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Time to Onset of Stroke and Predictor Factors among Cardiovascular Patients in Addis Ababa, Ethiopia, Retrospective Cohort Study.

By: ***Mahlet Addis (BSc)***

A Research Thesis to be Submitted to St Paul's Hospital Millennium Medical College School Of Nursing Department Of Medical Surgical Nursing, For the Fulfillment of the Master of Cardiovascular Nursing Specialty Program

July, 2024

Addis Ababa, Ethiopia

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Abstract

Introduction: A stroke occurs when there is a sudden interruption of blood flow to the brain that gives oxygen to brain cells. Considering the lack of research in this study topic this study fills the knowledge gap by assessing predictor variables that increase the time to onset of stroke development among cardiovascular patients in Addis Ababa, Ethiopia.

Objective: To assess the time to onset of stroke and identify predictors among cardiovascular patients in Addis Ababa, Ethiopia.

Method and Materials: Institiution based retrospective cohort study was conducted from January, 1, 2019 to December 30, 2023 on 471 cardiovascular patients. The study institutons were selected purposevilley and simple random sampling techniques was used to reach each stydy units. The data entered into Epi-data version 4.1 and exported to STATA version 14.0 for further analysis and interpretation. The incidence of stroke was found to be predicted by Cox proportional hazards regression model with a P-value of less than 0.05 and 95% CI.

Results: From 471 medical records 94.27% met the enrollment criteria and the overall incidence rate of stroke among cardiovascular patients were 9.1 per 1000 person month. The independent predictor factors associated with stroke were type of cardiovascular disease of Hypertension 3.0, 95%CI (1.78-5.07), type of cardiovascular disease of atrial fibrillation 2.8, 95%CI (1.76-4.47), comorbid disease of HIV 2.24, 95%CI (1.45-3.48), comorbid disease of pancytopenia 1.98, 95%CI (1.25-3.14), DBP>100mmgh 2.92, 95%CI (1.55-5.51), EF<40% 3.34, 95%CI (1.26-8.88), and HDL < 40mg/dl 4.12, 95%CI (2.0-8.49).

Conclusion: According to this study, stroke occurred frequently in patients with cardiovascular disease. In order to reduce the incidence of stroke and the associated morbidity and mortality, this study recommends performing stroke screening in cardiovascular patients during their follow-up period and identifying its predictor factors.

Key words: Addis Ababa, Cardiovascular patients, Comorbid disease, Time to onset of stroke

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Acronyms and Abbrivations

AF: Atrial Fibrillation

AR: Aortic Regurgitation

AS: Aortic Stenosis

ASD: Atrial Septal Defect

CABG: Coronary Artery Bypass Grafting

CAD: Coronary Artery Disease

CDC: Chronic Disease Control

CHD: Congenital Heart Disease

CMP: Cardiomyopathy

CT: Computerized Tomography

CVA: Cerebro-Vascular Accident

CVD: Cardiovascular Disease

CVP: Cardiovascular Patients

CVRF: Cardiovascular Risk Factor

DCA: Directional Coronary Atherectomy

DM: Diabetes Mellitus

DBP: Diastolic Blood Pressure

EF: Ejection Fraction

ESRD: End Stage Renal Disease

GBD: Global Burden of Disease

HbA1C: Hemoglobin A1C

HDL: High Density Lipoprotein

HHD: Hypertensive Heart Disease

HF: Heart Failure

HR: Hazard Ratio

HS: Hemorrhagic Stroke

HTN: Hypertension

IVSD: inter Ventricular Systolic Diameter

IS: Ischemic Stroke

LDL: Low Density Lipoprotein

LP: Lipoprotein

LV: Left Ventricle

LVID: Left Ventricle Internal iDameter

LVPWD: Left ventricular Posterior Wall Diameter

MI: Myocardial Infraction

MR: Mitral Regurgitation

MS: Mitral Stenosis

PCI: Percutaneous Intervention

PR: Pulmonic Regurgitation

PS: Pulmonic Stenosis

PVD: Peripheral Vascular Disease

PVI: Pulmonary Vein Isolation

RHD: Rheumatic Heart Disease

RV: Right Ventricle

RVSP: Right Ventricle Systolic Pressure

SBP: Systolic Blood Pressure

TAPSE: Tricuspid Annular Plane Systolic Excursion

TCM: Takotsubo Cardiomyopathy

TIA: Transient Ischemic Attack

TR: Tricuspid Regurgitation

TS: Tricuspid Stenosis

VHD: Valvular Heart Disease

1. Introduction

1.1. Background

Stroke is rapidly developing manifestations of focal or global disturbance of brain function, lasting more than one day or leading to mortality, with no apparent cause rather than blood vessel related (1). The two main types of stroke are ischemic stroke (IS) and hemorrhagic stroke (HS) (2). The underlying reason for the brain injury is the primary distinction between the two forms of stroke such as HS and IS (3).When blood flow toward the brain interrupted for short period of time around 5min transient ischemic attack occur (TIA)(4).

Cardiovascular disease (CVD) is a general term for conditions affecting the heart or blood vessels. (5). Cardiovascular risk factors (CCVRF) such as Diabetes Mellitus (DM), Hypertension (HTN), hyperlipidemia, smoking, alcohol consumption, physical inactivity and a body mass index (BMI) are considered to have a risk of occurring around 90 % of CVD and stroke patients (6).

A methodical examination for the 2019 Global Burden of Disease (GBD) Study shows 12.2 million new cases of stroke (7). In the European Union, 1.12 million stroke incidents occurred in 2017 (8). In 2020, mainland China's estimated rates of stroke incidence was 505.2 per 100,000 person-years (9). In Africa yearly incidence rate of stroke is approximately 316 incidents per 100,000 person-years (10). Over the past 20 years, stroke incidence has significantly increased in Sub-Saharan Africa (11).

In Ethiopia the magnitude of Ischemic Stroke (IS) was 51. 40% and Hemorrhagic Stroke (HS) was 46.42% in 2021(12). In 2021 incident of stroke was 3.15% at Sidama region of Ethiopia and majority of patients had CVD and HTN (13). There was also 1 per 100 person year or 106 cases of stroke among 583 hypertensive patients at Bahir Dar, Ethiopia in 2023 (14).

As we see the overall trend of stroke globally had been increased time to time and more prevalent in patient with cardiovascular patients. This study will address the time to onset of stroke and predictor factors among CVD patients and this used for to establish preventive methods, early detection and management of stroke through using screen methods in their treatment follow up time and this will reduce morbidities and mortality related to stroke. It also again reduce hospital admission rate related to stroke and their related costs.

1.2. Statement of the problem

A stroke is an abrupt interruption of the blood supply toward the brain that gives oxygen to brain cells(15). Around the world, 15 million people get strokes each year from them Five million of them pass away, and a further five million become chronically crippled (16). Stroke continues to be the second leading cause of death globally, with 6.55 million stroke-related deaths in 2019. Again the risk of stroke is 2-4 times higher in those with cardiovascular disease than in the general population (17).

In Australia, stroke was listed as the primary cause of 8,500 deaths and top five causes of death in 2021 (18). Case fatality rate of stroke in Africa by 2017 reached 46%. In Sub-Saharan Africa (SSA) 4% of all death from stroke among 34% of CVD deaths(19,20). In Ethiopia according to WHO data in May 2018, mortality related to stroke reached 5.38% of total death. It becomes the fourth leading cause of mortality(21).

In 2021 study conducted in Ethiopia shows, stroke-related fatality rate reached 6.23% overall and an 89.82% age-adjusted stroke death rate per 100,000 people (12). In 2023 Jima Medical Center Hospital incident death related to stroke reached 20.23 per 1000 person days (22). In Ethiopia, the stroke rate in patients with AF is reached 19.4% and from them most of patients have a history of stroke, HTN, HF, 33.9% have history of RHD, and history of thyroid disorder (23).

As national center for chronic disease control (CDC) report several modifiable factors result in blood clots and are the main risk factors for stroke (2,24).There is a hypothesis that a notable percentage of stroke patients will also have co-morbid DM and age above 54, the risk of developing stroke increased (25,26). Lipoprotein (LP) is higher in individuals with CVD and is measured in a tiny proportion of patients (27). As per the National Institutes of Health Stroke Scale (NIHSS) in Sweden Atrial Fibrillation (AF), Heart Failure (HF), and pre-stroke dementia are risk factors for having a severe stroke (28). HTN and AF was more strongly associated with stroke than other types of cardiovascular disease (21,29).

The complication related to stroke, both stroke and heart damage are caused by risk factors and preexisting heart disease. In the days following an acute stroke, cardiac problems such as heart

attack, congestive heart failure, cardiac arrest, and irregular heart rhythms like atrial fibrillation can cause morbidity and even death (30).

From 2018-2022 World Stroke Organization (WSO) develop and implement strategic plan to reduce the burden of stroke worldwide and saw good progress in money area of stroke, Also WSO again expand strategic plan toward 2026 for further progress (31). World Health Organization (WHO) also develop clinical guidelines for the management of stroke(32). New data show that d/t types of stroke may respond differently to antiplatelet drugs, and that atherosclerotic stroke in these diseases may particularly benefit from more aggressive antiplatelet therapy (33).

However the incidence, morbidity, and mortality of stroke among cardiovascular patients has been increased time to time and this lead Ethiopia phases the triple burden of disease such as communicable, non-communicable and trauma. By considering this, this study addressed stroke events among cardiovascular patients and it would be evidence-based input for further studies and clinicians.

1.3. Significance of the study

In order to intervene appropriately for both research participants and other community members, this study utilized to detect several predictor variables that are associated with stroke outcome. This is also used to monitor and identify the risk of stroke in all individuals with heart disease, allowing for early stroke prevention, identification, and treatment before complications occur.

Based on associated predictive characteristics, this enables policy makers to develop effective stroke risk management plans for cardiac patients. Healthcare professionals (cardiologist, cardiac nurse) utilize it once again to make evidence-based judgments regarding patient treatment. This lowered the number of hospital admissions, length of stay, associated expenses, and stroke-related morbidity and mortality. Additionally, this lessened the disease's detrimental emotional effects and economic cost in Ethiopia.

Furthermore, this study provided the foundation for upcoming public health studies on other subjects because it increased our understanding of the issue. Researchers, administrators, and health planners also received data from it, which they used for a variety of global evidence-based projects. This aids in my academic progress once more by giving me a range of learning opportunities, pushing me to repeat research and challenge conventional wisdom, and supporting me throughout the entire learning process.

2. Literature Review

2.1. Time to onset of stroke among cardiovascular patients

A nationwide cohort study conducted in Europe revealed that patients with AF were 2.5 times at higher risk of developing stroke than patients without AF. In this study the risk of stroke was highly increased in presence of prior stroke and atrial fibrillation is associated with an increased risk of stroke in the absence of other risk factors but only a moderate increase in risk when other risk factors are present. Yet as limitation the study not include BMI and smoking status of the study participants(34).

A retrospective cohort study conducted on Western Australia that assess the incidence of stroke among cardiac disease such as: CAD, AF, and VHD from 175, 560 participants in the cohort, 69.9% had CAD, and 16.3% had more than one heart disease. On Age specific ratio the incidence was 20% higher in older women than men those age greater than 75 years. Although this study didn't consider study groups who have been taken Anti-coagulant medications, which lower the risk of stroke, this may affect the true burden of stroke among those listed cohort groups(17) .

A population based retrospective Cohort study conducted in French showed that the incidence of stroke among AF patients were 1/100-person time. In this study non adherence to Direct Oral Anti-Coagulant Therapy (DOAC) and coronary vascular disease were factors associated with stroke. Adherence issues therefore need to be addressed, as they represent a challenge to the benefits of DOAC and, more generally, OAC in AF patients(35).

A cohort study that assess the Incidence and predictors of stroke in patients with RHD shows an overall incidence of strokes was 1.47 per 100 patient, 5.2% experienced a stroke during the mean follow-up of 3.9 years. The predictor factors became age, prior stroke, and AF adjusted HR of 1.591, 5.395, and 2.945 respectively. The effect of AF on the risk of stroke was lessened by taking death into account as a competing risk (36).

Retrospective study that assessed the temporal trends in the incidence of IS among patients hospitalized with takotsubo cardiomyopathy (TCM) stratified by the subtypes of IS (cardio-embolic versus thrombotic) in contrast to cardio-embolic stroke (0.5%-0.7%), the incidence of thrombotic stroke (4.7% to 9.5%) increased between 2008 and 2017. PAD, previous history of

stroke, and hyperlipidemia were found to be significantly associated with thrombotic stroke. On the other hand, Asian race (as opposed to White race), CS, and AF were linked to cardio-embolic stroke (37).

A prospective cohort study conducted in Ghana shows the incidence of stroke among HTN patients were 1.4/100 person years. Factors such as previous physical inactivity and cigarette smoking were factors independently associated with the incidence of HTN with hazard ratio of 2.59 and 1.81 respectively (38).

A retrospective follow-up study conducted in the university of Gondar that assess The development and Validation of a Risk Prediction Model to Estimate the Risk of Stroke Among Hypertensive Patients shows the incidence of stroke were 3/100 person time and the combinations of six predictors were selected for model development such as: sex, residence, baseline diastolic blood pressure, comorbidity, diabetes, and uncontrolled hypertension (39).

A hospital-based cross-sectional study conducted in Gondar, Ethiopia to evaluate the prevalence and predictors of stroke among AF patients. The results showed that stroke was 19.4% more common in cardiac patients and that it was linked to HF, thyroid disorders, diabetes mellitus, and a history of stroke. Because holter monitoring is not available for individuals with paroxysmal AF, this study may overstate the prevalence of stroke (23).

A retrospective follow-up study conducted in Bahir-Dar, Ethiopia, that assess the incidence of stroke and its predictors among hypertensive patients shows; the overall incidence of stroke among hypertensive patients was 18.18%. It again shows there is one incidence of stroke per 100 person-years. Independent predictors of the incidence of stroke among hypertensive patients included comorbidities stage two HTN, uncontrolled SBP, uncontrolled DBP, alcohol consumption, age 45–65, and medication discontinuation. Because this is a single hospital-based study, it is not possible to extrapolate the findings to the entire population (14).

2.2. Socio-demographic variables

A retrospective longitudinal study conducted on United State from 2002-2017 that assess the burden of stroke among different age group in shows there is 66.6% stroke among older adult, 27.7% midlife, and 5.7% among young adults. 81.6% of IS hospitalization among older adults and 35.9% of HS hospitalization among young adults. This study also indicate there is variation

on stroke incidence among age recommend the management have to consider all age groups. But the research focused on more of hospitalization and the other burden of stroke according to different age groups remained ignored (40).

An observational study conducted on European prospective investigation into cancer and nutrition-CVD study shows from 204,244 postmenopausal women developed, IS, HS, intra-cerebral hemorrhage and sub-arachnoid hemorrhage was 6770, 5155, 1615, and 976 respectively. To sum up this study shows an increased risk of stroke was linked to an earlier menopausal age. But this study unable to account for all factors that attributed for this results (41).

A retrospective study conducted in Italian hospital that assess age-related burden and characteristics of embolic stroke admitted to stroke unit of first level shows cryptogenic stroke diagnosed with in patients age <65 years was 21.1%, age 65-74 years was 24.2% and age ≥75 years was 15.5%. After diagnostic work up 17.9% of patient's age < 65 years also had patent foramen ovale and 10.5% of age ≥75 years also had AF. Though this study had some limitations, such as it has small sample size, single center and short length of follow up and this may affect the power of the study (42).

The study conducted in India shows there is different stroke incidence among different sex groups, From their total patients 33.7% were female, 9.5 more severe stroke cases among female and male were (9.5% vs. 8.4%) respectively. Large artery occlusion common in men than female (21.3% vs. 14.8%) cardio-embolic stroke secondary to RHD 27.2% in women vs. 19.7% in men. At all it shows stroke in both sex groups have also some difference mechanism as well outcome. But this study haven't given any emphasis on older age groups of female and didn't consider it (43).

A study conducted in Ethiopia that assess sex differences in stroke risk factors, clinical profiles, and in-hospital outcomes among stroke patients admitted to the Dessie Hospital shows 28.5%, 14.4%, and 6.1 percent of male patients developed hemiplegia, aphasia, and facial palsy respectively. However 15.1% of female patients were unconscious and it may be due to females were older at the time to stroke onset. Due to retrospective nature of the study difficult to avoid bias (44).

2.3. Clinical variables

Stroke and co-morbid disease

A retrospective cohort study conducted in Tiawin that assess the association between anemia and stroke revelaed that Patients with moderate anemia had a 1.20 significant increase in stroke risk compared to the non-anemia group in AHR p-value 0.032. Beside this diabetes and hyperlipidemia also affect stroke development. But this study had a limmitation of to describe the incidence rate in number rather to say only high incidence rate subjectively(45).

In a case report study evaluating potentially fatal pancytopenia with tislelizumab, cerebral infarction occurs in a patient with lung adenocarcinoma. The patient experiences a stroke subsequent to receiving intensive pancytopenia treatment. Since this study is a case report study cannot to acertain that pancytopenia a significant risk for stroke (46).

A nationwide population-based cohort study conducted using national health insurance research database shows; the risk of both ischemic and hemorrhagic stroke was 1.14 times and 1.93 times higher among thrombocytopenic patients and it is associated with increased risk of both ischemic and hemorrhagic stroke (47).

A journal American health association revealed that patients with cyopenia had a high risk of cardiovascular disease related morbidity and mortality. After a median follow-up of 9.5 years 4.3% developed stroke. Participants who developed stroke were older, more likely to be men, had lower education and annual income, lived in rural areas, were smokers, and had more comorbidities and higher CRP (48).

A population-based study in Taiwan that assess the incidence of stroke in patients with HIV was 1.98/1000 person years. HIV infection was associated with an elevated risk of developing total stroke with adjusted HR 1.57 and ischemic stroke 1.91 in patients aged less than 45 years(49).

A systematic review and meta-analysis that show the prevalence and incidence of stroke among people with HIV (PWH) shows 1.3% of stroke among age at lest15 years, and 3.98% age at least 50 years. This group of people develop stoke due to HIV vasculopathy and it leads to the

occurrence of stroke become common in those population groups. But different predictors or risk factors lead to the development of HIV vasculopathy is not addresse (50).

A large international multicenter case-control study involving 32 nations showed that 26% of acute stroke inpatients and 22% of non-stroke controls had diabetes, which was defined as HbA1c of ≥ 6.5 (48 mmol/mol). Diabetes increased the risk of IS 1.33 in comparison to HS, it is 0.72. Furthermore, research indicates that between 20 and 33 percent of acute stroke inpatients may have diabetes. The inconsistent definition of diabetes diagnosis in the literature continues to be an issue (51).

Stroke and cardiac catheterization procedures

A prospective cohort study conducted in German that assessed the Risk of stroke after diagnostic coronary angiography or Intervention, Of patients receiving cardiac catheterization, 0.29% experienced a TIA or stroke. Periprocedural TIA/stroke risk was unaffected by access site selection, with age being the only significant predictor of TIA/stroke in multivariate analysis(52).

Retrospective observational study in the United States that assessed Incidence, predictors and impact of stroke on mortality among patients with IHD following Percutaneous intervation (PCI), A total of 221 patients (2.16%) had a stroke with neurologic impairment after prcedure. Of these, 53 patients (24%) had an increasing vascular blockage. Older women were more likely than younger women to have a stroke after procedure. This study also cautions against making definitive inferences regarding the effectiveness of endovascular therapy in stroke treatment (53).

Incidence, Predictors, and Outcomes of Acute IS Following PCI shows, during the study period, the adjusted incidence of post-PCI ischemic stroke increased from 0.6% to 0.96% after PCI for STMI, from 0.5% to 0.6% after PCI for NSTMI, and from 0.3% to 0.72% after PCI for unstable angina or stable ischemic disease. Older age, AF, cardiogenic shock, and carotid disease were the best indicators of post-PCI ischemic stroke. The primary research limitation was the diagnosis of stroke. There was no availability of computed tomographic imaging findings or disability scores (such as the Rankin score) for stroke patients (54).

Incidence and predictors of 30-day acute Cerebrovascular Accidents (CVA) Post AF and had done catheter ablation procedure from the Nationwide Readmissions Database, 0.8% of AF hospitalized patient and had done ablation experienced a CVA within 30 days of the procedure.

A lower procedural volume, HF, prior stroke/TIA, and HTN were among the factors linked to CVA in multivariate regression analysis.. In summary, 0.8% of patients experienced a CVA within 30 days of receiving catheter-based AF ablation therapy (55).

Stroke and medication

The Cochrane database of systematic reviews evaluates the impact of early anticoagulants on acute IS. It reveals that early anticoagulant therapy is linked to a lower risk of extra-cranial hemorrhage, an increase in symptomatic intracranial hemorrhage at odds of 2.55, a decrease in symptomatic pulmonary emboli at odds of 0.60, and fewer recurrent IS at odds of 0.76. Ascertainment bias may have been exacerbated by un-blinding in the largest trial, especially in light of the preliminary findings (56).

2.4. Laboratory variable and Imaging

A systematic review that assess the Relationship between Hyperlipidemia, CVD and Stroke, observational studies conducted in many populations have consistently shown a favorable correlation between the occurrence of coronary heart disease and the cholesterol concentration of low-density lipoprotein (LDL). Therefore, the risk of vascular illnesses can be decreased by lowering LDL cholesterol in those people, especially in relation to baseline cholesterol concentrations. However, a number of studies have shown that the use of lipid-reducing medications, such as statins, has a significant influence on lowering the death and morbidity rates of individuals with CVD and stroke (57).

A cohort study that is conducted in Jichi Medical School revealed that Low HDL levels with other dyslipidemias may contribute to the incidence of stroke with HR of 1.44. This study also conclude that isolated low HDL level had less impact regardless of other dyslipidemia(58).

A descriptive cross-sectional study on dyslipidemia in patients with IS in a tertiary care center's medical department shows, among the patients with ischemic stroke, 80% had dyslipidemia; Of the patients, 53.33% had high total cholesterol, 58.33% had high triglycerides, 45% had high low-density lipoprotein cholesterol, and 42.50% had low high-density lipoprotein cholesterol. In this study, the commonest hazard calculate for the stroke was HTN which was appear in 61.67% of patients. At that point taken after by 58.33% were current smokers and 54.17% were alcohol drinkers (59).

A study that assess the cardio-embolic stroke in patients with left atrial dilation and reduced left ventricular ejection fraction revealed that the odds of cardio-embolic stroke was 2.4 times higher in patients with enlarged LA than in patients with normal LA size. Compared with patients with normal LA and EF, patients with combined enlarged LA and reduced EF had significantly higher rates of AF and cardio-embolic stroke. Left Atrial Dilatation and Reduced Left Ventricular Ejection Fraction Are Associated with Cardio-embolic Stroke (60).

Multi-center retrospective cohort study that assess the effect of Echo cardiac findings on the incidence of AF and IS shows from the total study population, 13.4%, and 10.2% patients develop AF and IS among patients with reduced EF and patients without reduced EF. On multivariate analysis reduced EF not associated with the outcome but associated with increased risk of mortality and morbidity. But this study average follow up time was 7.7 months; that may not be enough to detect the true outcome of the study and also doesn't collect data regarding the patients' pharmaceutical therapy this may result in bias (61).

Single center, retrospective observational study shows the incidence of stroke in patients with early echocardiography after acute MI, within a year following STEMI, 2.6% experienced a cerebrovascular event; among them, 8.3% had LV thrombus and 2.5% did not have LV thrombus on the baseline echocardiogram. One study weakness is that there were no established criteria for at-risk patients, therefore echo were not regularly repeated before discharge. Therefore, it was impossible to validate the frequency and timing of the subsequent production of LV thrombi. Second was unable to verify that all cerebrovascular accidents had a cardio embolic cause (62).

2.5. Risk assessment variable

A Mendelian randomization analysis that assess modifiable lifestyle factors and risk of stroke shows; ischemic and large artery stroke were linked to smoking, body mass index, and waist-hip ratio. But this study only acess individual participant data rather than summary-level data (52).

Long-term risk of stroke and its predictors in Transient Ischemic Attack (TIA) patients in Germany shows Within 10 years of the initial TIA diagnosis, 18.3% of individuals were diagnosed with stroke. Age was positively associated with stroke, with HR of 1.88 and for patients aged 51–60 years, and aged >80 years. But this study lack information regarding

diagnostic procedures performed to diagnose TIA and stroke, including physical examinations, MRI, CT and others (63).

A Mendelian Randomization Study that shows the odd of having stroke among smoker group's accounts 1.22, 1.59, 1.35, 1.11, and 0.83 for any IS, for large artery stroke, for small vessel stroke, for cardio-embolic stroke and for intra-cerebral hemorrhage. But this study use small sample size to ascertain the association between intra-cerebral hemorrhages with smoking, the result may be not accurate (64).

A prospective observational single center study conducted in Holland that assess the effect of alcohol intoxication as a Stroke Mimic and the Incidence of acute alcohol Intoxication in stroke development shows 6% of the patients who appeared to be at risk for an acute stroke also consumed alcohol. Stroke mimic was detected in 18% of the whole cohort. But as this study is a single-center study, there may be less external validity (65).

A matched case-control study that assessed Predictors of IS for low-risk patients with AF shows, Age, sex, BMI, comorbidities, left atrial size, and left ventricular EF did not differ significantly. In comparison to the non-stroke group, smokers were more common in the stroke group (54.5% vs. 10.0%). The only factor that was found to be significantly associated with multivariate analysis was smoking. There are no data on the serum levels of high-sensitive C-reactive protein or brain natriuretic peptide in this study (66).

Conceptual FrameWork

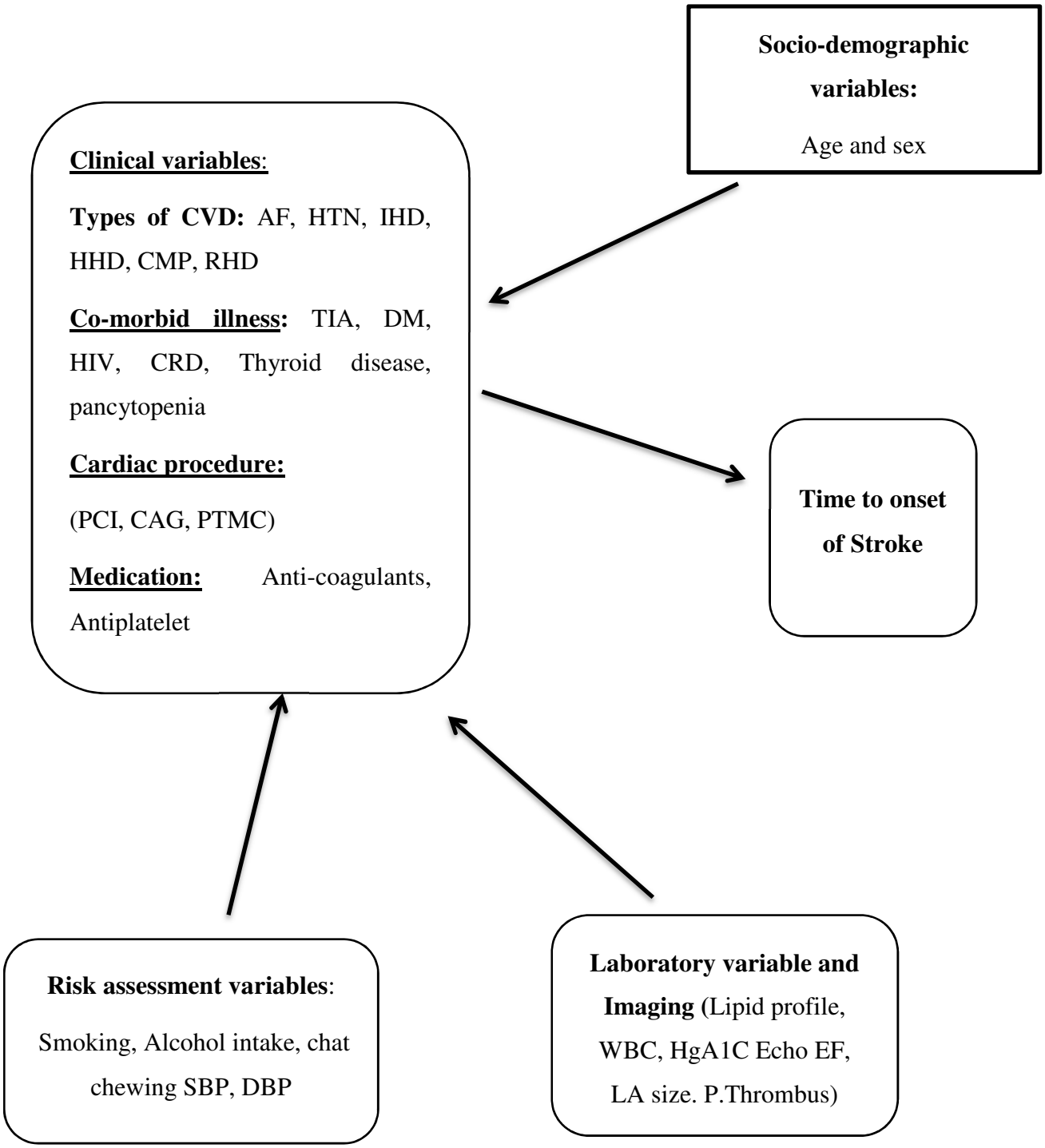

Figure 1: Conceptual frame-work that predict time to onset of stroke and predictor factors among study cohort adapted from different literatures (14,17,23,36,37,44,56,66–68)

3. Objectives

3.1. General objectives

To assess the time to onset of stroke and predictor factors among cardiovascular patients at selected public hospitals in Addis Ababa, Ethiopia.

3.2. Specific objectives

To determine the time to onset of stroke among cardiovascular patients in Addis Ababa, Ethiopia.

To identify predictor factors of stroke among cardiovascular patients in Addis Ababa, Ethiopia.

4. Methods and Materials

4.1. Study areas

The study conducted at selected public hospitals in Addis Ababa, Ethiopia. In Addis Ababa, there are around 12 public hospitals; from them purposively 3 public Hospitals are selected that those hospitals have cat-lab rooms to diagnosis and treatment of cardiac patients than other hospitals and numerous cardiac patients followed here. Such as: St. Paulo's Hospital Millennium medical college, St. Peter Hospital, and Black Lion Hospital.

St. Paul's Hospital Millennium Medical College was established in 1968 by Emperor Haile-selassie and the medical school opened in 2007. It also one of largest referral hospital has more than 700 beds, an average of 1200 clients seen both on Emergency and outpatient department. Average 64 cardiac patients seen monthly in this hospital.

St. Peter Specialized Hospital established in June, 1961 also largest referral hospital. It also provides varies Emergency, Inpatient, and outpatient service for different catchment area. Averagely 60 cardiac patients seen monthly in this hospital.

Black Lion Hospital established in 1964. It is a main teaching hospital for both preclinical and clinical training of most disciplines in the School of Medicine of Addis Ababa University. It has also again provided varies Emergency, inpatient, and outpatient service for different catchment areas. Averagely 72 cardiac patients seen monthly in this hospital.

4.2. Study design

An institution based retrospective cohort study design were employed.

4.3. Study period

The data collection was conducted out from April 8, 2024 to May 8, 2024 based on medical chart review of cardiac patients enrolled in selected public hospitals from January 1, 2019 to December 30, 2023.

4.4. Population

4.4.1. Source population

All cardiovascular patients who were on follow up at selected public hospitals in Addis Ababa, Ethiopia.

4.4.2. Study population

Cardiovascular patients who were on follow-up from January1, 2019 to December 30, 2023 at selected public hospitals.

4.4.3. Study unit

All cardiovascular patients under follow-up clinic at selected public hospitals and who fulfill the inclusion criterias.

4.5. Eligibility criteria

4.5.1. Inclusion criteria

Cardiovascular patients their medical records are available in the institution during the study period irrespective of their sex was included in this study.

4.5.2. Exclusion criteria

Pregnant mother and

Patients diagnosed for stroke

4.6. Sampling procedure

4.6.1. Sample size determination

For objective one

Use single population proportion formula taking 0.18 proportion of stroke incidence among hypertensive patients study conducted Bahir-Dar, Ethiopia(14). By considering 95%CI, 10% non-response rate and 5% margin of error. The required sample size is calculated using the following formula

$$n = \frac{\left(\frac{z\alpha}{2}\right)^2 \mathrm{p}(1-\mathrm{p})}{\mathrm{d}^2}$$

Where: n= total number of sample size

p= proportion and

d= margin of error

Z= 1.96 at 95%CI

$$n = \frac{(1.96)^2 0.18(1-0.18)}{0.05^2}$$

n = 227

n = 227 + 10% incomplete medical records

n = 249.7~ 250

For objective Two

Sample size for the second objective estimated by STATA version 14. By considering 95% CI, two sided, level of significance at 0.05, 80% power, 0.18 probability of stroke incidence and adjusted hazard ratio of 1.9 which was taken from a study done in Bahir-Dar Ethiopia (14). By considering 10% incomplete medical records, the minimum sample size required for the study was 471 cardiovascular patients.

Table 1 : Sample size estimation for study using predictor variables for study participants.

S.no	Predictors	AHR	Stroke incidence	Sample size
1	Stage II HTN	5.21	0.18	72
2	Uncontrolled SBP	2	0.18	404
3	Uncontrolled DBP	1.9	0.18	471
4	Alcohol consumption	2.04	0.18	382
5	Age	10.25	0.18	68
6	Drug Discontinuation	2.05	0.18	377

After taking the AHR of predictor variables and keep constant the stroke event of 0.18 for all predictors; the larger sample size gained was 471.

The calculated sample size for second objective used to reach the study unit since it gained large sample size.

4.6.2. Sampling Technique

Initially, all medical records of individuals with a confirmed diagnosis of cardiovascular disease recorded between January 1, 2019, and December 30, 2023 were evaluated. Purposively three public Hospitals are selected that they are the only hospitals they provide a cardiac catheterization procedure for cardiovascular patients and use proportional allocation to reach the required sample size in selected hospitals, such as St. Paulo's Hospital Millennium Medical College, St. Peter Hospital, and Black Lion Hospital.

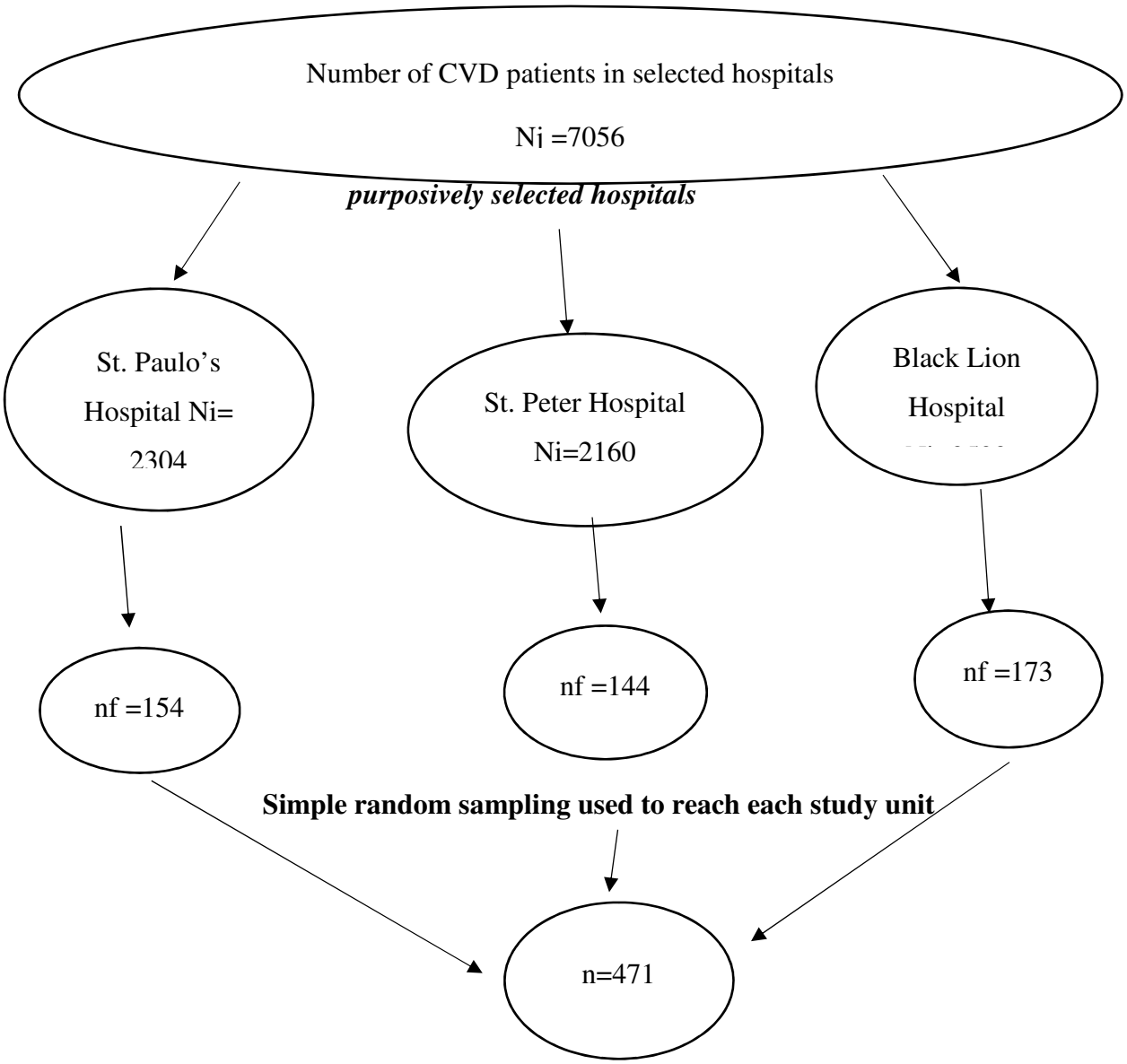

Figure 2: proportional allocation of sample size in each study area

Formula for proportional allocation for each study area (nf) = $\frac{Ni}{Nj}$*n, Where

- n_f = Proportional allocated sample size in specific study area
- N_i = Total population of specified area
- N_j = Total population of all selected area
- n = Estimated sample size

4.7. Variables of the study

4.7.1. Dependent variables

Time to onset of stroke among cardiovascular patients.

4.7.2. Independent variables

Socio-demographic variables: Age, and Sex

Risk assessment variables: History of smoking, and alcohol consumption.

Clinical variables: Type of cardiovascular disease, comorbid disease, Current medication, and cardiac procedures

Laboratory variables and imaging: lipid profile, HgA1C, Hgb, Ceratine and Echo EF, and left atrium size

4.8. Operational Definition and Definition of Terms

Cardiovascular patients: The physician uses different diagnostic techniques and diagnosed the patient as Atrial Fibrillation, Carditis, Cardiomyopathy, Ischemic Heart Disease, Heart Failure, Hypertension, Hypertensive Heart Disease, and Rheumatic Heart Disease at the time that they came in to OPD of study area and if the patient diagnosed at least one disease consider as cardiovascular disease.

Cardiac catheterization procedure: is a medical procedure used to diagnose and treat certain cardiovascular diseases (69).

Censored- indicates any patients who lost to follow-up, referred out to other hospital or not develop the stroke outcome during the follow-up period.

Comorbid disease: diseases that are diagnosed and co-exist with the cardiovascular disease.

Pancytopenia: a reduction in all blood cells count such as: white blood cell, red blood cell and platelet (70).

Time to onset of stroke - is the time interval from the first day the patient is diagnosed with cardiovascular disease at selected hospital up to the time when the stroke diagnosis is confirmed by the physician.

4.9. Data collection procedures

A structured checklist prepared after reviewing different scientific literature on the title of time to onset of stroke and predictor factors among cardiovascular patients, and it used to collect data. After gaining Ethical clearance from SPHMMC ethical review board and accepted from the respective data collection areas, the data collection started through identifying cardiovascular patients medical card at OPD, bring out from the card room and used simple random sampling techniques to reach each study units.

4.10. Data quality control

Data quality was assured by designing appropriate data extraction tools. Data was checked for completeness and consistency at the site of data collection. Data collectros were two BSc Nurses and training on data collectrors was given before the time of data collection. The principal investigator supervised the data collectors at the site of data collection. After doing pretest on 5%(24) of sample size in SPHMMC, some unclear or vague checklists were modified and wrong skip patterns were also corrected. The pretested medical records coded separately and excluded on main analysis. Data entered in to two professional's separately and checked for its consistency. The data was coded and cleared before data analysis. The Cronbach's Alpha test was calculated by using STATA version 14.1 to test reliability of the tool and it was 90%.

4.11. Data processing and analysis

For analysis, the data were collected into Epi-data version 4.1 and exported to STATA version 14.0 for analysis. The study was determined using descriptive statistics, such as frequencies and percentage, to enumerate the study's participants. Person-month of follow-up were serve as the denominator for the computation of the incidence rate of stroke for the whole cohort. The likelihood of surviving a stroke was calculated using a Kaplan–Meier plot and log-rank test. The independent variables that fit on the P-value less than or equal to 0.25 level of significance were be included in the stepwise multivariable analysis after bivariable Cox regression was fitted. The incidence of stroke was found to be predicted by multiple Cox regression tests with a P-value of less than 0.05 and the gobal test was used to evaluate the cox proportional hazard regression assumption and it was 0.24 with 8 degree of freedom . Multicollinearity of independent variables

was checked using Variance Inflation factors (VIF) and it was 2. The event of stroke outcome and censored was coded as 1 and 0 respectively during the analysis.

4.12. Ethical considerations

Ethical clearance letter gained from SPHMMC school of nursing research department on April 18, 2024, Ref N/S/506862/10 and sent to respective bodies. Due to the absence of participant interaction, informed consent was not requiring from study participants. Only used medical card number to identify study population and in order to collect pertinent variables and the medical number again will be coded during data recording and not registered.

4.13. Dissemination of results

The result of the study will be present to Saint Paulo's Hospital Millennium Medical College community. The result will also disseminate and presented to hospitals in study areas. Moreover, the result will be published on internationally journal reputable.

5. Result

5.1. Socio-demographic characteristics of cardiovascular patients

A total of 471 medical records of cardiovascular patients were reviewed, with response rate of 94.27% that 444 medical records met the enrollment criteria in the final analysis. The remaining 27 charts were excluded as due to data was incomplete, and the medical card also not found in card room. Among 444 revised medical records, the mean (± standard deviation) of age groups were 53.72 ± 15.31 years old. The frequency of sex groups was 54.73% were Male and 45.27% were Female respectively (Figure 3).

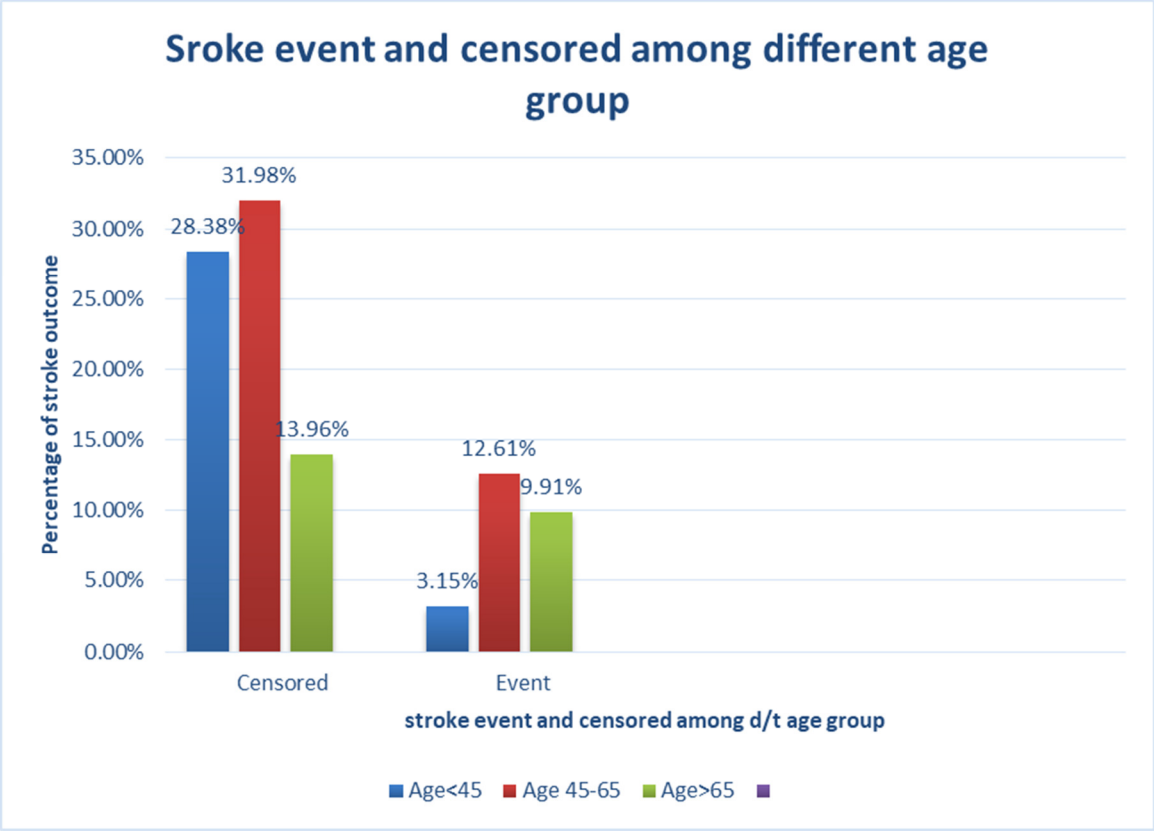

Figure 3: Socio demographic characteristics of cardiovascular patients in Addis Ababa, Ethiopia, from January 1, 2019- December 30, 2023.

5.1. Type of cardiovascular disease among cardiovascular patients

The total analysis time was 12516.3-person month and the overall incidence rate of stroke among cardiovascular patients were 9.1 per 1000 persons. Among the medical records most of the patient develops Rheumatic Heart Disease, followed by Hypertension, Heart failure, Ischemic Heart Disease, Atrial Fibrillation, Cardiomyopathy, Hypertensive Heart Disease, and Cardities respectively in (Table 2).

Table 2: Type of cardiocascular disease among cardiovascular patients in Addis Ababa, Ethiopia, from January 1, 2019- December 30, 2023.

Type of cardiovascular disease	Frequency	Person time in months	Incidence rate Per 100 persons.	Survival status	
				Event	Censored
Atrial Fibrillation	99(22.30%)	2306.4	2.2	51(44.7%)	48(14.5%)
Cardiomyopathy	90(20.27%)	2536.47	0.3	9(7.9%%)	81(24.5%)
Cardities	36(8.11%)	896.13	1.4	13(11.4%)	23(7.0%)
Hypertension	115(25.90%)	2888.57	2.5	73(64%)	42(12.7%)
Hypertensive heart disease	63(14.19%)	1315.47	2.7	36(31.6%)	27(8.2%)
Heart failure	105(23.65%)	2385.17	1.3	32(28.1%)	73(22.1%)
Ischemic heart disease	104(23.42%)	3227.9	0.5	19(16.7%)	85(25.8%)
Rheumatic heart disease	149(33.56%)	4198.2	0.7	30(26.3%)	119(36.1%)

5.3. Clinical status of cardiovascular patients

Among the total cardiovascular patients 63.06% of peoples had comorbid disease of Diabetes Mellitus. From the type of cardiac procedure done most of the patients did Percutaneous Mitral Valve Commisurectomy (PTMC), followed by Coronary Angiography (CAG) and Percutaneous Intervention (PCI) with a frequency of 1.80%, 1.35%, and 2.93% respectively. Most of patients had a medication history of Warfarin, followed by Atorvastatin, Aspirin, and other (Beta blockers, and Diuretics, ACI and ARBS) with a frequency of 31.31%, 25.68%, 24.55%, and 87.16% respectively (Table 3).

Table 3: Clinical status of cardiovascular patients in Addis Ababa, Ethiopia, from January 1, 2019 – December 30, 2023.

Clinical Status	Frequency	Incidence rate Per 100 persons.	Survival status	
			Event	Censored
Diabetes	147(33.11%)	2.0	77(65.7%)	70(21.2%)
Chronic Kidney Disease	54(12.16%)	2.3	33(28.9%)	21(6.4%)
Thyroid Disease	49(11.04%)	2.1	29(25.4%)	20(6.1%)
HIV/AIDS	49(11.04%)	2.7	31(27.2%)	18(5.5%)
COPD	70(15.77%)	2.3	43(37.7%)	27(8.2%)
PHTN	121(27.25%)	2.6	74(64.9%)	47(14.2%)
Pancytopenia	35(7.88%)	3.2	26(22.8%)	9(2.7%)
Total Cardiac procedure done	27(6.08%)	1.5	10(8.8%)	17(5.2%)
History of	412(92.79%)	1.2	104(91.2%)	308(93.3%)

medication				
History of medication Discontinuation	115(25.90%)	2.9	79(69.3%)	36(10.9%)

5.4. Risk status of cardiovascular patients

The study has tried to identify risk factors of the stroke among study cardiovascular patients. Accordingly, patients with family history of chronic disease account 60.36%. Among all cardiovascular patients majority had family history of HTN, followed by family history of cardiac disease and family history of stroke and other (such as family history of DM and Epilepsy) as 44.37%, 12.61%, and 5. 63% and 9.68% respectively (Table 4).

Table 4: Risk status of cardiovascular patients in Addis Ababa, Ethiopia, from January 1, 2019-December 30, 2023.

Risk Status	Frequency	Incidence rate Per 100 persons	Survival status	
			Event	Censored
History of Smoking	162(36.49%)	2.0	86(75.4%)	76(23.0%)
History of Alcohol	212(47.75%)	1.8	100(87.7%)	112(33.9%)
History of Chat	173(38.96%)	1.6	72(63.2%)	101(36.8%)
History of TIA	83(18.69%)	2.9	54(47.4%)	29(8.8%)
History of Stroke	47(10.59%)	3.1	38(33.3%)	9(2.7%)
Family history of Chronic	268(60.36%)	1.4	97(85.1%)	171(51.8%)

disease					
SBP	<140	220(49.55%)	0.2	12(10.5%)	208(63.0%)
	140-160	124(27.93%)	0.9	34 (29.8%)	90(59.6%)
	>160	100(22.52%)	2.7	68(59.6%)	32(9.7%)
DBP	<90	241(54.28%)	0.2	15(13.2%)	226(9.7%)
	90-100	110(24.77%)	0.85	26(22.8%)	84(25.5%)
	>100	93(20.95%)	3.4	73(54.3%)	20(24.8%)

5.5. Laboratory and Echocardiography findings of cardiovascular patients

Cardiovascular patients with abnormal finding of laboratory and echocardiography were more likely to develop stroke than cardiovascular patients with normal range of laboratory and echocardiography value (Table 5).

Table 5: Laboratory and Echocardiography findings of cardiovascular patients in Addis Ababa, Ethiopia, from January 1, 2019 - December 30, 2023.

Laboratory and imaging value		Frequency	Incidence rate Per 100 persons	Survival status	
				Events	Censored
Total Cholesterol	<200	300(67.57%)	0.3	27(23.7%)	273(82.7%)
	>200	144(32.43%)	2.5	87(76.3%)	57(17.3%)
LDL	<100	249(56.08%)	0.3	24(21.1%)	225(68.2%)
	100-160	113(25.45%)	0.9	30(26.3%)	83(25.2%)

	>160	82(18.47%)	2.8	60(52.6%)	22(6.7%)
HDL	< 41	93(20.95%	0.09	83(72.8%)	10(3.0%)
	41-59	128(28.83%)	0.7	25(21.9%)	103(31.2%)
	>59	223(50.23%)	4.2	6(5.3%)	217(65.8%)
TGL	<150	271(61.04%)	0.02	20(17.5%)	251(76.1%)
	150-200	105(23.65%)	1.3	38(33.3%)	67(20.3%)
	>200	68(15.32%)	4.4	12(49.1%)	12(3.6%)
EF	>50	254(57.21%)	0.2	13(11.4%)	241(73.0%)
	40-50	90(20.27%)	0.7	15(13.2%)	75(22.7%)
	<40	100(22.52%)	3.8	86(75.4%)	14(4.2%)
Left atrium size	<27	15(3.38%)	0.3	2(1.8%)	13(3.9%)
	27-38	213(47.97%)	0.5	20(57.5%)	19(58.5%)
	>38	216(48.65%)	1.8	92(80.7%)	124(37.6%)
LVIDs	21.6-34.8	216(48.65%)	0.8	20(17.5%)	196(59.4%)
	<21.6	61(13.74%)	1.8	29(25.4%)	32(9.7%)
	>34.8	167(37.61%)	1.7	65(57.0%)	102(30.9%)
LVIDd	37..8-52.2	211(47.52%)	0.3	2(18.4%)	190(9.7%)
	<37.8	80(18.02%)	1.7	31(14.8%)	49(27.2%)
	>52.2	153(34.46%)	1.8	62(54.4%)	91(27.6%)

5.6. The frequency of type of stroke among cardiovascular patients

There was a high prevalence of Ischemic Stroke (IS) among cardiovascular patients when compared with Hemorrhagic Stroke (Figure 4).

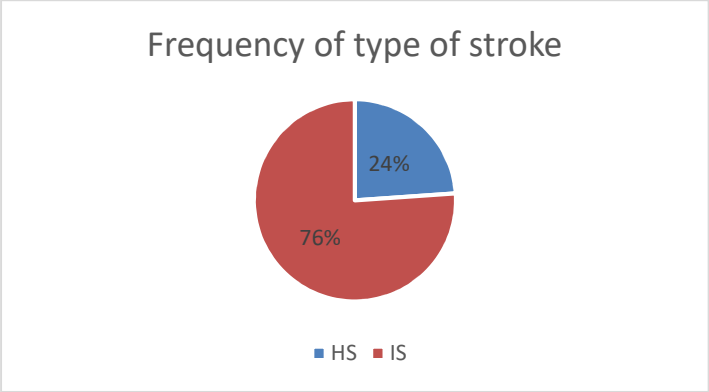

Figure 4: Frequency of type of stroke among cardiovascular patients in Addis Ababa, Ethiopia, from January 1, 2019- December 30, 2023.

5.7. Overall survival rate of stroke-free cardiovascular patients

The overall median survival time of stroke-free cardiovascular patients were 19 months over 2436.6 total person month at risk. The overall incidence rate of stroke among cardiovascular patients were 9.1/ 1000 persons with a CI of (7.5-10.9) (Figure 5).

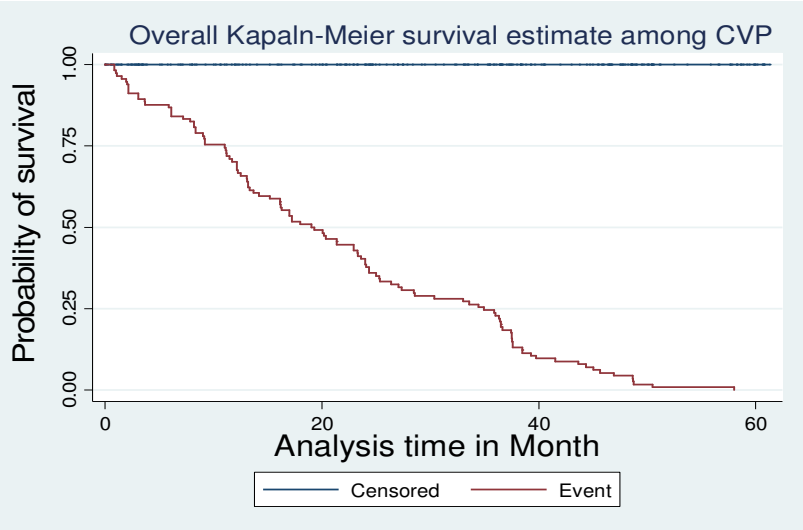

Figure 5: Kaplan-Meier survival estimate shows overall survival time of cardiovascular patients.

5.8. Kaplan-Meier survival estimate among CVP with Atrial Fibrillation

The median survival time of stroke-free atrial fibrillation patients were 36.4 months over 2306.4 total person month at risk. The incidence rate of stroke among atrial fibrillation patients were 2.2 /100 persons with a CI of (1.7 - 2.9) (Figure 6).

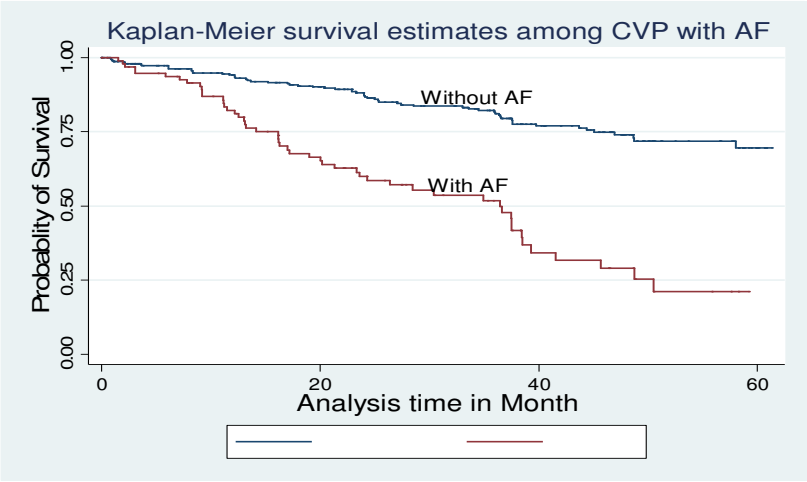

Figure 6: The difference between the survival function of CVP with and without Atrial fibrillation.

5.9. Kaplan-Meier survival estimate among CVP with Hypertension

The median survival time of stroke-free hypertension patients were 27.03 months over 2306.4 total person month at risk. The incidence rate of stroke among hypertension patients were 2.5 /100 persons with a CI of (2.5-20) (Figure 7).

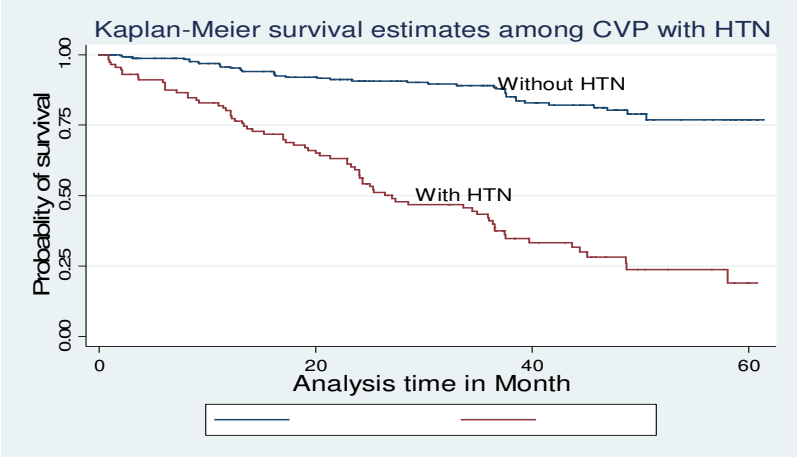

Figure 7: The difference between the survival function of CVP with and without Hypertension.

5.10. Kaplan-Meier survival estimate among CVP with HIV/AIDS

The median survival time of stroke-free HIV/AIDS patients were 28.5 months over 1128.1 total person month at risk. The incidence rate of stroke among HIV/AIDS patients were 2.5 /100 persons with a CI of (1.9-3.9) (Figure 8).

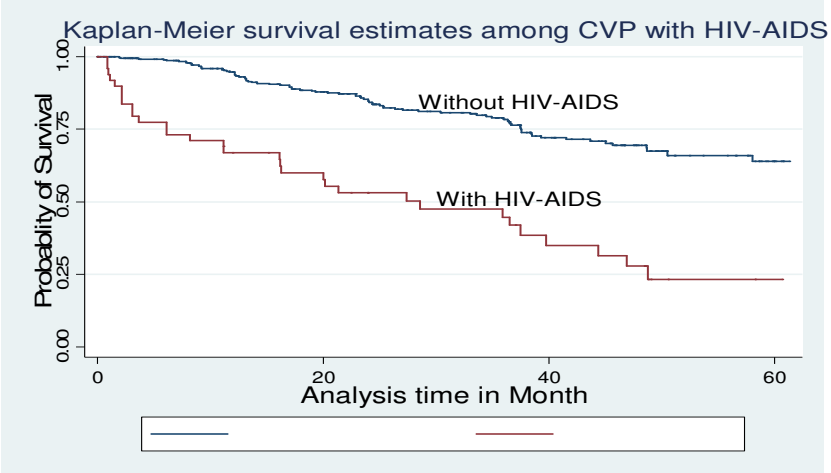

Figure 8: The difference between the survival function of CVP with and without HIV-AIDS.

5.11. Kaplan-Meier survival estimate among CVP with varying level of DBP

The survival time of stroke-free CVP were highest in patients with DBP < 90mmgh and the median stroke free CVP with DBP > 100mmgh were 24 months over 2129.8 total person month at risk. There were a direct relation between incidence of stroke and varying level of DBP as 0.2, 0.8 and 3.4 per 100 persons with a CI of (1.2-3.4, 5.8-12, and 2.7-4.3) with DBP less than <90mmgh, 90-100mmgh, and >100mmhg respectively (Figure 9).

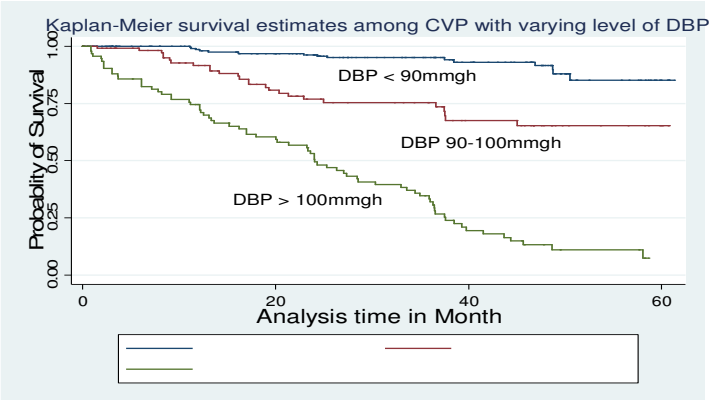

Figure 9: The difference between the survival function of CVP with varying level of DBP.

5.12. Kaplan-Meier survival estimate among CVP with varying level of HDL

The survival time of stroke-free CVP were highest in patients with HDL > 60mg/dl and the median stroke free CVP with HDL 40mg/dl were 20 months over 1954 total person month at risk. There were an inverse relation between incidence of stroke and varying level of HDL as 0.09, 0.6 and 4.2 per 100 persons with a CI of (3.9-19, 4.6-10, and 3.4-5.2) with HDL value of >60mg/dl, 40-60mg/dl, and <40mg/dl respectively (Figure 10).

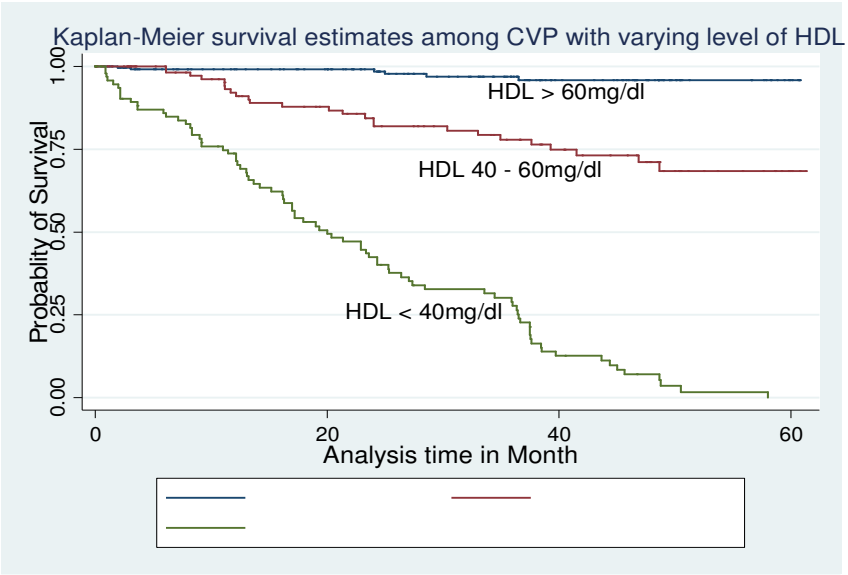

Figure 10: The difference between the survival function of CVP with varying level of HDL

5.13. Kaplan-Meier survival estimate among CVP with varying level of EF

The survival time of stroke-free CVP were highest in patients with EF > 50% and the median stroke free CVP with EF < 40% were 21.3 months over 2260.4-person month at risk. There were an inverse relation between incidence of stroke and varying level of EF as 0.15, 0.7 and 4.8 per 100 persons with a CI of (9.2-27, 4.4-12, and 3.1-4.7) with EF value of >50%, 40-50% , and <40% respectively (Figure 11).

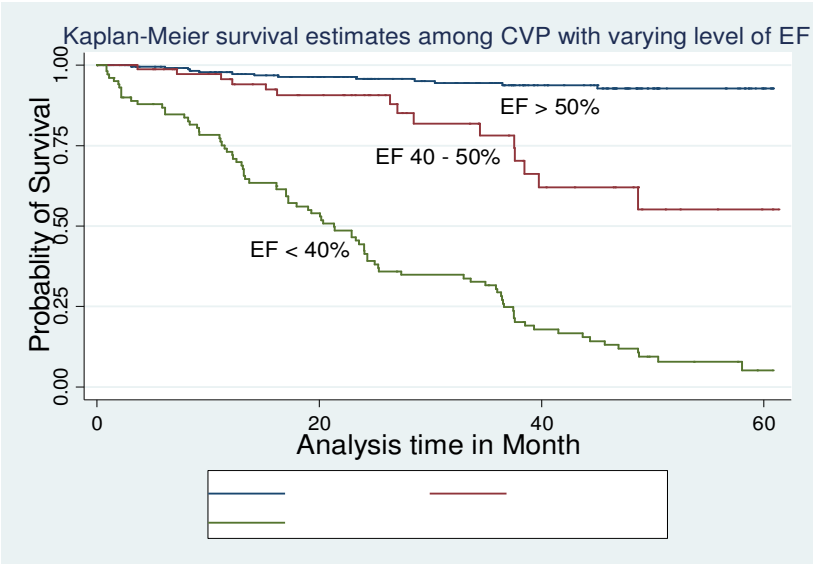

Figure 11: The difference between the survival function of CVP with varying level of EF.

5.14. Kaplan-Meier survival estimate among CVP with Pancytopenia

The median survival time of stroke-free Pancytopenia patients were found to 25.3 months over 939.7-person month at risk. The incidence rate of stroke among Pancytopenia patients were 3.1 /100 persons with a CI of (2.2-4.7) (Figure 12).

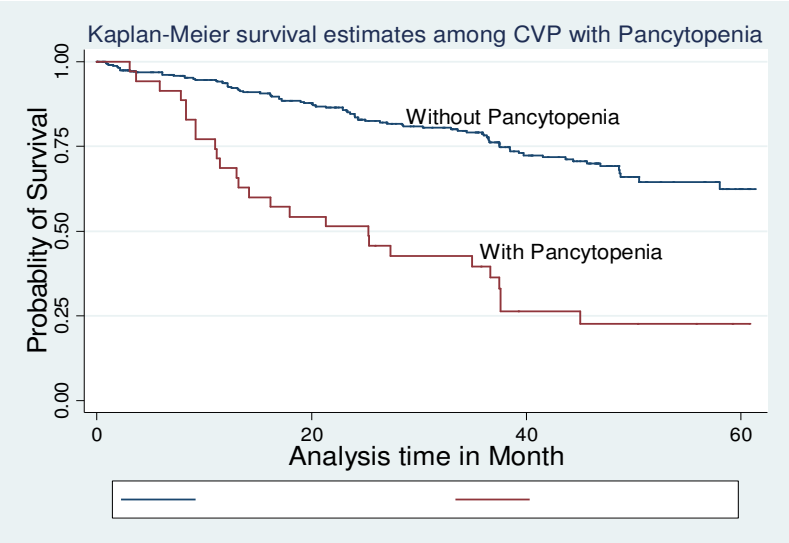

Figure 12: The difference between the survival function of CVP with and without pancytopenia.

5.15. Log rank test

Log rank test was performed to identify the significance difference in stroke incidence rate among different independent categorical variables and dependent variable and also compare the survival distributions of two samples (Table 6).

Table 6: Variables that have significant p-value in log rank test

Variables	Chi-Square	Df	P- value
AF	54.30	1	<0.001
Cardiomyopathy	10.72	1	0.0011
Hypertension	110.87	1	<0.001
HHD	55.81	1	<0.001
HF	5.94	1	0.0148
IHD	5.07	1	0.0244
Sex	10.62	1	0.0011
Age	30.31	2	<0.001
Comorbid illness	44.42	1	<0.001
Presence of DM	79.25	1	<0.001
Presence of CKD	33.41	1	<0.001
Presence of Thyroid	24.77	1	<0.001
Presence of HIV	45.98	1	<0.001
Presence of COPD	47.21	1	<0.001
Presence of PHTN	121.29	1	<0.001
Presence of Pancytopenia	50.51	1	<0.001

Procedure of Angiography	9.94	1	0.0016
History of Medication Discontinuation	172.34	1	<0.001
SBP	124.39	2	<0.001
DBP	195.08	2	<0.001
Hx of Stroke	83.08	1	<0.001
Hx of Alchol	90.07	1	<0.001
TIA	99.18	1	<0.001
Hx of stroke	74.73	1	<0.001
Family history of chronic disease	42.78	1	<0.001
Cholesterol	140.33	1	<0.001
LDL	114.10	2	<0.001
HDL	301.80	2	<0.001
TGL	222.60	2	<0.001
INR	56.40	2	<0.001
WBC	182.42	1	<0.001
Platelet	151.09	2	<0.001
Ejection Fraction	267.23	2	<0.001
Left Atrium size	81.66	2	<0.001
Pulmonary Thrombus	111.04	1	<0.001
TAPSE	141.87	1	<0.001

5.16. Test of Proportional Hazard Assumption

The global test was used to test the cox proportional hazard assumption statistically and overall scheoenfeld global tests were 0.24 with 8 degree of freedom.

5.17. Model goodness of fit test

Cox snell residuals test was used to check the overall goodness of fit test for survival data. The Cox-Snell residual plot follows the reference line tangentially (within a 45-degree alignment), which confirms that the model is good to fit the observed data in (Figure 13).

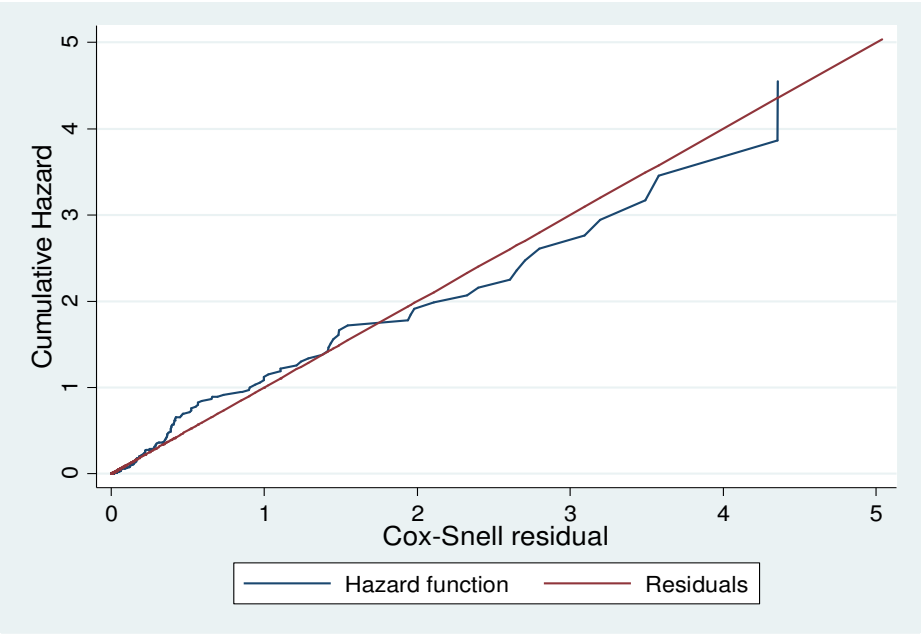

Figure 13: Cox-Snell residual test that show model goodness of fit test.

5.18. Predictors of stroke among cardiovascular patients

The bivariate analysis was done for each dependent and independent variable and the variables with p-value of <0.25 was included in stepwise multivariate analysis. All independent variables with p-value of <0.25 was run in the model together and from them a variable with greatest p-value selected and drop step by step until the remaining all variables are significance. After then the drop variables again give a chance in step by step fashion together with the reaming significant variables. The reaming variables with a p value of < 0.05 were significant predictor's variables of stroke outcome. The significant predictor variables in bivariate analysis were colored in Table 7.

Table 7: All variables with p value less than 0.25 that were included in stepwise multivariate analysis.

Variables	Categories	CHR (95%CI)	P-Value
AF	(ref=No)	1	
	Yes	3.7, 95CI (2.55-5.38)	<0.001**
CMP	(ref=No)	1	
	Yes	0.33,95%CI (0.17- 0.67)	<0.002*
Cardities	(ref=No)	1	
	Yes	1.67, 95%CI (0.94-2.98)	<0.082
HTN	(ref=No)	1	
	Yes	6.13, 95%CI (4.17-9.01)	<0.001**
HHD	(ref=No)	1	
	Yes	4.07, 95%CI (2.73-6.07)	<0.001**
HF	(ref=No)	1	
	Yes	1.65, 95%CI (1.1-2.49)	<0.016*
IHD	(ref=No)	1	
	Yes	0.57, 95%CI (0.35-0.94)	<0.026*
RHD	(ref=No)	1	
	Yes	0.71, 95%CI (0.46-1.07)	<0.101
Sex	(ref=No)	1	

	Yes	0.53, 95%CI (0.36-0.78)	<0.001*
Age	(ref, <45years)	1	
	45-65years	2.85, 95%CI (1.59-5.13)	<0.001**
	>65years	4.78, 95%CI (2.62-8.73)	<0.001**
Presence of comorbidities	(ref=No)	1	
	Yes	7.22, 95%CI (3.65-14.26)	<0.001**
DM	(ref=No)	1	
	Yes	5.01, 95%CI (3.38-7.43)	<0.001**
CKD	(ref=No)	1	
	Yes	3.11, 95%CI (2.07-4.66)	<0.001**
Thyroid	(ref=No)	1	
	Yes	2.79, 95%CI (1.83-4.25)	<0.001**
HIV	(ref=No)	1	
	Yes	3.78, 95%CI (2.5-5.71)	<0.001**
COPD	(ref=No)	1	
	Yes	3.48, 95%CI (2.38-5.09)	<0.001**
PHTN	(ref=No)	1	
	Yes	6.58, 95%CI (4.47-9.69)	<0.001**
Pancytopenia	(ref=No)	1	

	Yes	4.3, 95%CI (2.77-6.67)	<0.001**
Other((Epilepsy, AKI, PAD, DVT)	(ref=No)	1	
	Yes	0.71, 95%CI (0.41-1.23)	<0.221
CPD	(ref=No)	1	
	Yes	1.79, 95%CI (0.93-3.42)	<0.08
CAG	(ref=No)	1	
	Yes	3.83, 95%CI (1.56-9.40)	<0.003*
Medication discontinuation	(ref=No)	1	
	Yes	5.77, 95%CI (3.97-8.38)	<0.001**
Patients on Warfarin	(ref=No)	1	
	Yes	1.73, 95%CI (1.1-2.74)	<0.019*
Other medications (BBs, Diuretics, ACI and ARBS,)	(ref=No)	1	
	Yes	1.48, 95%CI (0.86-2.55)	<0.16
SBP	(ref, <140mmgh)	1	
	140-160mmgh	4.97, 95%CI (2.57-9.59)	<0.001**
	>160mmgh	14.33, 95%CI (7.75-26.49)	<0.001**
DBP	(ref, <90mmgh)	1	
	90-100mmgh	4.3, 95%CI (2.28-8.13)	<0.001**

	>100mmgh	17.97, 95%CI (10.27-31.42)	<0.001**
Smoking	(ref=No)	1	
	Yes	5.77, 95%CI (3.76-8.83)	<0.001**
Alchol	(ref=No)	1	
	Yes	9.23, 95%CI (5.27-16.15)	<0.001**
Chat	(ref=No)	1	
	Yes	3.1, 95%CI (2.12-4.55)	<0.001**
Hx of TIA	(ref=No)	1	
	Yes	5.33, 95%CI (3.69-7.71)	<0.001**
Hx of stroke	(ref=No)	1	
	Yes	4.76, 95%CI (3.22-7.03)	<0.001**
Family Hx of CD	(ref=No)	1	
	Yes	4.76, 95%CI (2.84-7.98)	<0.001**
Family Hx of Stroke	(ref=No)	1	
	Yes	3.1, 95%CI (1.835.27)	<0.001**
Famiy Hx of HTN	(ref=No)	1	
	Yes	5.8, 95%CI (3.71-9.04)	<0.001**
Famiy Hx of cardiac disease	(ref=No)	1	
	Yes	2.47, 95%CI (1.59-3.83)	<0.001**

Total cholesterol	(ref<200)	1	
	>=200	9.1, 95%CI (5.87-14.11)	<0.001**
LDL	(ref<100)	1	
	100-160	2.81, 95%CI (1.64-4.81)	<0.001**
	>160	8.69, 95%CI (5.40-13.97)	<0.001**
HDL	(ref>60)	1	
	40-60	7.53, 95%CI (3.0918.36)	<0.001**
	<40	54.01, 95%CI (23.48-124.23)	<0.001**
TGL	(ref<150)	1	
	150-200	6.13, 95%CI (3.54-10.59)	<0.001**
	>200	20.41,95%CI (12.15-34.31)	<0.001**
INR	(ref, 1-2)	1	
	<1	4.01, 95%CI (2.57-6.28)	<0.001**
WBC	(ref, 4.5-11)	1	
	>11	10.91, 95%CI (7.0-17.02)	<0.001**
Platelet	150-450	1	
	<150	5.7, 95%CI (2.88-11.27)	<0.001**
	>450	10.78, 95%CI (6.76-17.19)	<0.001**
HgA1C	(ref, <5.7)	1	

	5.7-6.4	3.33, 95%CI (1.79-6.21)	<0.001**
	>6.4	7.14, 95%CI (4.49-11.35)	<0.001**
EF	(ref, >50%)	1	
	40-50%	4.95, 95%CI (2.35-10.42)	<0.001**
	<40%	25.83, 95%CI (14.37-46.42)	<0.001**
LA size	(ref27-38)	1	
	>38	6.79, 95%CI (4.18-11.04)	<0.001**
Presence of cardiac thrombus	(ref=No)	1	
	Yes	5.9, 95%CI (4.06-8.58)	<0.001**
Function of heart valve	(ref=Normal)	1	
	Abnormal	2.93, 95%CI (1.96-4.37)	<0.001**
TAPSE	(ref,>16)	1	
	<=16	7.2, 95%CI (4.93-10.53)	<0.001**
LVIDs	(ref=21.6-34.8)	1	
	<21.6	6.54, 95%CI (3.69-11.58)	<0.001**
	>34.8	6.52, 95%CI (3.93-10.8)	<0.001**
LVIDd	(ref=37.8-52.2)	1	
	<37.8	6.42, 95%CI (3.68-11.21)	<0.001**
	>52.2	6.79, 95%CI (4.11-11.22)	<0.001**

TRV	(ref, <3)	1	
	>=3	3.99, 95%CI (2.73-5.84)	<0.001**
RVSP	(ref, <37)	1	
	>=37	4.11, 95%CI (2.74-6.16)	<0.001**
Presence of Cardiomegally	(ref=No)	1	
	Yes	3.91, 95%CI (2.67-5.71)	<0.001**
Presence of Plureal effusion	(ref=No)	1	
	Yes	2.54, 95%CI (1.73-3.74)	<0.001**

Cardiovascular patients with type of disease of Hypertension were 3.0 times at high hazard of developing stroke than patients with not having Hypertension with (AHR: 3.0, 95%CI 1.78-5.07).

Cardiovascular patients with type of disease of Atrial Fibrillation were 2.8 times at high hazard of developing stroke than patients with not having Atrial Fibrillation with (AHR: 2.8, 95%CI 1.76-4.47).

Those cardiovascular patient with a comorbid disease of HIV were 2.24 at higher hazard to develop stroke than patients with no comorbid disease of HIV with (AHR: 2.24, 95%CI 1.45-3.48)

Those cardiovascular patient with a comorbid disease pancytopenia were 1.98 times at higher hazard to develop stroke than patients with no comorbid disease of pancytopenia with (AHR: 1.98, 95%CI 1.25-3.14).

The hazard of having stroke among cardiovascular patients with DBP value >100mmgh were 2.92 times higher than cardiovascular disease patients with DBP <100mmgh with (AHR: 2.92, 95%CI 1.55-5.51).

The hazard of having stroke among cardiovascular patients with HDL value <40mg/dl were 3.34 times higher than cardiovascular patients with HDL value > 40mg/dl with (AHR: 3.34, 95%CI (1.26-8.88).

The hazard of having stroke among cardiovascular patients with EF value < 40% were 4.12 times higher than cardiovascular patients with EF value >40% (AHR: 4.12, 95%CI 2.0-8.49) Table 8.

Table 8: Significant predictor variables that have p-value less than 0.05 in stepwise multivariate analysis.

Variables	Categories	CHR(95%CI)	AHR(95%CI)	P- value
AF	(ref=No)	1	1	
	Yes	3.7, 95CI (2.55-5.38)	2.8, 95%CI (1.76-4.47)	<0.001**
HTN	(ref=No)	1	1	
	Yes	6.13, 95%CI (4.17-9.0	3.0, 95%CI (1.78-5.07)	<0.001**
HIV	(ref=no)	1	1	
	Yes	6.3, 95%CI (2.50-5.71)	2.24, 95%CI (1.45-3.48)	<0.001**
Pancytopenia	(ref=No)	1	1	
	Yes	4.30, 95%CI (2.77-6.67)	1.98, 95%CI (1.25-3.14)	0.004*
DBP	(ref=<90)	1	1	
	90-100	4.30, 95%CI (2.28-8.13)	2.54, 95%CI (1.29-4.99)	0.007*
	>100	17.97, 95%CI (10.27-31.42)	2.92, 95%CI (1.55-5.51)	0.001*
HDL	(ref=>60)	1	1	
	40-60	7.53, 95%CI (3.09-18.36)	2.99, 95%CI (1.17-7.64)	0.022*
	<40	54, 95%CI (23.48-124.22	3.34, 95%CI (1.26-8.88	0.016*

Ejection Fraction	(ref=.>50%)	1	1	
	40-50%	4.95, 95%CI (2.35-10.42)	2.4, 95%CI (1.06-5.47)	0.036*
	<40%	25.85, 95%CI (14.37-46.42	4.12, 95%CI (2.0-8.49)	<0.001**

6. Discussion

Among cardiovascular patients, the overall incidence of stroke was 9 per 1000 persons. Significant predictor factors linked to stroke included AF, HTN, HIV, DPB 90-100 mmgh, DBP > 100 mmgh, HDL 40-60 mg/dl, HDL < 40 mg/dl, EF 40-50 percent, and EF< 40 percent.

Incidence of stroke among CVP with AF disease was 2.2/100 persons, and patients with AF had a 2.8 times higher risk of developing stroke than CVP without AF, according to the overall incidence of stroke among cardiovascular patients. The findings of this study are consistent with two studies: the French study found that the incidence of stroke among AF patients was 1/100 persons, and the European study found that patients with AF had a 2.5-fold increased risk of stroke compared to those without AF (34,35). Due to decreased atrial contractility, which results in uncoordinated myocyte activity, stasis, and an elevated risk of thromboembolism, it may be implied that atrial fibrillation can ultimately cause stroke (71).

Incidence of stroke among CVP having type of disease of HTN were 2.5/100 person time and the risk of having stroke were 3.0 time higher than patients not having type of disease of HTN. This result similar with the study conducted in Gonder, Ethiopia that the incidence of stroke among HTN patients were 3/100 person time and; the study conducted in Bahir-Dar, Ethiopia showed incidence of stroke among HTN patients were 1/100 person time (14,39). Again this study comparable with the study conducted in Ghana that incident of stroke among HTN patients were 1.4/100 persons (38). These also occur due to vascular changes: such as vascular remodeling, inflammation, oxidative stress and baroreflex dysfunction contribute to the pathogenesis of stroke in hypertension (72).

The hazard of having stroke among cardiovascular patients with DBP >100 were 2.92 higher than cardiovascular patients with DBP <100mmgh. This result ties well with the study conducted in Gonder, Ethiopia that hypertensive patients who had uncontrolled diastolic blood pressure were 2.14 times more likely to develop stroke than those who controlled their blood pressure (14). High diastolic blood pressure can indicate and eventually lead to hypertension. It is linked to an increased burden and the advancement of cerebral small vessel disease. As demonstrated by neuroimaging markers such as brain atrophy, microhemorrhages, and compromised white matter integrity, this is linked to an increased risk of stroke and may exacerbate the severity of the problem (73).

This incidence of stroke among Cardiovascular patients having comorbid disease of HIV were 3/100persons. This study contrary to the findings of study conducted in Taiwan; that the incidence of stroke among HIV infection groups were decreased 2/1000 persons. This might be due to that numbers of study population were vary and there sample size is different that 5,961 patients with HIV and 23,844 peoples with non HIV controlled groups (49).HIV infection can lead to stroke through various mechanisms, including increased risk of opportunistic infections and direct cardiac involvement with HIV leading to cardio-embolic stroke, and potential interference with blood coagulation (74).

Those cardiovascular patients with HDL value < 40mg/dl were 4.12 times higher risk of developing stroke than cardiovascular patients with HDL value >40mg/dl in currently conducted research. This research supported by Jichi Medical School study that stroke were 1.44 times higher risk in patients with low HDL levels and other dyslipidemias (58). Low levels of HDL are linked to the advancement of atherosclerosis, which involves plaque buildup in the arteries and can result in narrowed or blocked blood vessels in the brain, raising the risk of ischemic stroke (75).

The hazard of having stroke among cardiovascular patients with EF 40-50% and <40% were 2.4 and 4.12 higher. This study in accordance with findings reported by California that risk of stroke were 2.0 and 8.8 times higher in patients with moderately and severely reduced EF, respectively, than in patients with normal EF (60). The reduced ejection fraction that is present in patients with heart disease may indicate result in hypotension and decreased tissue perfusion, which may cause tissue ischemia and stroke.(76).

Cardiovascular patients with having comorbid disease of pancytopenia were a signicant predictor factor of stroke. This finding supported by case report study that adenocarcinoma patients with pancytopenia on following and treatment for pancytopenia they were develop stroke (46). since this is a case report study this finding may not be totally support this research finding. Again this study comparable to study conducted in Taiwan revealed that patients with modernate anemia have a significan predictor for stroke otcome(45). American heart association also implicated that patients with decrease all blood cells or at least one lead to cardiovascular morbidity and mortality include stroke due to that patient with low red blood cell manifest oxygen deprevation and tissue ischemia, patient with low platelet manifest risk for high bleeding and patient with low

white blood cell manifest decrease immunity and increased risk of opportunistic infection that interfere blood coagulability(48).

6.1. Limitation

This study not certain the outcome of censored patients and it would reduce the true incidence of stroke and affect the true survival time of stroke patients. And also since this study is retrospective in nature it would examine only secondary data and variables like BMI, weight, height and difficult to measure the quantity of behavioral risk factors; such as number of cigarette smoking per day, amount of alcohol intake, and chat chewing, and also frequency of medication discontinuation not recorded. To overcome this limitation, it's better to do prospective cohort study.

7. Conclusion

This study allows to identify predictor factors that associated with the time to onset and incidence of stroke among cardiovascular patients. From the type of cardiovascular disease; patients with hypertensive heart disease had high incidence followed by hypertension, atrial fibrillation, cardities, heart failure, ischemic heart disease, and cardiomyopathy. Hypertension and atrial fibrillation also significant predictor factors that increase the incidence of stroke among cardiovascular patients. Comorbid disease of HIV, Pancytopenia, elevated diastolic blood pressure, lower high density lipoprotein level and lower cardiac output also another significant predictor variable associated in the study.

8. Recommendation

8.1. For patients

They well complied with the management of the disease, they take the medication appropriately.

They screened for comorbid disesases

They adhered well with their follow up time

8.1. For health professionals

To control patients blood pressure on follow up time

To identify patients comorbid disease of HIV and pancytopenia and give them priority and comphressive treatment

To workup on patients lipid profile of HDL and put on medical management and nutritional advice

Do screening of stroke for cardiovascular patients with type of disease of atrial fibrillation and hypertension and create awerness regarding their high risk for stroke than other types of cardiovascular patients and shorten their follow up time

Give health education regarding predictor factors of stroke among cardiovascular patients and increase patients awerness and continually give the health education program in their follow up time.

8.2. For policy makers

This study allows different stake holders and policy makers to recognize different predictor factors that increase the time to onset of stroke among cardiovascular patients and to incorporate those predictor variables in the management strategic plans.

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10. ANNEXS

ANNEX I- Consent Form

St. Paul's Hospital Millennium Medical College Nursing Department

Information Sheet and Consent Form to assess the time to onset of stroke and predictor factors among cardiovascular patients at selected public hospitals Addis Ababa, Ethiopia, 2024.

Name of principal investigator: Mahlet Addis

Email: mahletaddis72@gmail.com

Phone Number: +251954939716

Introduction

This Information Sheet and Consent form is prepared by the principal investigator in order to clarify about the study. Due to the study's retrospective design and the absence of participant interaction, informed consent will not require from study participants.

Purpose

The main purpose of this study is to assess the time to onset of stroke and predictor factors among study participants. The finding of this study will help me to address study objective and communicate the finding for respective bodies in order to give special concern for cardiovascular patients.

Confidentiality

The information gather from secondary data only include the variables that are essential for the study and used only for research purpose. The medical card number also coded during data recording. Patient name and address also not recoded during data collection.

Risks

There is no possible risk in this study.

If any who has concern and want to ask a question, can use the above address

Thank You

ANNEX II- English Questionnaire

Table 9: Tool that assess the time to onset of stroke among cardiovascular patients.

Cohort groups

Variables	Answers	Skip
CVD diagnosis date	dd/mm/year	
Types of CVD	1. Atrial fibrillation 2. Cardiomyopathy 3. Cardities 4. Heart failure 5. Hypertension 6. Hypertensive heart disease 7. Ischemic heart disease 8. Rheumatic heart disease	
Occurrence of stroke (event)	1. Yes 2. No	If No → 006
Types of stroke	1. Ischemic stroke 2. Hemorrhagic stroke	
Stroke diagnosis date (event date)	dd/mm/year	Then → 007
Censored date	dd/mm/year	
Days contribute to the study	_____	

Sociodemographic variables of cardiovascular patients

Numbers	**Variables**	**Answers**	**Skip**
1	Sex	1. Male 2. Female	
2	Age	_____ in years	

Clinical status variables of cardiovascular patients

Numbers	Variables	Answers	Skip
3	Comorbid disease	1. Yes 2. No	If No → 012
4	Types of comorbid disease	1. DM 2. CKD 3. Thyroid disease 4. HIV 5. COPD 6. Pulmonary HTN 7. Pancytopenia 8. Other _____	
5	Cardiac procedure done	1. Yes 2. No	If No → 014
6	If yes what type of cardiac procedure done	1. Angiography 2. PCI 3. Valvotomy 4. Pacemaker	
7	History of medication	1. Yes 2. No	If No → 016
8	Types of Medication	1. Warfarin 2. Atorvastatin 3. Aspirin 4. Other_____	

Risk variables for cardiovascular patients

Number	Variables	Answers	
9	BP		
10	History of smoking	1. Yes 2. No	

11	History of alcohol	1. Yes 2. No	
12	History of Kchat chewing	1. Yes 2. No	
13	History of transient ischemic attack	1. Yes 2. No	
14	History of stroke	1. Yes 2. No	
15	Family history of chronic disease	1. Yes 2. No	If No → 023
16	If yes, which type of family history of chronic disease	1. Stroke 2. HTN 3. Cardiac disease 4. DM 5. Other _____	
17	History of medication discontinuation	1. Yes 2. No	

Laboratory and Echocardiography imaging variables for cardiovascular patients

Number	**Variables**	**Answers**	
18	Lipid profile (mg/dl)		
	Total cholesterol level (mg/dl)		
	LDL (mg/dl)		
	HDL (mg/dl		

	TGL (mg/dl		
19	INR		
20	Cr (mg/dl)	_____	
21	Electrolyes		
	K		
	Na		
22	CBC	WBC_____	
	WBC		
	Hgb		
	Platelet		
23	HgA1C (mmol/mol)	_____	
24	Presence of intra-cardiac thrombus vegetation	1. Yes 2. No	
25	Function of heart valve	1. Normal 2. Abnormal	
26	Echo findings		
	Echo recent ejection fraction (%)		
	Echo recent left atrium size (mm)		
	RV systolic function preserved with TAPSE (mm)		

	LVID during systole (mm)		
	LVID during diastole (mm)		
	TR velocity (m/sec)		
	RVSP (mm/Hg)		
27	Presence of plural effusion	1. Yes 2. No	
28	Presence of cardiomegaly	1. Yes 2. No	

Declaration

I declare that this Research Thesis entitled "Time to onset of stroke and predictor factors among cardiovascular patient's in Addis Ababa, Ethiopia " is my own work that have not been addressed in the study area as far as my knowledge touched and all the sources I used has been indicated and acknowledged as complete reference.

Name of Investigator

Mahlet Addis (BSc) Date _____ Signature _____

Name of Advisers

1. Mr. Getahun Fetensa (BSc, MSc, MPH, MPM fellow, JBI fellow, assistant professor)

Date _____ Signature _____

2. Mr. Yared Getacheo (BSc, Msc)

Date _____ Signature _____

Name of Invigilators

1.

Date _____ Signature _____

2.

Date _____ Signature _____