcohol consumption, dyslipidemia, cardiac causes (atrial fibrillation, previous myocardial infarction, rheumatic valvular heart disease and prosthetic heart valve) and psychosocial stress or depression (2,3).

Stroke Patients commonly present with unilateral or bilateral motor or sensory deficits, speech disturbances, altered mentation, headache and vertigo. Stroke is diagnosed clinically and Computerized Tomography scan (CT scan) or Magnetic Resonance Imaging (MRI) used to confirm the diagnosis and to specify the sub-type of stroke. Treatment of stroke depends on the type of stroke identified, but general supportive measures like airway management, coma care, catheterization and selective provision of anti-platelets, anti-coagulants, thrombolytic therapy using intravenous recombinant tissue Plasminogen activator(rtPA), and thrombectomy (which do not exist in the Ethiopian setup (4)) for ischemic stroke patients, treatment of co-morbidities and neurosurgical measures can be used (1).

The objectives of stroke management are to reduce intra-hospital mortality, complications, hospital stay and to improve functional outcome of the patient. The prognosis of acute stroke could be improved by providing more targeted interventions for the ten modifiable traditional risk factors by promoting physical activity, healthy diet, smoking cessation, early detection and better control of hypertension, prevention of intra-hospital complications and good comprehensive stroke care potentially decreases the morbidity and mortality of acute stroke (3,5).

1.2 Statement of the problem

According to the latest global burden of disease (GBD) 2018 report, globally there were around 105 million prevalent cases of stroke and 11.9 million new stroke cases. Almost 1 in 8 deaths worldwide (12%, 6.5 million deaths) were attributable due to stroke, whereby stroke takes life every five seconds, making stroke the second leading global cause of death following ischemic heart disease (14.8%, 8.76 million deaths) and stroke is the third most common cause of adult disability (4.6%) of the global Disability Adjusted Life Years (DALYs) (6,7). The global economic cost of adult stroke care is significant and costs more than 25 billion dollar per year (8).

In the absence of a significant global public health response stroke is projected to rise to 23 million new cases and 7.8 million deaths per year by the end of 2030 (9). This will be worsened by the increase in the age of the population, the global population aged over 65 years is increasing by 9 million per year, and by year 2025 there will be more than 800 million people aged over 65 years of age in the world and two-thirds of them will be living in developing countries. With the growing world-wide burden of stroke, someone in the world will have a stroke every two seconds (10).

Low and middle-income countries are particularly at risk from the rising cost burden of stroke in the coming decades. From 1990 to 2018 the proportional contribution of stroke related DALYs increased from 3.5% to 4.6% and stroke related deaths increased from 9.7% to 12% respectively showing a significant increase (6). Developing countries account for 85% of the global stroke death and 87% of the global stroke DALYs which is 3.5-3.8 times higher than developed countries (9). Ischemic stroke is the predominant type of stroke among Caucasian population which accounts for around 85-90% of all stroke types and hemorrhagic stroke accounts for 10-15% of stroke cases (1).

Approximately 8-12% of ischemic strokes are fatal compared to 37-38% hemorrhagic strokes and this depends on stroke severity, advanced age, comorbidities and effectiveness of treatment of complications (11). The intra hospital mortality of stroke in developed countries is 3-11%, where as in low and middle income countries it is 7-15% (12), but in Sub-Saharan African (SSA) countries it is much more significant, three to four times higher than that of developed countries which ranges from 11-43.4% (13,14).

In Middle East Asia, the incidence rate of stroke ranges from 22.7-250/100,000 populations per year. The overall case-fatality rate within one month was 12–32%. The incidence of first ever and recurrent stroke in the Middle East, was 22.7 and 180 per 100,000 populations per year respectively (15). In Africa, the burden of stroke is increasing overtime due to the epidemiologic transition, adoption of western lifestyle, dietary changes, urbanization, and demographic transition with population growth and increasing life expectancy, which leads to more geriatric population. In Africa there is high incidence of severe stroke with high mortality, this was exacerbated by poor access to health facility and high intra-hospital stroke mortality (16).

Even though the exact emergency burden of stroke in Ethiopia is not known, it has been estimated to be increasing and stroke accounts for 2.5% of all hospital admissions and 13.7% of medical admissions (17). According to the GBD report of 2015 in Ethiopia, hemorrhagic stroke was the fifth leading cause of death, which accounts for 62.7 deaths per 100,000 people (18). According to the latest WHO data published in 2017, stroke deaths in Ethiopia reached 39,571 or 6.23% of total deaths. The age adjusted death rate of stroke accounts for 89.82 per 100,000 population (19).

Stroke affects individuals at the peak of the productive age group and despite its enormous impact on the socioeconomic development; this emerging public health crisis has received very little attention to date (20). In the previous studies, there were conflicting results in the independent survival effect of pre-stroke hypertension among adult stroke patients admitted in different specialized hospitals (5) and community based stroke registries (21). In Ethiopia, there is no methodologically robust incidence study of adult stroke death and the previous studies conducted were using variable methods of classifying stroke types and subtypes, which are not according to the recommended epidemiologic stroke study. The survival status of adult stroke patients' admitted to tertiary teaching hospitals and the potential predictors of survival were not yet determined in our set up.

1.3 Rationale of the study

Stroke is a poorly addressed emerging public health problem and in the past, previously stroke was the disease of the developed countries, but now stroke is becoming a public health problem in developing countries as well with huge consequences in terms of lost productivity, premature deaths and long-term disability. The previously conducted stroke studies in the African Continent and particularly in Ethiopia mainly focused on descriptive summary of types and sub-types of stroke, risk profiles of patients and magnitude of risk factors.

To the best of our knowledge (unlike western countries), we did not get studies conducted in Sub-Saharan Africa including in Ethiopia on determining whether there is a difference in the survival time between hypertensive and non-hypertensive first ever stroke patients. As there is a significant knowledge gap in the area of stroke research, this study is intended to fill the existing knowledge gap on survival status of first ever stroke patients in the Ethiopian context.

1.4 Significance of the study

Intrahospital stroke-death is an excellent tool for measuring the quality of hospital management of stroke. Evaluation and better understanding of the survival status and predictors of survival will reduce intra hospital mortality, complications and improves the quality of care given for stroke patients. This study will help clinicians and other service providers in designing interventions to reduce earlier intra-hospital mortality, by providing more targeted interventions in high-risk patients.

This study will also help policy makers in designing context specific appropriate strategies for addressing the traditional modifiable risk factors of stroke by early screening, detection, treatment and control of stroke complications. Finally, this study will help researchers and the scientific community in updating their knowledge on current incidence of adult stroke death in Ayder Comprehensive Specialized Hospital and this study will further serve as baseline information for future research.

2. LITERATURE REVIEW

2.1 Pathophysiology of hypertension induced stroke

Stroke is a disease with multiple risk factors, and hypertension is the most commonly identified risk factor among stroke patients. Hypertension accounts for 54% of the global stroke risk factor. The specific mechanisms by which hypertension causes stroke are; hypertension causes vascular remodeling, where by hypertension promotes the development of an atherosclerotic plaques in cerebral arteries and arterioles and this will induce lipohyalinosis of penetrating arteries and arterioles, which lead to development of brain infarcts or hemorrhage. The other possible mechanisms by which hypertension causes stroke are; hypertension causes arterial baroreflex dysfunction, oxidative stress and inflammation, all those ultimately lead to infarction or intracerebral hemorrhage (22,23).

2.2 Socio-demographic characteristics and patient survival

According to the GBD 2018 report there is significant disparity in stroke burden between men and women, with men having consistently greater incidence of ischemic stroke than women (133/100,000 person-years and 99/100,000 person-years). Globally males are more likely to develop stroke than females, but the mortality is the reverse, females die more from stroke than males, because women had stroke in the later age than and women had higher life expectancy than males (6). Many studies show that stroke is the disease of elderly population, where majority of stroke cases occur among older individuals (≥65 years) (24,25).

However one prospective hospital based study conducted in Kenya found that, females (56.7%) were more likely to develop stroke than males (43.3%).The commonest age group by which these patients developed stroke was 60-69 years (19.6%) (26). A retrospective record review done in Saint Paulo's hospital, Addis Ababa found that, the most commonly affected age groups for stroke were 64-84 years, which accounts for 41.1% of stroke cases. Males (56.4%) were most affected by stroke than females, in contrary to the above findings, the majority of deaths were among men (59.2%) and the larger proportion (48.9%) of deaths were observed in the age group of 45-64 years (27).

In line with the findings of the above study, an institutional based prospective study conducted in Hawassa showed that males (66.3%) were predominantly affected by stroke than females and majority (27%) of the patients were above the age of 65 years (17). A retrospective record review conducted among 427 adult patients admitted to the medical wards of Felegehiwot Referral Hospital, Bahirdar found that, 56.7 % of the stroke patients were found to be urban residents and majority (71%) patients were followers of Christian religion (28). This finding was in line with the study done in Gondar where by 55.4% of the patients were urban residents and 44.6% of them were rural residents (29).

2.3 Antecedent risk factors and patient survival

An international, multicenter case-control study conducted in 22 countries found that, the odds of developing stroke among patients who had previous history of hypertension were 2.64 times higher than non-hypertensive patients (AOR=2.64, 99% CI, 2.26-3.08). Similarly, current smokers were 2.09 times more likely to develop stroke than non-smokers with (AOR=2.09, 95% CI, 1.75-2.51). The odds of developing stroke among diabetic patients was 36% higher than non-diabetic patients with (OR=1.36, 95% CI, 1.10-1.68). The probability of developing stroke among those patients who had cardiovascular risk factors was 2.38 times higher than their counter parts (AOR= 2.38, 95% CI, 1.77-3.20) (3).

A facility based prospective study conducted in Saudi Arabia found that, a one unit increase in the number of cigarettes smoked increases the hazard of stroke by 2.4 (AHR=2.4). The effect of hypertension (AHR=1.77) on the cumulative survival of stroke patients revealed a significantly lower cumulative survival percentage among hypertensive patients compared to non-hypertensive patients. Contrary to the findings of other studies, other risk factors of stroke (diabetes, hypercholesterolemia, atrial fibrillation) were not found to be statistically significant predictors of stroke mortality (5). In line with this study, a community based prevalence study of stroke conducted in Egypt found that, hypertension was the most common identified stroke risk factor followed by hyperlipidemia and diabetes mellitus (30).

A retrospective record review conducted among adult stroke patients admitted to Gondar University Hospital found that, hypertension (55.9%) followed by any type of structural heart disease (44.6%) and atrial fibrillation (28.7%) were the most commonly identified risk factors. Unlike the findings of other studies, tobacco smoking and dyslipidemia were not found to be common stroke risk factors (29).

An institutional based cross-sectional study conducted in the adult emergency center of Tikur Anbessa Specialized Hospital in Addis Ababa, Ethiopia found that hypertension was the most common identified risk factor for stroke, followed by cardiac illness and diabetes mellitus identified in around 49%, 20% and 11% of patients respectively (4).

2.4 Neurological factors and patient survival

An international, multicenter case-control study conducted in 22 countries found that, ischemic stroke was the predominant type of stroke which accounts for 78% of stroke cases and hemorrhagic stroke accounts 22% of stroke cases (3). A community based prevalence study of stroke conducted in Egypt found that, ischemic stroke was the predominant type of stroke which accounts for 85.1% of stroke cases (30). In line with the findings of the above study, a facility based prospective study conducted in Burkina Faso found that, ischemic stroke was the predominant type of stroke identified among patients which accounts for 72% of stroke cases and hemorrhagic stroke accounts 28% of stroke cases (31).

Similarly, an institutional based prospective cohort study conducted in Kenya found that ischemic stroke was the dominant type of stroke which accounted for 56.1% of the stroke cases (24). In line with this finding, a retrospective record review of adult stroke patients admitted to Gondar University Hospital found that, ischemic stroke was the predominant type of stroke identified which accounts for 69.4% of stroke cases, while hemorrhagic stroke accounts for 30.6% cases (29). Similarly, a prospective facility based study conducted in Hawassa found that, the most commonly identified stroke type was ischemic stroke which accounts for 50.3% of stroke cases followed by hemorrhagic stroke which accounts for 49.7% of stroke cases (17).

In contrary to the findings of the above studies, in developed countries unlike in SSA, the proportion of hemorrhagic stroke is substantially lower (10-15%) (20), but in SSA the proportion of hemorrhagic stroke is 3-4 times higher than higher income countries. Similar to this argument an institutional based cross-sectional study conducted in the adult emergency center of Tikur Anbessa Specialized Hospital in Addis Ababa, Ethiopia showed that hemorrhagic stroke was found to be the most common type of stroke which accounts 56% of stroke cases and ischemic stroke accounts for 44% of stroke cases (4).

Similarly, a retrospective record review conducted in Tikur Anbessa Specialized Hospital and Saint Paulo's Hospital showed that hemorrhagic stroke accounts for 46 and 61.3% of stroke cases respectively (27,32).

2.5 Acute stroke information and patient survival

An Institutional based prospective study conducted in Saudi Arabia found that; the total mortality rate of stroke was 5.58 per 100,000 populations. In hospital mortality rate was 13% and respiratory failure secondary to aspiration pneumonia and increased intracranial pressure were the most common immediate causes of death among stroke patients (5)**.** In line with this finding, a facility based prospective cohort study conducted in Kumasi, Ghana found that of the 115(43.4%) stroke patients who died, 35% of them developed aspiration pneumonia and the majority of stroke death occurs after a median of 5 days (range 1-21 days). The median duration of hospitalization was 6 days (range 1-42 days) and of the 226(85%) hypertensive patients identified only 79(35%) of them were found to be adherent to their anti-hypertensive medications (13).

A retrospective record review conducted in Saint Paul's Millennium Medical College found that, the median length of hospital stay was 9 days with intra-hospital mortality rate of 14.7% and the intra-hospital stroke mortality was higher for hemorrhagic stroke (23.5%) patients compared to ischemic stroke (6.1%) patients. Increased intracranial pressure (75%) and aspiration pneumonia (20.8%) were found to be the most commonly identified immediate causes of intra-hospital stroke mortality (27). A similar study conducted in Ayder Comprehensive Specialized Hospital found that, among those admitted adult stroke patients, only 9.9% patients presented to the hospital within the first 3 hours of stroke symptom onset and the in-hospital case fatality rate was 12% (33).

In line with above studies, a retrospective record review conducted in Felegehiwot Referral Hospital found that, the intra-hospital mortality rate of stroke was 11% and 59.3% of them had hemorrhagic stroke (14). A facility based retrospective descriptive study conducted to assess the pattern of treatment outcome and associated factors among 73 hospitalized stroke patients in Shashemene Referral Hospital, Oromia Region, found that the majority (54.79%) of the patients had good treatment outcome(discharged without any complications). The mean length of hospital stay of the patients was 6.7±2.5 days, while the mean time from symptoms onset to hospital admission was 23.50 ± 13.14 hours (34).

A facility based prospective cohort study conducted to determine the medical and neurological complications among 71 hospitalized adult stroke patients found that the mean delay of presentation from stroke symptoms onset to hospital arrival was 38 hours and 71.8% of patients developed at least one complication. The most commonly observed neuro-medical complications developed were aspiration pneumonia in 24(33.8%) of cases, followed by urinary tract infection in 13(18.3%) of cases and this commonly occurred within 11 to 21 days of admission in 41.7% of cases (35).

A facility based cross sectional study conducted to determine the risk factors and clinical presentation of patients among 104 adult stroke patients at the Emergency Department of Tikur Anbessa Specialized Hospital found that, the median arrival time to the emergency center was 24 hours after symptoms onset (4). A retrospective record review study done in Gondar University Hospital found that around 15% of patients were found to be anemic (hemoglobin level<12 mg/dL) and thrombocytopenic (platelet count<150,000 cells/mm^3). Hyperglycemia (random blood sugar level >180mg/dL) and deranged renal function test (creatinine >1.2 mg/dL) were found in 12.5 and 15.7% of patients respectively (29).

Studies conducted in sub-Saharan African countries and particularly in Ethiopia were deficient on the gold standard recommendations for assessing stroke epidemiological studies. There should be well defined stroke diagnostic criteria and case ascertainment by the WHO case definition, more than 80% of stroke cases should be confirmed by Neuroimaging modalities (CT scan/MRI), further classifications of stroke subtypes based on imaging findings, classification of stroke cases as first and recurrent stroke cases (36).

Even though there are recommendations for high quality epidemiologic stroke study, they recommend community based studies prospectively for at least 3 years, within 5 years of the population census. This is methodologically difficult to apply in SSA and particularly in our set up since population based stroke registries, population census and neuro-imaging modalities are not totally available and scarce in these resource limited countries (36). So fulfilling at least the minimum requirements and by addressing the gaps of the previous studies we can get an approximate recent facility based incidence of adult stroke death.

2.6 Conceptual framework

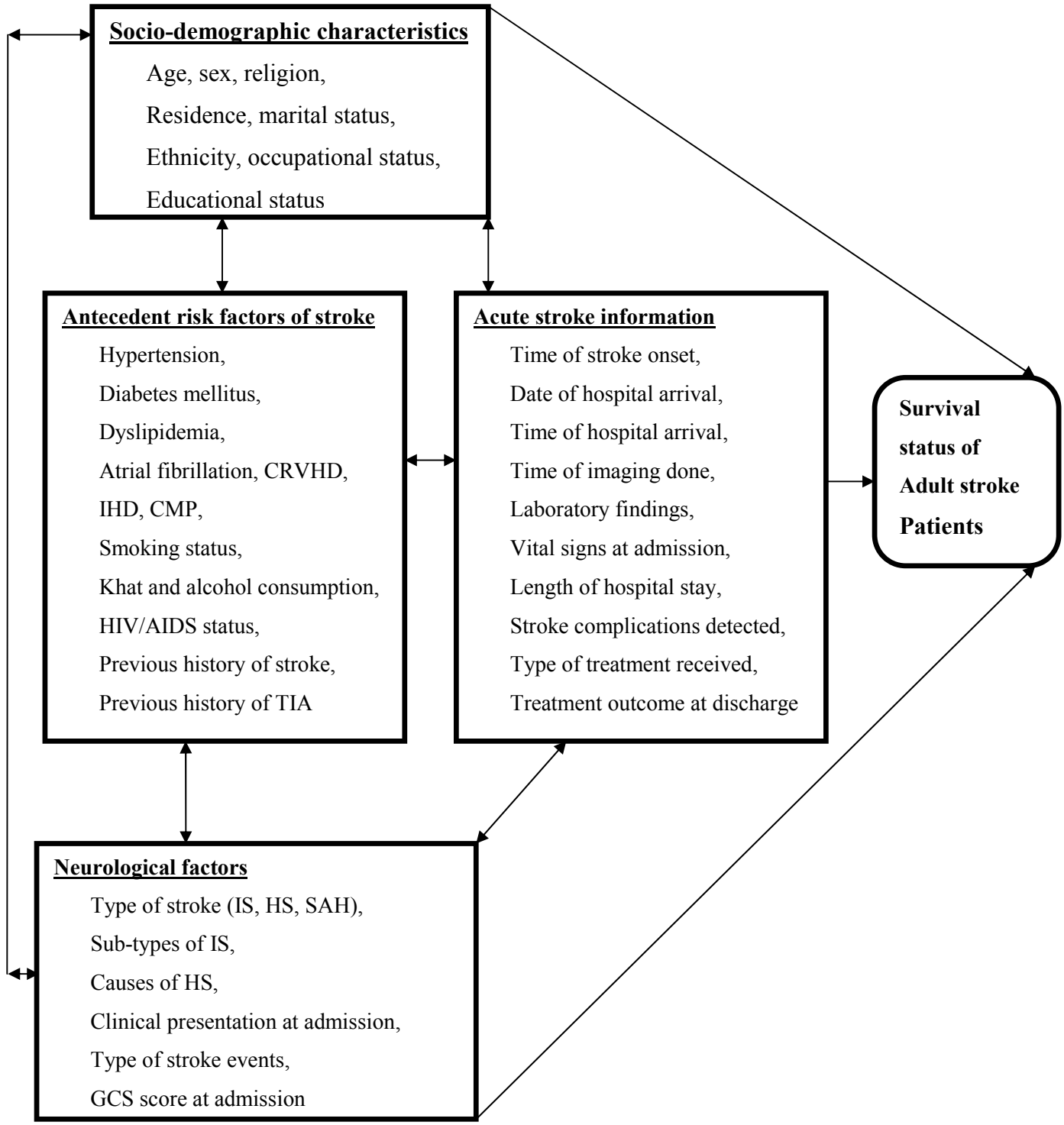

Figure 1: Adapted and modified conceptual framework for comparing survival time difference between hypertensive and non-hypertensive stroke patients taken from the WHO (1) STEPwise approach to stroke surveillance manual, 2019.

2.7 Research questions

1. Is there any difference in the survival time between hypertensive and non-hypertensive first ever stroke patients?

2. What are the predictors of mortality among first ever stroke patients?

2.8 Hypothesis

There is a difference in the overall survival time between hypertensive and non-hypertensive first ever stroke patients.

3. OBJECTIVES

3.1 General objective

To determine the survival of stroke patients according to their hypertension status admitted in Ayder Comprehensive Specialized Hospital, Northern Ethiopia from March 1, 2012 to February 28, 2019.

3.2 Specific objectives

1. To compare the survival probability between hypertensive and non hypertensive first ever stroke patients

2. To identify predictors of mortality among first ever stroke patients

4. METHODS AND MATERIALS

4.1 Study area and period

The study conducted in Ayder Comprehensive Specialized Hospital (ACSH), Mekelle city, Tigray Regional State, Northern Ethiopia, which is 783 Kilometers North of Addis Ababa, the capital city of Ethiopia. It is a government owned teaching hospital and research center in Northern Ethiopia, rendering its referral and specialized medical services to more than 9 million people in its catchment areas of Tigray, Afar and North-Eastern parts of the Amhara Regional States, including Eritrean refugees. It stands as the second largest hospital in the nation with the total capacity of about 500 inpatient beds in all departments and other specialty units, with more than 170,000 patient flow per year (37). All patients presenting with acute neurological symptoms initially evaluated at the emergency department of the hospital, when there is a need they investigated with CT scan or MRI, severe cases admitted to the medical wards and adult intensive care units. The study period was seven years period from March 1, 2012 (where the hospital started using CT scan/MRI machine) to February 28, 2019 and data extraction period carried out from January 1 to March 31, 2019.

4.2 Study design

A facility-based retrospective cohort study conducted among confirmed stroke patients.

4.3 Populations

4.3.1 Target population

All confirmed stroke patients admitted with the primary diagnosis of stroke as per the WHO clinical case definition.

4.3.2 Source population

All confirmed stroke patients admitted to the emergency rooms, medical wards and adult intensive care units of ACSH from March 1, 2012 to February 28, 2019 with the primary diagnosis of stroke as per the WHO clinical case definition.

4.4 Eligibility criteria

4.4.1 Inclusion criteria

All confirmed adult stroke patients admitted in ACSH and diagnosed as per the WHO clinical case definition during the specified period were included in the study.

4.5 Sample size determination and sampling technique

4.5.1 Sample size determination

The sample size was determined using two population proportion formula using Epi info version 7.2.2.6 software (38), taking hypertension status of adult stroke patients as a primary exposure variable and with the assumptions of two-sided significance level (α=5%), power (1-β) =80%, 95% confidence level, ratio of non-exposed to exposed (R) 1:1. Accordingly, the sample size was calculated for each specific objective, the first specific objective provides the largest sample size, with assumptions of percent of exposed (hypertensive) with outcome =59.2% (27), percent of non-exposed (non-hypertensive) with outcome =40.8% (27) and an adjustment made for irretrievable patient medical records by taking 15%. The final sample size required to get a statistically meaningful difference between the two groups was 298.

4.5.2 Sampling technique

Since the total numbers of adult stroke cases were manageable (503 patients) and we want to increase, the power of the study all confirmed adult stroke patients were included in the study.

4.6 Data collection instrument and process

4.6.1 Data collection instrument

Data collected using a data abstraction checklist, after review of different literatures and previous similar studies, and then organized according to the objectives of the study. The checklist was prepared in English and for ease of data abstraction; it contained four parts, socio-demographics of stroke patients, antecedent risk factors of stroke, neurological factors and acute stroke event factors.

4.6.2 Data collection process

Five data collectors who are first year master of Public Health students of Mekelle University collected the data, one experienced supervisor with master's degree in emergency and critical care nursing selected from the same hospital. Training was given for data collectors on the contents of the data abstraction checklist, how to abstract data from patient medical records and health facility logbooks for two days prior to data collection period by the principal investigator.

4.7 Operational definitions

1. Definition of the exposure variable

Exposed group (Hypertensive patients): If a patient was taking antihypertensive medications before admission, history of being diagnosed as hypertensive by a health professional prior to onset of stroke, documented blood pressure of ≥140/ 90 mm Hg before onset of stroke or persisting after the acute phase of stroke (1).

Non-exposed group (Non-hypertensive patients): It was defined as having a blood pressure reading of <140/90 mmHg prior or after onset of stroke (1).

2. Definition of the outcome variable

Adult Stroke death: It was defined as, recorded stroke death within the follow-up time occurring among first ever adult stroke patients aged 18 years and above and ascertainment of death was from death records on the patient's medical record (1).

Censored: Those subjects who were discharged against medical advice, discharged with significant neurologic deficit, death other than stroke (accident or any cause not related to stroke), referred to other health facilities or event free until the end of the study whichever occurred first were considered as censored.

3. Definition of the covariates

Atrial fibrillation: It was defined if the patient had an atrial fibrillation in ECG prior to stroke (records seen) or after onset of stroke (1).

Current tobacco use: An individual who is a current tobacco user (smoking and other forms of tobacco), or was a recent tobacco user, but stopped less than 3 months before acute stroke event (1).

Diabetes mellitus: It was defined as when the patient was taking any antidiabetic medication or when random blood sugar level of ≥ 200 mg/dL or two consecutive fasting venous plasma glucose levels of ≥ 126 mg/dL which persists beyond acute phase of stroke (40).

Dyslipidemia: It was defined as when the patient was taking lipid-lowering medications or total cholesterol level ≥ 240 mg/dL (41).

Entry date: The date of admission taken from the patient medical record

Event (failure): All cause intra hospital adult stroke death from all types of stroke which occurred within 90 days of admission (5).

Excessive alcohol consumption: It was defined as consuming more than 200 gram of pure alcohol per week (42).

Exit date: The date of event or censored which was taken from the record

First ever stroke: A stroke which occurred in persons who never had stroke before (1).

Recurrent stroke: It was defined as a history of a previous stroke event at some time in the past which meets the WHO definition or a history of a new stroke event occurring more than 28 days after onset of a stroke event already registered (1).

Survival time: The survival time calculated in completed days using the time between dates of admission and to the date of event (death) or date of censored coded as one and zero respectively

Survival: Lack of experience of death within the admission period

Time of onset of stroke: It was defined as the time when the patient or observer first became aware of stroke symptoms (1).

Time to Event: The time from first day of admission to the occurrence of adult stroke death

4.8 Study variables

4.8.1 Dependent variable

Time to death

4.8.2 Independent variable

Hypertension status (hypertensive/non-hypertensive)

4.8.3 Covariates

The covariates of interest were:

1. **Socio-demographic characteristics of adult stroke patients**: Age, sex, educational status, occupational status, religion, ethnicity, residence and marital status
2. **Antecedent risk factors of stroke :**Diabetes mellitus, dyslipidemia, atrial fibrillation, rheumatic valvular heart disease, ischemic heart disease, dilated cardiomyopathy ,smoking status, Khat/alcohol consumption, HIV/AIDS status, previous history of TIA and previous history of stroke.
3. **Neurologic factors:** Type of stroke identified by neuro-imaging modalities as (IS, HS, SAH), sub-type of ischemic stroke, causes of hemorrhagic stroke, clinical presentation at admission, type of stroke event and level of consciousness at admission by GCS.
4. **Stroke event factors:** Time from stroke onset to hospital arrival, laboratory findings, vital signs on admission, length of stay in the hospital, occurrence of stroke related complications, type of treatment received and treatment outcome

4.9 Data processing and management

The collected data coded and checked for its clarity, consistency and completeness up to the end of each data collection period. Prior to the analysis, 20% of the data were double entered randomly in order to check data entry errors and Epi info Version 7.2.2.6 (38) was used for data entry.

4.10 Data analysis

The entered data was exported to STATA version 14.0 (43). Open Epi version 3.03 soft ware was used for determining after study power calculation by taking proportion of stroke death among hypertensive and non-hypertensive adult stroke patients (44). Descriptive statistics of numeric variables presented in medians with inter quartile range (IQR), categorical variables presented using frequency and percentages and the outcomes of each patient dichotomized into censored or dead. The person-days of follow-up computed from admission to death, loss to follow-up, or the end of the study. Chi-square test ($\chi 2$) used to assess associations among categorical variables and incidence rate of stroke death calculated by dividing the number deaths among first-ever stroke cases occurring to person days of follow up. Cumulative survival rate after admission among first-ever stroke cases was estimated using Kaplan Meier survival analysis method at day 2, day 7, day 10, day 14 and day 28 after onset of stroke symptom.

The observed difference in survival time between hypertensive and non-hypertensive first ever-adult stroke patients compared using the Log rank test. To assess the association among baseline variables and patient survival two strategies used, first each baseline variable that did not violate the assumptions of Cox proportional hazards regression model entered into a separate Cox regression model. Second, a multivariable Cox proportional hazards regression model was fitted containing predictors that were clinically important and those variables, which had $P < 0.25$ in the bivariate model (39). The assumptions of Cox proportional hazard regression model checked by the following procedures: Log (-log (St) plots, Schoenfeld residual plots and by regressing Schoenfeld residuals against time to test for independence between time and residuals.

The covariates, which violate the assumptions of the Cox proportional hazards regression model, were not included in to the model and missing data, handled by simple deletion from the bivariate and multivariable analysis. The influential observations on the parameter estimate in this survival analysis assessed by DFBETA plots, confounding was checked, percentage change in the regression coefficients (β) less than 20% reveals absence of confounder. Interaction for the main effect model was also checked by using partial likelihood ration test P-value > 0.05 and variance inflation factor less than 10 indicating non-existence of multi-collinearity among the variables in this study. Breslow test used to handle those tied failures, the summary measures of estimated Crude Hazard Ratio (CHR) and

Adjusted Hazard Ratio (AHR) with 95% confidence interval for the survival rate among first ever- adult stroke patients estimated. P-value < 0.05 used to declare statistical significance and goodness of fit of the model assessed by Cox-Snell residuals plot.

4.11 Data quality assurance

To assure the quality of data, properly designed data collection tool was prepared before beginning of the actual data collection. The principal investigator carried out close supervisions, any problems faced in the time of data collection discussed and corrective measures made immediately. Pre-test was done one week prior to the actual data collection period on 5% (35 medical records which were not included in the final analysis) of similar study populations in the same study area. The objectives of pre-test were to insure clarity, wordings, logical sequence and availability of important variables in the patient medical records and some or total modification made on questions that affect the consistency of data.

4.12 Ethical considerations

Ethical approval obtained from the research and ethical committee of the School of Public Health, College of Health Sciences Addis Ababa University. The chief executive director of ACSH briefly informed about the objectives of the study and written permission obtained before starting data collection. The department head of the patient medical records office gave permission for extracting data from patient medical records. The data from the medical records handled with strong confidentiality, neither the case records nor the data extracted used for any other purpose and all the collected patient information was stored anonymous.

4.13 Dissemination of findings

After the completion of the study, the findings are going to be presented at the School of Public Health, Addis Ababa University then submitted to School of graduate studies of Addis Ababa University, principal and co-dvisors of the thesis, ACSH medical director office and concerned others. Dissemination of the findings of this study will be through workshops, seminars and published in one of the international, professional high impact journal.

5. RESULTS

5.1 Socio-demographic characteristics of patients

Between March 1, 2012 and February 28, 2019 there were 503 cohorts of confirmed adult stroke patients admitted in Ayder Comprehensive Specialized Hospital, among these 323(64.21%) of them were hypertensive and 180(35.79%) of them were non-hypertensive adult stroke patients. The power of the study was 100% and the overall median age was 65 years with IQR (53-75) years. According to their exposure status, hypertensive patients' median age was 65 years with IQR (53-75) years, among non-hypertensive patients their median age was 68 years and IQR (54-76) years.

Concerning sex distribution 252(50.1%) of them were male patients and 285(56.66%) of the patients were urban residents. Concerning their educational status, 500 (99.4%) patients educational status was not recorded, similarly marital and occupational status of the patients were not recorded among 481(95.63%) and 492(97.81%) patients medical record respectively (Table 1).

Table 1: Socio-demographic characteristics of first ever-adult stroke patients admitted in Ayder Comprehensive Specialized Hospital, Northern Ethiopia, 2012- 2019

Baseline variables		**Exposure category**		**Total**	**P-value (χ^2)**
		Hypertensive	**Non-hypertensive**		
		Frequency (%)	Frequency (%)	**Frequency (%)**	
Age (years)	<45	44(8.75)	30(5.96)	74(14.71)	0.1
	45-54	40(7.95)	14(2.78)	54(10.74)	
	55-64	68(13.52)	31(6.16)	99(19.68)	
	65-74	87(17.3)	45(8.95)	132(26.24)	
	75-84	64(12.72)	38(7.55)	102(20.28)	
	≥85	20(3.98)	22(4.37)	42(8.35)	
Sex	Female	162(32.21)	89(17.69)	251(49.9)	0.88
	Male	161(32)	91(18.09)	252(50.1)	
Religion	Orthodox	96 (19.09)	62(12.33)	158(31.41)	0.43
	Muslim	29(5.77)	15 (2.98)	44(8.75)	
	Catholic	3 (0.6)	0	3(0.6)	
	Unrecorded[1]	195(38.77)	103 (20.48)	298(59.24)	

Residence	Urban	199(39.56)	86 (17.1)	285(56.66)	0.01*
	Rural	114 (22.66)	88 (17.5)	202 (40.16)	
	Unrecorded [1]	10 (1.99)	6 (1.19)	16(3.18)	
Ethnicity	Tigrian	281(55.86)	159(31.61)	440(87.48)	0.85
	Afar	12(2.39)	7(1.39)	19(3.78)	
	Others ǂ	8(1.59)	5(0.99)	13(2.59)	
	Unrecorded[1]	22(4.37)	9(1.79)	31(6.16)	

1 = implies if the particular variable was not documented in the patient's medical record
ǂ = implies Amhara, Philippians (there was one non-Ethiopian patient)
*= implies that except the place of residence (urban/rural), there was no significant difference in the baseline socio demographic characteristics of hypertensive and non-hypertensive adult stroke patients.

5.2 Antecedent risk factors of stroke

Among the 323(64.21%) hypertensive adult stroke patients admitted, 275(85.14%) of them were diagnosed before admission and 48(14.86%) of them were diagnosed after hospital admission. Among those hypertensive patients diagnosed before admission 199(72.4%) of them were not adherent to their respective anti-hypertensive medications and the median time since when patients were told to be hypertensive was 2 years with IQR(1-5) years.

Khat chewing was not recorded in 477(94.83%) patients medical record similarly alcohol consumption and cigarette smoking were not recorded among 427(84.89%) and 429(85.29%) patients medical record respectively. Following hypertension, Atrial fibrillation and chronic rheumatic valvular heart disease were the most commonly identified risk factors for stroke detected among 91 (18.09%) and 74(14.71%) patients respectively(Table 2).

Table 2: Antecedent risk factors identified among first ever adult stroke patients admitted in Ayder Comprehensive Specialized Hospital, Northern Ethiopia, 2012- 2019.

Patient profile		**Exposure category**		**Total**	**P-value (χ^2)**
		Hypertensive	**Non-hypertensive**		
		Frequency (%)	Frequency (%)	Frequency (%)	
Diabetes mellitus	Yes	25 (4.97)	11 (2.19)	36 (7.16)	0.5
	No	298 (59.24)	169 (33.6)	467 (92.84)	
	Total	323 (64.21)	180(35.79)	503 (100)	
Dyslipidemia (n=449)	Yes	36(8.02)	8(1.78)	44(9.8)	0.02*
	No	259(57.68)	146(32.52)	405(90.2)	
	Total	295(65.7)	154(34.3)	449(100)	
Atrial fibrillation	Yes	58(11.53)	33 (6.56)	91 (18.09)	0.92
	No	265 (52.68)	147 (29.22)	412 (81.91)	
	Total	323 (64.21)	180(35.79)	503 (100)	
RVHD	Yes	43(8.55)	31(6.16)	74(14.71)	0.24
	No	280(55.67)	149(29.62)	429(85.29)	
	Total	323 (64.21)	180(35.79)	503 (100)	
IHD	Yes	3(0.6)	9 (1.79)	12 (2.39)	0.004*
	No	320 (63.62)	171 (34)	491 (97.61)	
	Total	323 (64.21)	180(35.79)	503 (100)	
Cardiomyopathy	Yes	4(0.8)	6 (1.19)	10 (1.99)	0.11
	No	319 (63.42)	174 (34.59)	493 (98.01)	
	Total	323 (64.21)	180(35.79)	503 (100)	
HIV/AIDS	Reactive	8(1.59)	4(0.8)	12(2.39)	0.88
	Non-reactive	78(15.51)	47(9.34)	125(24.85)	
	Unknown	237(47.12)	129(25.65)	366(72.76)	
	Total	323 (64.21)	180(35.79)	503 (100)	
Previous TIA	Present	9(1.79)	4(0.8)	13(2.58)	0.92
	Absent	71(14.12)	41(8.15)	112(22.27)	
	Unrecorded	243(48.31)	135(26.84)	378(75.15)	
	Total	323 (64.21)	180(35.79)	503 (100)	

RVHD = Rheumatic valvular heart disease , IHD= Ischemic heart disease, HIV = Human immuno-deficiency virus, AIDS = Acquired immuno deficiency syndrome, TIA = transient ischemic attack, *= Implies that except their dyslipidemia and IHD status, both group of patients were comparable by their additional co-morbid conditions.

5.3 Neurological factors

Ischemic stroke was the most common type of stroke identified among 285(56.66%) of stroke patients and among those known sub-types of ischemic stroke, Cardio-embolic stroke was the most common sub-type identified among 69 (24.21%) ischemic stroke patients. The most frequent clinical presentations seen among first ever adult stroke patients were hemiparesis and speech disturbances found among 397(78.93%) and 227 (45.13%) patients respectively. Concerning patient's level of consciousness during hospital arrival 227(45.13%) patients had mild level of unconsciousness, GCS score of 13-15 (Table 3).

Table 3: Neurological characteristics of first-ever adult stroke patients admitted in Ayder Comprehensive Specialized Hospital, Northern Ethiopia, 2012- 2019.

Patient profile	**Response**	**Exposure category**		**Total**	**P-value (χ^2)**
		Hypertensive	**Non-hypertensive**		
		Frequency (%)	Frequency (%)	Frequency (%)	
Type of stroke identified	IS	137 (27.24)	148 (29.42)	285 (56.66)	<0.001¶
	HS	180 (35.79)	29 (5.77)	209 (41.55)	
	SAH	6 (1.19)	3 (0.6)	9 (1.79)	
Etiologic sub-types of Ischemic stroke (n=285)	Cardio-embolic	30 (10.53)	39 (13.68)	69 (24.21)	0.53
	LAA	8 (2.81)	13 (4.56)	21 (7.37)	
	SAO	33 (11.58)	29 (10.18)	62 (21.75)	
	Unclassified [a]	66 (23.16)	67 (23.51)	133 (46.67)	
Causes of HS (n=209)	Hypertension	177 (84.69)	1(0.48)	178 (85.17)	<0.001¶
	Others [‡]	1 (0.48)	4 (1.92)	5 (2.4)	
	Unclassified [b]	2 (0.96)	24 (11.48)	26 (12.44)	
Clinical presentation at admission (multiple clinical presentations were possible)	Coma	85 (16.9)	44 (8.75)	129(25.65)	0.65
	Aphasia	145 (28.83)	82 (16.3)	227 (45.13)	0.89
	Hemiparesis	253 (50.3)	144 (28.63)	397(78.93)	0.67
	Hemiplegia	24 (4.77)	15 (2.98)	39 (7.75)	0.72
	CN palsy	44(8.75)	28 (5.57)	72 (14.31)	0.55
	Head ache	127 (25.25)	47(9.34)	174(34.59)	0.3
	Vomiting	125 (24.85)	37 (7.36)	162 (32.21)	0.19
	Others [ǂ]	22 (4.37)	10(1.99)	32(6.36)	0.56

GCS at admission	3-8	61 (12.13)	32 (6.36)	93 (18.49)	0.45
	9-12	111 (22.07)	72 (14.31)	183 (36.38)	
	13-15	151 (30.02)	76 (15.11)	227 (45.13)	

a = indicates for ischemic stroke sub types not classified according to TOAST classification, ¶= Fisher's exact
ǂ =indicates for Amyloid Angiopathy, Vascular aneurism and anticoagulant related causes, IS=ischemic stroke
b = indicates f or those causes of hemorrhagic stroke which were not further classified, HS=hemorrhagic stroke
♯ =indicates vertigo, abnormal body movement, fecal and urinary incontinences, CN= Cranial nerve
SAH= Sub-arachnoid hemorrhage, LAA=Large artery atherosclerosis, SAO=Small artery occlusion
¶= implies that patients were not comparable based on their type of stroke and causes of Hemorrhagic stroke

The median duration from onset of stroke symptoms to hospital arrival for the cohort was 24 hours with IQR (12-72) hours. According to their exposure status, the median duration from onset of stroke symptoms to hospital arrival for hypertensive patients was 24 hours, IQR (12-72) hours and for non-hypertensive patients was 48 hours, IQR (24-96) hours. Four hundred eighty three (96.02%) of stroke patients present to hospital after six hours of stroke symptom onset and CT/MRI investigation was done after 3 hours of hospital arrival for 502(99.8%) adult stroke patients.

Concerning the length of stay in the hospital 203(40.36%) of the patients stayed up to two weeks and 128(25.45%) patients stayed in the hospital for more than two weeks. Carotid Doppler ultrasound was done for 26(5.27%) patients, from these 18(3%) patients had normal Carotid Doppler finding. Two hundred thirty six (46.92%) of the patients develop at least one neuro-medical stroke complications, from these the top three complications were aspiration pneumonia, increased intracranial pressure (ICP) and urinary tract infection which occurred among 183(36.38%), 58(11.53%) and 38(7.55%) of stroke patients respectively (Table 4).

Table 4: Stroke event factors[1] at admission among first ever adult stroke patients admitted in Ayder Comprehensive Specialized Hospital, Northern Ethiopia, 2012- 2019

Patient profile	**Categories**	**Exposure category**		**Total**	**P-value (χ^2)**
		Hypertensive	**Non-hypertensive**		
		Frequency (%)	Frequency (%)	Frequency (%)	
Time from stroke onset to hospital arrival (in hours)	>6	308(61.23)	175(34.79)	483(96.02)	0.31
	Others [a]	15(2.98)	5(1)	20(3.98)	
	Total	323 (64.21)	180(35.79)	503 (100)	
Timing of brain imaging done (in hours)	≤3	0	1(0.2)	1(0.2)	0.18
	>3	323(64.21)	179(35.59)	502(99.8)	
	Total	323 (64.21)	180(35.79)	503 (100)	
Length of hospital stay (in days)	1-7	117(23.26)	55(10.93)	172(34.19)	0.42
	7-14	125(24.85)	78(15.51)	203(40.36)	
	≥14	81(16.1)	47(9.34)	128(25.45)	
	Total	323 (64.21)	180(35.79)	503 (100)	
Presence of stroke Complications	Yes	152(30.22)	84(16.7)	236(46.92)	0.93
	No	171(34)	96(19.09)	267(53.08)	
	Total	323 (64.21)	180(35.79)	503 (100)	
Types of stroke complications detected (a patient can have more than one complication)	Aspiration Pneumonia	115(22.86)	68(13.52)	183(36.38)	0.63
	Increased ICP	45(8.95)	13(2.58)	58(11.53)	0.24
	UTI	25(4.97)	13(2.58)	38(7.55)	0.83
	DVT	10(1.99)	9(1.79)	19(3.78)	0.28
	Seizure	18(3.58)	7(1.39)	25(4.97)	0.41
	Others[#]	15(2.98)	4(0.8)	19(3.78)	0.55
Hgb level of males (g/dL) (n=252)	≤13	29(11.51)	16(6.35)	45(17.86)	0.93
	>13	132(52.38)	75(29.76)	207(82.14)	
	Total	161(63.89)	91(36.11)	252(100)	
Hgb level of females (g/dL) (n=251)	≤12	27(10.76)	19(7.57)	46(18.33)	0.36
	>12	135(53.78)	70(27.89)	205(81.67)	
	Total	162(64.54)	89(35.46)	251(100)	
Platelet count (cells/mm^3)	<150,000	37(7.36)	24(4.77)	61(12.13)	0.21
	150-450,000	269 (53.48)	140(27.83)	409(81.31)	

	>450,000	17(3.38)	16(3.18)	33(6.56)	
	Total	323(64.21)	180(35.79)	503(100)	
Serum creatinine (mg/dL) (n=491)	≤ 1.6	296 (60.29)	164(33.4)	460(93.69)	0.99
	>1.6	20(4.07)	11(2.24)	31(6.31)	
	Total	316(64.36)	175(35.64)	491(100)	

[a] = includes those patients who present to the hospital within 3 hours , 3 to 4.5 hours and 4.5 to 6 hours of stroke symptoms onset**.** # = includes Gastro-intestinal bleeding, Mayocardial infarction, hypokalemia, hypocalcaemia and bedsore**,** [1]= Hypertensive and non-hypertensive adult stroke patients were comparable by all of the acute stroke event factors (P-value was non-significant in all of the event factors).

5.4 Survival analysis

The total person-days of observation for the entire cohort was 5,281 person-days (3,380 person-days for hypertensive patients and 1,901 person-days for non-hypertensive patients), with median follow-up time of 8 days and IQR (5-14) days. According to exposure status, the median follow up time for hypertensive patients was 8 days with IQR (5-14) days and the median follow up time for non-hypertensive patients was 9 days with IQR (5-14) days.

The overall median survival time among first ever-adult stroke patients was 48 days (95% CI; 48-not reachable), the median survival time among hypertensive patients was 48 days (95% CI 48-not reachable), the median survival time for non-hypertensive patients was not reachable, but 25% of them survive up to 25 days of admission. The median time of death for the entire cohort was four days with IQR (1-7) days. Among hypertensive patients, the median time of death was four days with IQR (1-7) days after admission.

The median time of death for non-hypertensive adult stroke patients was two days with IQR (1-7.5) days and the overall 30-day case fatality rate was 15%(74/489), among hypertensive 15.97%(50/313) and 13.64%(24/176) among non-hypertensive adult stroke patients. The cumulative survival probability for hypertensive adult stroke patients up to the end of first week was 87 %(95% CI 82-90) and by the end of the first month was 80 %(95% CI 73- 85). Similarly, among non-hypertensive patients was 89% (95% CI 84-94) and 73 %(95% CI 55-85) respectively (Table 5).

Table 5 : Kaplan – Meier estimate of survivor function among first ever-adult stroke patients admitted in Ayder Comprehensive Specialized Hospital, Northern Ethiopia, 2012- 19.

Exposure status	Time (days)	Beginning total	Fail	Survivor function	Std. error	95% CI
Hypertensive	2	301	17	0.95	0.013	0.92, 0.97
	7	206	39	0.87	0.02	0.82 ,0.90
	10	136	6	0.83	0.02	0.78,0.87
	14	81	3	0.81	0.03	0.75,0.86
	28	14	1	0.80	0.03	0.73,0.85
Non-hypertensive	2	163	14	0.92	0.02	0.87, 0.95
	7	125	18	0.89	0.024	0.84,0.94
	10	78	1	0.89	0.025	0.83,0.93
	14	47	2	0.85	0.033	0.76,0.91
	28	9	3	0.73	0.075	0.55,0.85

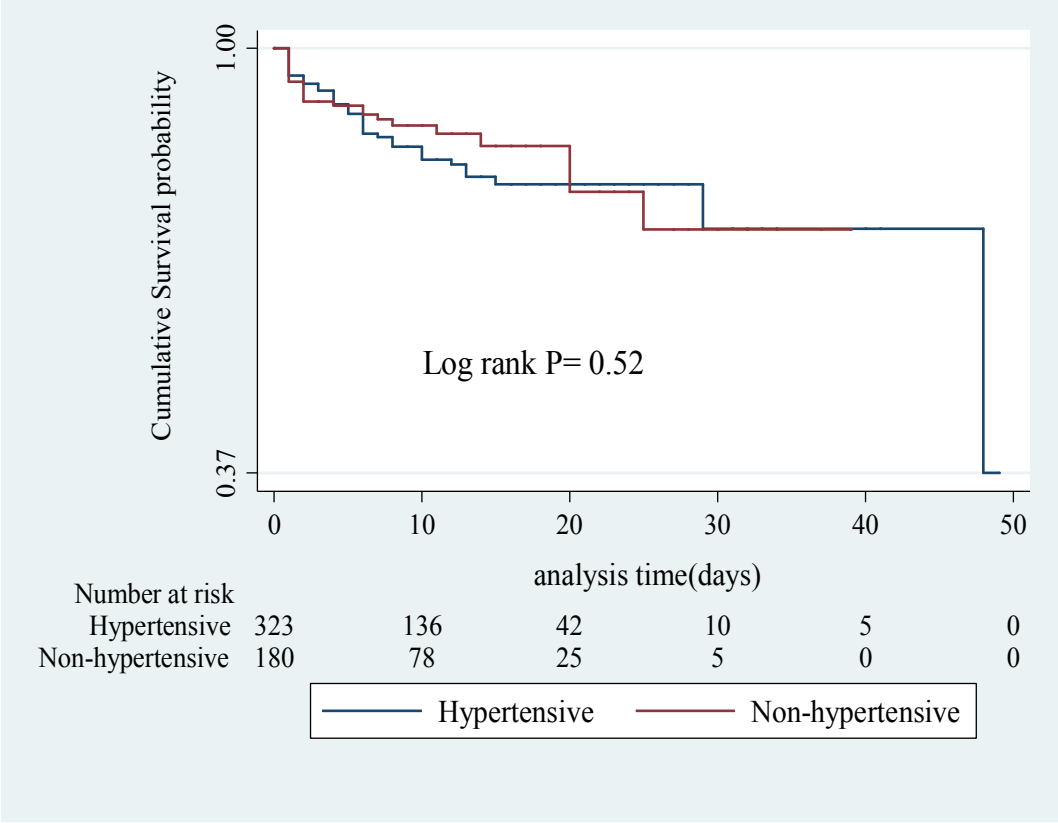

Figure 2 : Kaplan-Meier survival curve based on exposure status among first ever-adult stroke patients admitted in Ayder comprehensive specialized hospital, Northern Ethiopia, 2012-2019.

A comparison of the survival curves between hypertensive and non-hypertensive adult stroke patients by Kaplan-Meier survival analysis revealed that there was no statistically significant difference in the overall survival time (Log rank test = 0.42, df =1, P= 0.52). The number of at risk patients by the end of 10th day were 136 hypertensive and 78 non-hypertensive patients, by the end of the first month there were only 10 hypertensive and 5 non-hypertensive first ever-adult stroke patients as shown above (Figure 2).

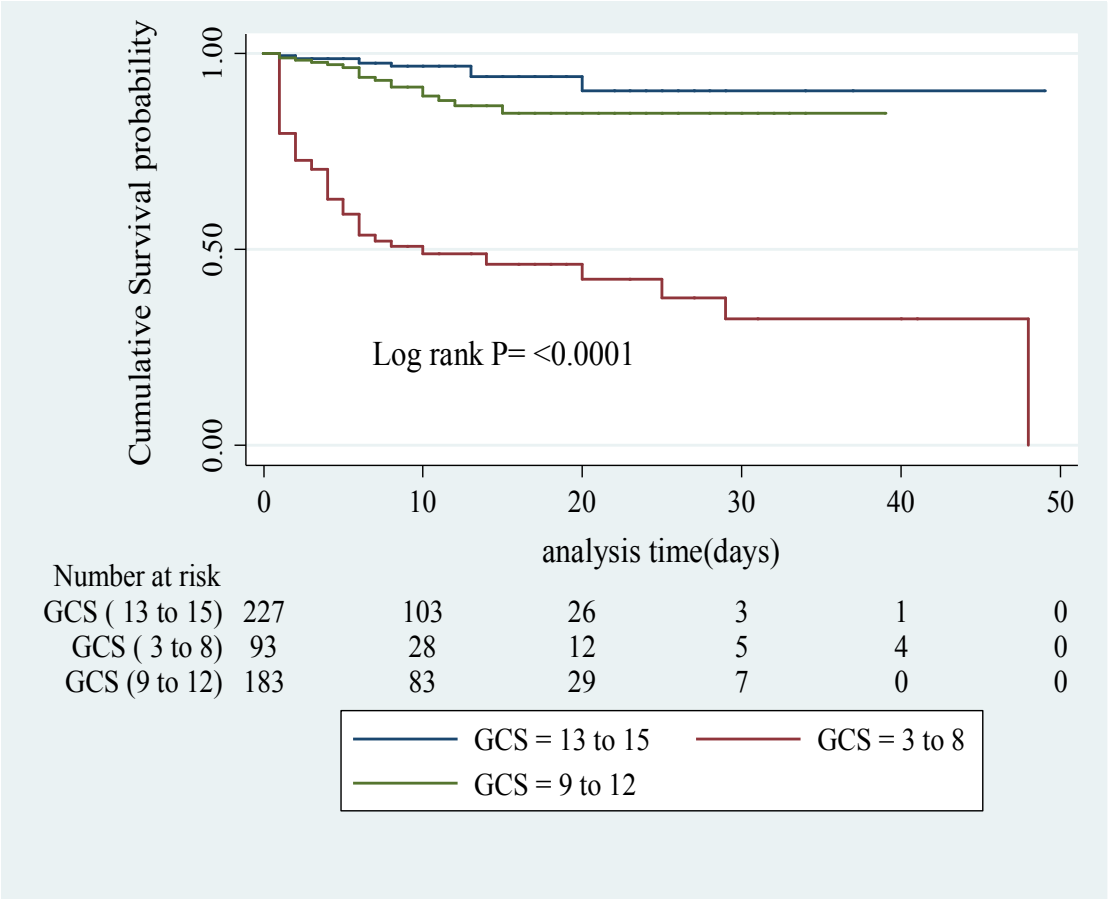

Figure 3 : Kaplan-Meier survival curve based on admission GCS among first ever-adult stroke patients admitted in Ayder comprehensive specialized hospital, Northern Ethiopia, 2012-2019.

There was a faster drop in the cumulative survival probability of patients with GCS score of 3-8 compared to the survival curve of patients with GCS score of 13-15. This shows that patients with GCS score of 13-15 had better survival than patients with GCS score of 3-8 which was found to be statistically significant (Log rank test = 139.59, df=2, P<0.0001) as shown above (Figure 3).

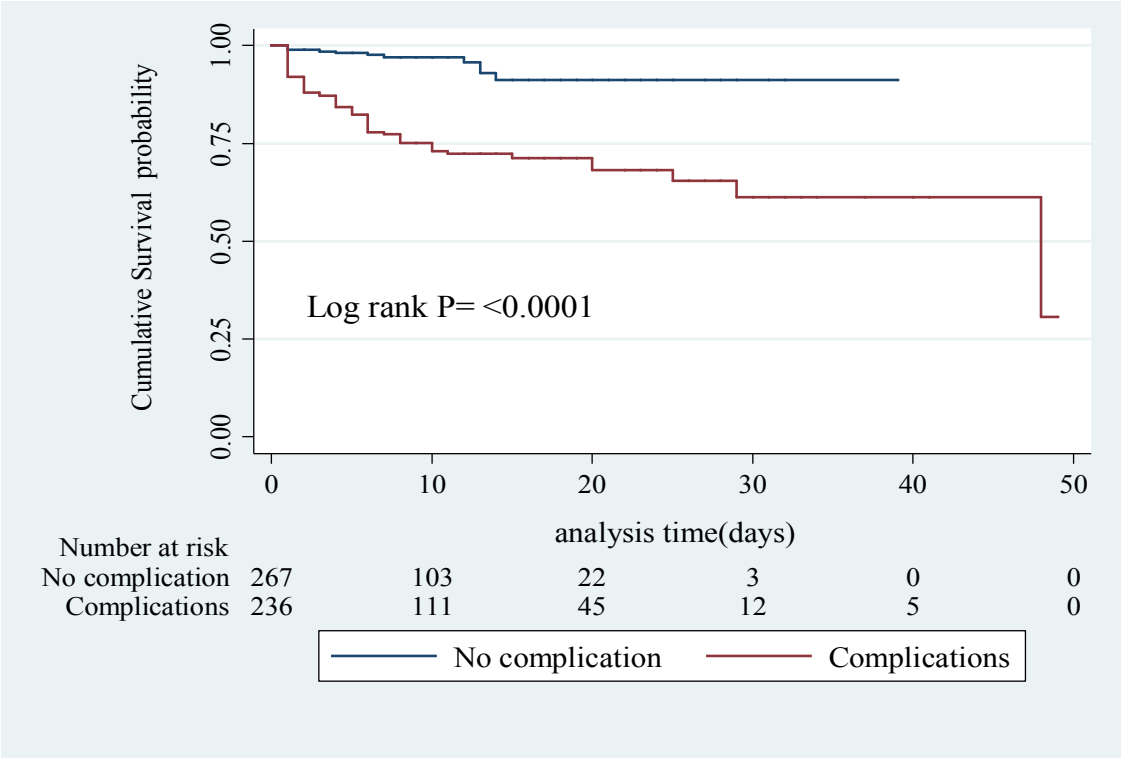

Figure 4 : Kaplan-Meier survival curve based on development of stroke complications among first ever-adult stroke patients admitted in Ayder comprehensive specialized hospital, Northern Ethiopia, 2012-2019.

Similarly, there was a faster drop in the cumulative survival probability of patients who developed any of the stroke complications as compared to their counter parts who did not develop any stroke complications. This was also found to be statistically significant (Log rank test 42.21, df=1, P= <0.0001) as shown above (Figure 4).

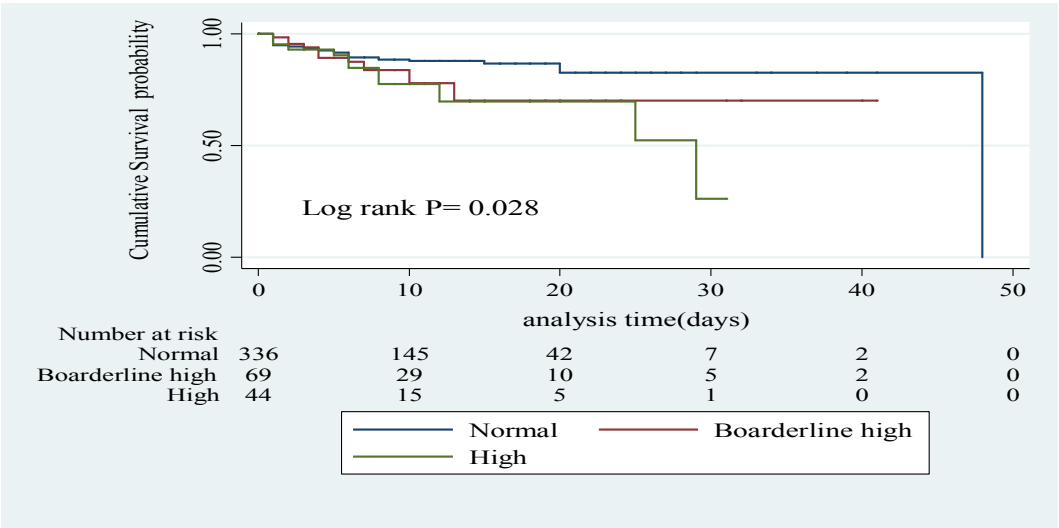

Figure 5 : Kaplan-Meier survival curve based on total cholesterol level among first ever-adult stroke patients admitted in Ayder comprehensive specialized hospital, Northern Ethiopia, 2012-2019.

As shown in the above (Figure 5), adult stroke patients who had borderline high cholesterol level had lower cumulative survival probability as compared to those who had normal total cholesterol level (Log rank test= 7.19, df=2, P=0.028). There was also a statistically significant difference in their cumulative survival probability among the following groups of patients; urban and rural residents, Type of stroke identified, causes of hemorrhagic stroke, and anemic and non-anemic female patients showed a statistically significant Log rank test as shown below (Table 6).

Table 6 : Log-rank test for equality of survivor functions among first ever-adult stroke patients admitted in Ayder Comprehensive Specialized Hospital, Northern Ethiopia 2012-2019

Covariates	**Category**	**Observed deaths**	**Expected deaths**	χ^2 **(df)**	**P-value**
Hypertension status	Hypertensive	51	48.35	0.42(1)	0.52
	Non-hypertensive	24	26.65		
	Total	75	75		
Residence (n=579)	Urban	51	42.37	4.28(1)	0.039*
	Rural	22	30.63		
	Total	73	73		
Type of stroke	Ischemic	35	42.92	5.99(2)	0.05*
	Hemorrhagic	37	30.97		
	SAH	3	1.11		
	Total	75	75		
Causes of HS (n=183)	Hypertension	30	32.27	7.47(1)	0.0063*
	Non-hypertension	3	3		
	Total	33	33		
GCS at admission	3-8	48	11.83	139.59 (2)	<0.001**
	9-12	18	28.43		
	13-15	9	34.75		
	Total	75	75		
Stroke complications	Yes	64	36.63	42.21 (1)	<0.001**
	No	11	38.37		
	Total	75	75		
Aspiration Pneumonia	Yes	57	29.17	46.68 (1)	<0.001**
	No	18	45.83		
	Total	75	75		

ICP	Yes	30	7.23	83.78 (1)	<0.001**
	No	45	67.77		
	Total	75	75		
Anemia among Female (n=251)	Anemic	12	6.39	6.1(1)	0.014*
	Non-anemic	24	29.61		
	Total	36	36		
Total cholesterol (n=449)	Normal	40	48.80	7.19(2)	0.028*
	Borderline high	14	10.07		
	High	11	6.13		
	Total	65	65.00		
Serum creatinine (n=491)	≤1.6	64	67.37	2.68(1)	0.101
	>1.6	8	4.63		
	Total	72	72		

*= shows significant difference at P<0.05, **= shows significant difference at P<0.001, HS=Hemorrhagic stroke, GCS=Glasgow coma scale, SAH=Sub-arachnoid hemorrhage, ICP= Increased intra-cranial pressure

In the final multivariable Cox proportional hazards regression model those variables which were clinically important (hypertension status), variables which had p-value <0.25 in the bivariate analysis and non-collinear independent variables were the candidate variables included (causes of hemorrhagic stroke was found to have a collinearity with type of stroke identified and it was excluded from the final model). The variables selected for the multivariable analysis were hypertension status, age of the patient, place of residence, type of stroke identified by CT/MRI, GCS score at admission, stroke complications, total cholesterol level, anemia among female patients, platelet count and serum creatinine level.

The multivariable Cox Proportional hazards regression model shows that, at any particular point in time the hazard of death among hypertensive adult stroke patients was two times higher (AHR=2.13; 95% CI 0.66-6.81) than non-hypertensive adult stroke patients by controlling the effect of other variables, but this finding was not statistically significant. The hazard of death at any particular point in time among those adult stroke patients admitted with GCS score of 3-8 had 10.12(AHR= 10.12; 95% CI 2.58-40.68) times higher hazard of death as compared to those who had GCS score of 13-15, by controlling the effect of other variables.

The hazard of death at any particular point in time among adult stroke who had GCS score of 9-12 was 75% (AHR= 1.75; 95% CI 0.44-7.3) higher than those who had GCS of 13-15 by controlling the effect of other variables, but it was not found to be statistically significant. Similarly at any particular point in time those adult stroke patients who developed any stroke complications had 7.23 times (AHR= 7.23; 95% CI 1.86-28.26) higher hazard of death as compared to their counter parts who had no stroke complications, by controlling the effect of other variables. Concerning the total cholesterol level, at any particular point in time those patients who had borderline high total cholesterol level had 3.57 times (AHR=3.57; 95% CI 1.15-11.1) higher hazard of death than those who had normal total cholesterol level, by adjusting the effect of other variables.

The hazard of death at any particular point in time among those adult stroke patients who had higher cholesterol level was 57% higher (AHR= 1.57; 95% CI 0.31-7.96) as compared to those who had normal cholesterol level by adjusting the effect of other variables, but this was not found to be statistically significant. There was no statistically significant difference in the hazard of death among adult stroke patients who had different age categories, place of residence, types of stroke identified, anemia status among female, platelet count and serum creatinine level after adjusting the effect of other variables (Table 7).

Table 7: Bivariate and adjusted predictors of mortality among first ever adult stroke patients admitted in Ayder Comprehensive Specialized Hospital, Northern Ethiopia, 2012- 2019.

Covariates		**Survival status**		**CHR**	**P-value**	**AHR**	**95% CI**	**P-value**
		Dead (%)	Censored (%)					
Age (in years)	<45	13(2.58)	61(12.13)					1(base)
	45-54	10(1.99)	44(8.75)	1.12	0.79	1.05	0.15,7.41	0.96
	55-64	24 (4.77)	75(14.91)	1.51	0.24	1.41	0.25,8.04	0.70
	65-74	17(3.38)	115(22.86)	0.83	0.60	1.74	0.34,8.91	0.51
	75-84	7 (1.39)	95(18.89)	0.41	0.06	0.12	0.01,1.69	0.12
	≥85	4 (0.8)	38(7.55)	0.68	0.5	0.67	0.05,8.64	0.76
Sex	Male	39(7.75)	213(42.35)					1(base)
	Female	36(7.16)	215(42.74)	0.91	0.7			
Residence (n=487)	Urban	51(10.47)	234(48.05)					1(base)
	Rural	22(4.52)	180(36.96)	0.6	0.04	0.82	0.31, 2.13	0.68
Ethnicity (n=472)	Tigrian	67(14.19)	373(79.03)					1(base)
	Non-Tigrian	4(0.85)	28(5.93)	0.74	0.56			
Hypertension	No	24(4.77)	156(31.01)					1(base)
	Yes	51(10.14)	272(54.08)	1.17	0.52¶	2.13	0.66,6.81	0.2
Diabetes mellitus	No	68(13.52)	399(79.32)					1(base)
	Yes	7(1.39)	29(5.77)	1.22	0.61			
Atrial fibrillation	No	64(12.72)	348 (69.18)					1(base)
	Yes	11 (2.19)	80 (15.9)	0.74	0.36			
RVHD	No	63(12.52)	366(72.76)					1(base)
	Yes	12(2.39)	62(12.33)	1.09	0.78			
HIV/AIDS (n=137)	Negative	17(12.59)	107(79.26)					1(base)
	Positive	1(0.74)	10(7.41)	1.25	0.77			
Previous TIA (n=125)	Absent	15(12)	97(77.6)					1(base)
	Present	2(1.6)	11(8.8)	0.96	0.95			
Type of stroke	Ischemic	35(6.96)	250(49.7)					1(base)
	Hemorrhagic	37(7.36)	172(34.19)	1.47	0.11	0.71	0.26,1.96	0.51
	SAH	3(0.6)	6(1.19)	3.32	0.05	0.83	0.08,8.16	0.87

Sub-type of IS (n=152)	SAO	9(5.92)	53(34.87)					1(base)
	CE	6(3.95)	63(41.45)	0.7	0.51			
	LAA	4(2.63)	17(11.18)	1.3	0.67			
Causes of HS (n=183)	Hypertension	30(16.39)	148(80.87)					1(base)
	Non-hypertension	3(1.64)	2(1.09)	4.45	0.01			
Duration of symptoms	< 6	4(0.8)	16(3.18)					1(base)
	≥ 6	71(14.12)	412(81.91)	0.63	0.37			
GCS at admission	13-15	9(1.79)	218(43.34)					1(base)
	3-8	48(9.54)	45(8.95)	16.55	<0.001	10.12	2.58,40.68	0.001
	9-12	18(3.58)	165(32.8)	2.45	0.03	1.75	0.44,7.3	0.44
Stroke complications	No	11(2.19)	256(50.89)					1(base)
	Yes	64(12.72)	172(34.19)	6.3	<0.001	7.23	1.86,28.26	0.004
Total cholesterol (n=449)	Normal	40(8.91)	296(65.92)					1(base)
	Borderline	14(3.12)	55(12.25)	1.71	0.09	3.57	1.15, 11.1	0.03
	High	11(2.45)	33(7.35)	2.2	0.02	1.57	0.31, 7.96	0.58
Hgb male (n=252)	≥ 13	10(3.97)	35(13.89)					1(base)
	< 13	29(11.51)	178(70.63)	1.45	0.03			
Hgb female (n=251)	≥12	24(9.56)	181(72.11)					1(base)
	<12	12(4.78)	34(13.55)	2.32	0.02	2.04	0.75, 5.51	0.16
Platelet count (cells/mm^3)	Normal	57(11.33)	352(69.98)					1(base)
	<150,000	11(2.19)	50(9.94)	1.29	0.44	1.52	0.39,5.83	0.55
	>450,000	7(1.39)	26(5.17)	1.63	0.22	1.07	0.13, 9.15	0.95
Creatinine level (n=491)	≤1.6	64(13.03)	396(80.65)					1(base)
	>1.6	8(1.63)	23(4.68)	1.82	0.11	0.25	0.02,2.49	0.24
Global test[1]								**P(PH) =0.22**

¶= this variable was significant in the previous study (5), we included in the final model (P was >0.25)

CHR= Crude hazard ratio, AHR: Adjusted hazard ratio, CI= Confidence interval, Hgb= Hemoglobin, GCS= Glasgow coma scale, RVHD= Rheumatic valvular heart disease, HS= Hemorrhagic stroke, SAH= Subarachnoid hemorrhage, SAO= Small artery occlusion, CE= Cardio-embolic, LAA= large artery occlusion, AIDS= Acquired Immuno deficiency syndrome, HIV= Human Immuno-deficiency Virus, *: shows significant difference at P<0.05, [1]= P-value of Schoenfeld residuals for assessing Cox proportional hazards assumption

6. DISCUSSIONS

This study provided the first evidence on the survival of adult stroke patients and the predictors of mortality among Ethiopian first ever-adult stroke patients. There were 75 deaths (14.91%) over the seven years period (with one-month case fatality rate of 15%) out of 503 first ever-adult stroke patients. In our study, the mortality from stroke at day 10 and 28 was 14.8 and 23.1% as compared to the study conducted in Kenya (26), the overall mortality rates were 18.4 and 26.7% respectively.

We found a non-significant difference in the overall survival time between hypertensive and non-hypertensive first ever-adult stroke patients, in spite of having two times higher hazard of death among hypertensive patients. In agreement with our study, a study conducted in South London (21) found that, pre-stroke hypertension was not independent predictor of patient survival and hypertensive patients had 1% lower hazard of death as compared to non-hypertensive adult stroke patients. These findings were in contradiction with the study done in Saudi Arabia (5), whereby hypertensive patients had 77% higher hazard of death as compared to non-hypertensive adult stroke patients. This might be due to differences in sample size, follow up period and proportion of hypertensive and non-hypertensive patients.

This statistically insignificant result has no clinical importance, the possible mechanisms by which hypertension can lead to stroke and increases the hazard of death are; hypertension causes auto-regulatory dysfunction with excessive cerebral blood flow, which leads to higher risk of reperfusion injury and hemorrhagic transformation(22). The second mechanism is that chronic hypertension causes a small vessel vasculopathy, characterized by lipohyalinosis, fibrinoid necrosis and affects deep penetrating arteries/arterioles. The third mechanism is extreme arterial hypertension leads to development of encephalopathy, cardiac complications and renal insufficiency, which ultimately increases the hazard of stroke death (22,23).

Previous literatures indicated that for every 10-mmHg increase in Systolic blood pressure, the hazard of stroke mortality increases by 8-24% (45). Slight to moderate increase in arterial hypertension has an advantage for ischemic stroke patients as it increases cerebral perfusion of the ischemic tissue; however, persistently elevated blood pressure has been associated with worse clinical outcomes in a linear fashion.

Among hemorrhagic stroke patients, elevated blood pressure was associated with greater risk of hematoma expansion, neurological deterioration and death, so that elevated blood pressure treated aggressively. The median age at which stroke occurs was 65 years , IQR (53-75) years which was similar with the studies conducted in Addis Ababa (27) and Kenya (26), indicating that stroke is commonly the disease of the old age population. Even though there was no significant difference in the overall survival time among different age groups, those adult stroke patients aged 55-64 years had 41% higher hazard of death as compared to those aged less than 45 years after controlling for the potential confounders.

This was in contradiction with the study done in Kenya (26), for a one year increment in age of the patient the hazard of stroke death increases by approximately 2% after adjusting for potential confounders. Similarly a study done in Taiwan (46), showed that age of the patient was found to be the independent predictor of patient survival, patients aged 45-65 years of age had higher hazard of death as compared to those aged less than 45 years of age, after controlling the effect of other potential confounders. This might be due to differences in sample size and follow up period.

A study conducted in Iran (47) found that post-menopausal women were more likely to experience incident stroke death as compared to their age-matched male patients, in contrast to this study we found a non-significant difference in survival time between male and female adult stroke patients. In agreement with our study, the south London stroke register(21) also found that there was no significant difference in the survival time between male and female patients. The difference in survival time between male and females in the previous studies, explained by the reduced protective effect of estrogen during the menopausal period, old age women are more likely to experience depression than their age-matched males. Women had higher life expectancy as compared to males, where age is one of the independent non-modifiable risk factor for development of stroke.

During the reproductive age, women had lower incidence of stroke and males had higher incidence of stroke morbidity and mortality, in the young age males are highly exposed to different unhealthy behaviors (cigarette smoking, drinking of alcohol) as compared to their age-matched females. We have found that hemorrhagic stroke was second most common type of stroke identified among 41.55% of stroke cases which is in contrast to the study done in Addis Ababa (27).

This finding is three to four times higher than the studies done in western countries (20). Hemorrhagic stroke accounts only 10-15 % of stroke cases, the possible explanations could be due to high magnitude of hypertension in Africa and majority of patients were not adherent to their respective anti-hypertensive medications, in our study (72.4%) all of which contribute to the high magnitude of hemorrhagic stroke. In agreement with our finding, studies conducted in Hawassa (17) and University of Gondar (48), found that cardio-embolic sub-type of ischemic stroke was the most common sub-type identified, indicating the dominance of the cardiac causes of ischemic stroke.

There was no significant difference on the survival time among different types of stroke; the hazard of death among hemorrhagic stroke patients was 29% lower than patients who had ischemic stroke. Similarly, the hazard of death among patients who had sub-arachnoid hemorrhage was 17% lower than patients who had ischemic stroke after adjusting for the effect of age, stroke severity and presence of stroke complications. Our finding was in line with the study done in Netherlands (42).

In contrast to these studies, a study conducted in London (21) found that, patients with hemorrhagic stroke had 21% and subarachnoid hemorrhage 45% higher hazard of death in the acute phase as compared to patients who had ischemic stroke. In our study, admission GCS score was the independent predictor of patient survival, patients who had GCS score of 3-8 had ten times higher hazard of death as compared to those having GCS score of 13-15. This was in line with the study done in Saudi Arabia (5), where altered level of consciousness at presentation had significantly higher hazard of intra-hospital mortality.

Similarly, a study conducted in south London (21) found two times higher hazard of death among patients who had moderate to severe brain injury as compared to alert patients. The possible explanation could be comatose patients had a higher probability of developing acute phase neuro-medical stroke complications, which can predispose them to higher hazard of death. This finding had a clinical significance during patient management, as it affects the length of stay, functional outcome of the patient and overall costs of stroke treatment.

We found that at any particular point in time, the hazard of death among adult stroke patients who had any of the neuro-medical stroke complications was seven times higher than those who had no complications, after adjusting for potential confounders. This finding was in line with the studies done Italy (49), Taiwan (46), Saudi Arabia (5), this can be explained by the effect of stroke related depressed immunity; depressed gag-reflex and delayed mobilization of admitted patients. Early management of complications along with early mobilization and rehabilitation of patients, could significantly lower the incidence of complications, shortens length of hospital stay and disability after onset of stroke symptoms.

Adult stroke patients who had total cholesterol level of borderline high had almost four times higher hazard of death as compared to patients who had normal total cholesterol level. A non-significant difference in the hazard of death observed between patients who had high and normal total cholesterol level, in spite of having 57% higher hazard of death among patients who had high total cholesterol level. This was different from the study conducted in Sweden(50), high total cholesterol level was independent predictor of improved long term survival of ischemic stroke patients. This improved survival among high cholesterol patients created a sense of obesity paradox.

The median time of death among adult stroke patients was 4 days with IQR(1-7) days after admission and this was found to be in line with the study done in Hawassa (17), where the median time of death was 4.5 days (IQR 2 -7 days) after hospital admission. In our finding only 5% of patients present within the window period (4.5 hours) of stroke symptom onset and time from onset of symptoms to hospital arrival found to be associated with patient survival. In contrast to this a study done in Iran (47) found that, in around half of the patients the hospital arrival time after onset of stroke symptoms was within four hours. This difference might be due to the different level of health literacy and socio-economic status among the patients.

A study conducted in London (44) found that patients treated in specialized stroke units had 25% lower hazard of death as compared to patients treated in medical wards or some were else after adjusting for potential confounders. This finding indicates that establishment of specialized stroke centers capable of providing comprehensive treatment services for stroke patients can reduce the high intrahospital mortality of stroke if applied in our set up along with development of stroke quality-of-care indicators.

7. STRENGTH AND LIMITATIONS OF THE STUDY

Strengths: This was the first local study, which tried to estimate the incidence rate of stroke death among first ever-adult stroke patients by following the minimum gold standard recommendations of Epidemiologic stroke study and reporting of quality survival analysis data. We separately reported the number of first ever and recurrent cases, we had used only confirmed stroke cases, World Health Organization clinical case definition of stroke, stroke type and sub-types along with the adjusted estimate of predictor variables. The cohort groups were also comparable in most of their baseline characteristics.

Limitations: The result of this study was not without limitations. First, the study was limited to adult stroke patients who present to the hospital, we cannot rule out potential selection bias (referral bias) for those who died out of hospital. There was also a significant missing of socio-demographic variables; we excluded them from the Cox regression model, which might have an effect on the adjusted estimates of covariates. We studied all cause mortalities; we were not able to determine the exact causes of death for each admitted patient, which would have an implication during patient management, by acknowledging these potential limitations we hope that this finding can serve as baseline information for further research.

8. CONCLUSION AND RECOMMENDATIONS

8.1 Conclusions

We have found that there was no statistically significant difference in survival time between hypertensive and non-hypertensive first-ever adult stroke patients. The exposure status does not matter for patient survival rather; Glasgow coma scale at admission, presence of stroke complications and borderline high total cholesterol level were the independent predictors of patient mortality.

8.2 Recommendations

Clinicians: We recommend clinicians to strengthen early identification and treatment of stroke complications and other co-morbidities along with strict follow up of comatose adult stroke patients, which can ultimately improve survival of stroke patients.

Researchers: We recommend researchers and scientific community to estimate the incidence of stroke death by doing a prospective community based studies with large sample size which can approximate the exact burden of this underestimated public health problem.

Policy makers: We recommend policy makers to design context specific appropriate strategies for addressing the traditional modifiable risk factors of stroke by early screening, detection, treatment and control of stroke complications.

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Annex I: Data abstraction checklist

Data abstraction checklist used for determining the effect of hypertension on the survival of adult stroke patients admitted in Ayder Comprehensive Specialized Hospital, Northern Ethiopia: Seven years retrospective cohort study.

Specify whether the patient was in either of the

1. **Exposed group (hypertensive)** ☐ **2. Non-exposed group (Non-hypertensive)** ☐
   , and specify the place of admission of the patient in either of,

1**. Emergency Room** ☐ 2. **Medical Wards** ☐ 3. **Adult ICU** ☐

Name of data abstractor: _____

Name of supervisor: _____Date of data abstraction: _____/_____/_____

Part one: Socio-demographic characteristics MRN: Checklist code:

S.no	Variables	Category	S.no	Variables	Category
1.	Age (in years)____		**7.**	Ethnicity	1. Tigrian
2.	Sex	1. Male			2. Amhara
		2. Female			3. Afar
		99. Unrecorded			4. Others (specify)__
3.	Religion	1. Orthodox			99. Unrecorded
		2. Muslim	**8.**	Marital status	1. Single
		3. Catholic			2. Married
		4. Protestant			3. Divorced
		5.Others (specify)__			4.Widowed
		99. Unrecorded			5. Separated
4.	Residence	1. Urban			99. Unrecorded
		2. Rural	**9.**	Occupational status	1. Gov't employee
		99. Unrecorded			2. Self-Employed
5.	Educational status	1. Illiterate			3. Student
		2.Able to read & write			4. Daily laborer
		3. Primary completed			5. Retired
		4. Secondary completed			6. House wife
		5.College/university			7. Farmer
		6. Post graduate degree			8. Others (specify)__
		99. Unrecorded			99. Unrecorded

Part two: Antecedent risk factors for stroke MRN: Checklist code:

S.no	Risk factors	Response
1.	Hypertension status	1. Yes 2. No 99. Unrecorded
If S/he is a non-hypertensive patient please skip to question number 5		
2.	Duration of hypertension (in days/months/years)	_____
3.	Was the patient on his/her regular anti-hypertensive medications before admission	1. Yes 2. No 99. Unrecorded
4.	How long since start of using anti-hypertensive medications (in days/months/years)	_____
5.	Diabetes mellitus	1. Yes 2. No 99. Unrecorded
6.	Dyslipidemia	1. Yes 2. No 99. Unrecorded
7.	Atrial fibrillation	1. Yes 2. No 99. Unrecorded
8.	Rheumatic valvular heart disease	1. Yes 2. No 99. Unrecorded
9.	Ischemic heart disease	1. Yes 2. No 99. Unrecorded
10.	Cardiomyopathy	1. Yes 2. No 99. Unrecorded
11.	Khat chewing	1. Yes 2. No 99. Unrecorded
12.	Alcohol consumption	1. Yes 2. No 99. Unrecorded
13.	Smoking status	1. Non-smoker 2. Currently smoker
		3. Ex-smoker 99. Unrecorded
14.	HIV/AIDS status	1. Reactive 2. Non-reactive
		99. Unrecorded
15.	Previous history of TIA	1. Present 2. Absent 99. Unrecorded
16.	Previous history of stroke	1. Yes 2. No 99. Unrecorded

Part three: Neurological factors **MRN:_____** **Checklist code:_____**

S.no	Variables	Response
1.	Type of stroke identified by brain imaging modality (select only one)	1. Ischemic stroke 2. Hemorrhagic stroke
		3. Sub-arachnoid hemorrhage
		4. Unidentified type 99. Unrecorded
2.	Sub-type of Ischemic stroke (select only one)	1. Cardio-embolism 2. Large artery atherosclerosis
		3. Small artery occlusion 4. Other determined cause
		5. Undetermined cause 99. Unrecorded
3.	Causes of hemorrhagic stroke (select only one)	1. Hypertension 2. Vascular Aneurism
		3. Amyloid Angiopathy 4. Anticoagulant related
		99. Unrecorded
4.	Clinical presentation at admission (multiple responses are possible)	1. Altered mental status (Stupor/lethargy/coma)
		2. Speech disturbances 3. Hemiparesis
		4. Hemiplegia 5. Cranial nerve palsy 6. Head ache
		7. Vomiting 8.Vertigo
		9. Others (specify_____) 99. Unrecorded
5.	Type of stroke events	1. First ever 2. Recurrent
6.	GCS score at admission	1. 3-8 2. 9-12
		3. 13-15 99. Unrecorded

Part four: Acute stroke events, MRN: Checklist code:

S.no	Variables	Responses	
1.	Vital signs on admission	1. BP (mmHg)____	2. Temperature (^{o}c)__
		3. RR (breaths/min)_____	4. PR (beats/min)____
3.	Date of stroke symptoms onset	_____/_____/_____(DD/MM/YY)	
4.	Time of stroke onset	_____ AM/PM	
5.	Date of hospital arrival	_____/_____/_____(DD/MM/YY)	
6.	Time of hospital arrival	_____AM/PM	
7.	Date of brain imaging done	_____/_____/_____(DD/MM/YY)	
8.	Time of brain imaging done	_____ (AM/PM)	
9.	Carotid Doppler ultrasound findings	1. Normal 2. Atherosclerosis without stenosis	
		3. Atherosclerosis with stenosis	A. 0-30% stenosis
			B. 30-50% stenosis
			C. 50-70% stenosis
			D. >70% stenosis
		99. Unrecorded	
10.	Type of treatment received (multiple responses are possible)	1. Antiplatlets (Aspirin, Clopidogrel)	
		2. Anti-coagulants (Heparin, Warfarin)	
		3. Ani-hypertensives 4. Statins	
		5. Anti-diabetic drugs 6. Antibiotics	
		7. Others (specify) _____ 99. Unrecorded	
11.	Stroke complications detected (multiple responses are possible)	1. Aspiration pneumonia 2. Increased ICP	
		3. Urinary tract infections 4. DVT	
		5. Gastrointestinal bleeding 6. Seizure	
		7. Mayocardial infarction	
		8. others (specify_____) 99.Unrecorded	
13.	Treatment outcome	1. Dead 2. Censored 99. Unrecorded	
14.	Date of discharge (if alive)	_____/_____/_____(DD/MM/YY)	
15.	Date of death(if dead)	_____/_____/_____(DD/MM/YY)	
16.	1.Total cholesterol (mg/dL)_____	3. Serum Creatinine (mg/dL)_____	
	2. Hemoglobin level(g/dL)_____	4. Random Blood sugar(mg/dL)_____	

Annex II: Curriculum vitae of the principal investigator

Personal Information

Name: Zenawi Hagos Gufue

Age: 25

Sex: Male

Date of Birth: September 8, 1993

Place of Birth: Mekhoni, Raya Azebo, Southern Zone of Tigray, Northern Ethiopia

Marital status: Single

Address: Kebele 04 Adigrat town, Eastern Zone of Tigray, Northern Ethiopia

Phone number: +251 9 14 80 24 04, P.O. Box: 50

Email: Zenawi.2009@gmail.com

Nationality: Ethiopian

Education and Qualifications

A. **Master of Public Health in Epidemiology and Biostatistics** (September, 2017- present)
   - School of Public Health, College of Health Sciences, Addis Ababa University, Ethiopia

B. Bsc in public health (2011-2015)
   - College of Public Health and Medical Sciences, Jimma University, Ethiopia
   - **Undergraduate thesis:** Assessment of Knowledge, Attitude, Practice and factors associated towards of Prevention of Mother to Child Transmission of HIV/AIDS among pregnant mothers attending ANC clinic in Serbo Health Center, Oromia Region, Southwest Ethiopia.
   - **Undergraduate over all GPA:** 3.86

C. Preparatory school(2009-2011)
   - Fenkil Nihidase Major General Hayelom Araya Preparatory School, Raya-Azebo Woreda, Southern Zone of Tigray, Ethiopia

D. Secondary School (2007-2009)
   - Mekhoni Secondary School, Raya-Azebo Woreda, Southern Zone of Tigray, Ethiopia

E. Academic Awards: Gold medal award for very great distinction achievement from college of Public Health and Medical Sciences, Jimma University, Ethiopia

Employment History

1. 2017- present

   Serving as an Assistant Lecturer at the Epidemiology unit, Department of Public Health, College of Medicine and Health sciences, Adigrat University, Northern Ethiopia
2. 2015-2016

   Served as a Junior Public Health Professional and head of Wara Health center, Tocha woreda, Dawro zone, southern nations, nationalities and peoples regional state, Ethiopia

Research interest: Prevention and control of Non-communicable diseases (NCDs)

Doing a thesis paper "Effect of hypertension on the survival of adult stroke patients admitted in Ayder Comprehensive Specialized Hospital, Northern Ethiopia from 2012-2019. *Seven years retrospective cohort study"* (on progress)

Skills:

- Proficient ability of conducting any Epidemiologic research
- Very creative, innovative, self-motivated and strong problem solving ability
- Capable of manipulating statistical software's (SPSS, STATA, Epi info, and Open epi)
- Good computer skills such as MS word, Ms Excel & Ms power point
- Expertise in designing attractive presentations and demonstrations
- Exceptionally good communication skills both verbally and written

Professional trainings

1. Non-communicable disease (NCD) Epidemiology organized by Addis Ababa University and Martin – Luther University held at School of Public Health, Addis Ababa University, Addis Ababa, Ethiopia from November 26-30, 2018.
2. Clinical management of severe acute malnutrition for health care providers organized by integrated family health program, Tarcha, Dawro Zone, SNNPRs, South Ethiopia

Hobbies

Biking, Swimming, reading fictions and research articles on chronic, non-communicable diseases

Language

Fluent in speaking, reading, listening and writing Tigrigna, Amharic and English, I have passed the English Proficiency Exam given at Addis Ababa.

References

1. **Professor Ahmed Ali (PhD)**
   Professor of Public health and Epidemiology
   Department of Preventive Medicine, School of Public Health
   College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia
   ahmedaa5050@yahoo.com
2. **Professor Alemayehu Worku (PhD)**
   Professor of Public health and Biostatistics
   Department of Preventive Medicine, School of Public Health
   College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia
   alemayehu.worku@aau.edu.et
3. **Dr. Girma Taye (PhD, Associate Professor)**
   Department of Preventive Medicine, School of Public Health
   College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia
   Girmataye2009@gmail.com
4. **Dr. Naod Firdu (MD, MPH, Assistant professor)**
   Research thesis primary advisor
   Department of Preventive Medicine, School of Public Health
   College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia
   naodfirdu@gmail.com

Annex III: Curriculum vitae of advisor

Name: Yared Mamushet Yifru

Date of birth: June 28, 1973

Place of birth: Addis Ababa, Ethiopia

Nationality: Ethiopian

Address: P.O.Box -14654, Addis Ababa, Ethiopia

Telephone: +251-911 67 44 37

E-mail: yared_mty@yahoo.com

WORK EXPERIENCE

1. March 2007-present
- ✓ Assistant professor of Neurology, Department of Neurology, Faculty of Medicine, Addis Ababa University
2. January 2004-March 2007
- ✓ Department of Internal Medicine, Tikur Anbessa Hospital, Addis Ababa University
3. November 1999-January 2003
- ✓ General Medical Practitioner at Ambo Hospital , P.O.Box 3, Ambo, Ethiopia
4. January 1997-September 1999
- ✓ General Medical Practitioner at Awassa National Higher Clinic
5. June 1996-December 1997
- ✓ General Medical Practitioner at Metema Hospital

EDUCATIONAL BACKGROUND

1. Higher Diploma in Learning and teaching of Higher Education , 2016
2. 2009-2010 Masters in Headache Medicine , La Sapienza University , Rome, Italy
3. 2007-2009 Sub-specialty certificate in Neurology, School of Medicine , Addis Ababa University
4. 2003-2007 Specialty certificate in Internal medicine , School of Medicine, Addis Ababa University

5. September 1990-May 1995 Gondar college of medical science (Addis Ababa University) , Graduated with MD degree
6. September 1990-June 1991 , Addis Ababa University science Faculty
7. September 1986-June 1990 Shimelis Habte Secondary School
8. September 1984-June 1986 Menen Asfaw Junior Secondary School
9. September 1979-June 1983 with double pass Abay Minch Elementary school

Additional training

1. September 1997 , Protein Energy malnutrition the latest finding
2. DOTs treatment of Tuberculosis March 1998
3. Interpretation of basic Radiologic finding, 2006
4. Mental Health in Africa, a time for action April 2006, All African Psychiatric Association
5. CMC on common neurologic illness 2006
6. Neurology for non neurologists 2007
7. HIV treatment update workshop series 2007, St. Stephen Addis trust, London , UK and Ethiopia , North America Health care professionals Association , Detroit Michigan
8. Common medical emergencies, Ethiopian Medical Association 2008
9. Controversies in Neurology Athens, Greece October 23, 2008
10. Updates in Neurologic illnesses, European Neurological Society, August 2009

ACADEMIC RANK

- ✓ March 2007 still now Assistant Professor of Neurology , Department of Neurology, College of Health Sciences, Addis Ababa University

QUALIFICATION

- ✓ Higher Diploma in learning and teaching of Higher Education
- ✓ Masters in Headache Medicine
- ✓ Sub-Specialty certificate in Neurology
- ✓ Certificate of specialty in Internal medicine
- ✓ Doctor of Medicine

Publications (After last rank)

1. Mamushet Y, Zenebe G, Addissie A. Medical and Neurological complications among stroke patients admitted for inpatient care in Addis Ababa, Ethiopia. Ethiop Med J. 2015 Jan; 53(1):9-17.
2. Worku DK, Yifru YM, Postels DG, Gashe FE. Prevalence of depression in Parkinson's disease patients in Ethiopia. Journal of Clinical Movement Disorders. 2014; 1(1): p.10.doi: 10.1186/s40734-014-0010-3
3. Tiruneh GG, Regasa KD, Feleke Y, Kebede T, Yifru YM(2017). Magnitude, clinical presentation and outcome of patients with pituitary lesions: An experience from Tikur Anbessa Specialized Hospital, Ethiopia. EndocrinolMetabSyndr 6:263.doi: 10.4172/2161-1017.1000263.
4. Yared Mamushet Yifru, Mulugeta Biyadgie Ewnetu. Antiphospholipd syndrome –little to no attention in Ethiopian clinical setting. EJHD.Vol 32, No 2 (2018).
5. Biniyam A. Ayele ; Yared M.Yifru , MD"Migraine –related disability and comorbid depression among migraineurs in Ethiopia: a cross sectional study"
6. Yared M. Yifru. Unsuspected Reservoir of Rabies in Ethiopia: Mongoose. Ethiop Med J, 2018, Vol.56, No4.

Membership

1. Ethiopian Medical Doctors Association(EMA)science 2005
2. Ethiopian Society of Neurology since 2016
3. European Stroke Organization (ESO) since 2018
4. World Stroke Organization since 2018

Academic Affairs/contribution

1. **Department level**
   - ✓ Secretary for Department meetings 2014-2016
   - ✓ Department of Neurology research ethics and academic promotion committee member since 2017
2. **College level**

Representative the University in vaccine safety committee in FMHACA since 2016

Represented the University in manual production by the FMOH Neurologic part of National Health care guideline, 2017

Other Academic Contributions

I was part of Exam preparatory group of the ministry of Health for postgraduate entrance exam in Neurology, 2016

PERSONAL SKILLS

LANGUAGE

- ✓ Amharic : Mother tongue language (office language of Ethiopia)
- ✓ English : I do have a very good knowledge of writing , reading, understanding and speaking the language

Social skills

- ✓ Good relationship with working colleagues, friends, families and people in general

Technical skills

- ✓ Amateur painter
- ✓ Literate in Computer , with good knowledge in it

Hobbies

- ✓ Hearing news, walking

REFERENCES

1. **Dr. Adamu Addise**
   Associate Professor, School of Public Health, Addis Ababa University
   Addis Ababa, Ethiopia, Tel: +251911404954, E-mail: adamuaddissie@gmail.com
2. **Dr. Ayele Kalab**
   Assistant Professor, School of Public Health, Addis Ababa University
   Addis Ababa, Ethiopia, Tel: +251944739411, E-mail: Kalayeleb@gmail.com
3. **Dr. Hanna Demissie**
   Assistant Professor, Department of Neurology, Medical faculty
   Addis Ababa University, Addis Ababa, Ethiopia
   Tel: +2519212284348, E-mail; hanna.demissie@gmail.com

Annex IV: Declaration

Letter of declaration

I, the under signed, MPH student declared that this is my original work in partial fulfillment of the requirements for the degree of master of Public Health in Epidemiology and Biostatistics, which has never been presented in this or any other University. All the resources and materials used for the thesis development fully acknowledged as complete references.

Name**: Zenawi Hagos Gufue(BSc)**

Date of submission: July 8, 2019 **Signature:** _____

Approval of the primary advisor

This thesis work has been submitted for examination with our approval as University primary advisor

Name of primary advisor : Dr. Naod Firdu Gizaw (MD, MPH, Assistant Professor)

_____ **July 8, 2019**

Signature **Date**