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Development and Validation of Risk Score for in-Hospital Mortality of Stroke at Felege Hiwot Comprehensive Specialized Hospital, Bahir Dar, Ethiopia, Retrospective Cohort Study

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COLLEGE OF MEDICINE AND HEALTH SCIENCES

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DEPARTMENT OF EPIDEMIOLOGY AND BIostatISTICS

DEVELOPMENT AND VALIDATION OF RISK SCORE FOR IN-HOSPITAL MORTALITY OF STROKE AT FELEGE HIWOT COMPREHENSIVE SPECIALIZED HOSPITAL, BAHIR DAR, ETHIOPIA, RETROSPECTIVE COHORT STUDY

BY TIRUAYEHU GETINET (BSc, IN PUBLIC HEALTH)

A RESEARCH THESIS SUBMITTED TO THE DEPARTMENT OF EPIDEMIOLOGY AND BIostatISTICS, SCHOOL OF PUBLIC HEALTH, COLLEGE OF MEDICINE AND HEALTH SCIENCES IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF PUBLIC HEALTH IN EPIDEMIOLOGY

JULY 2021

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COHORT STUDY

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BAHIR DAR, ETHIOPIA

DECLARATION FORM

BAHIR DAR UNIVERSITY

College of Medicine and Health Sciences, School of Public Health Department of
Epidemiology and Biostatistics

Approval of Research thesis

I hereby certify that I have supervised, read, evaluated and examined this thesis entitled “DEVELOPMENT AND VALIDATION OF RISK SCORE FOR IN HOSPITAL MORTALITY OF STROKE AT FELEGE HIWET COMPREHENSIVE SPECIALIZED HOSPITAL, BAHIR DAR, ETHIOPIA, RETROSPECTIVE COHORT STUDY,” by Tiruayehu Getinet. We recommend and approve the thesis a degree of “Master of Public Health in Epidemiology”.

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ABSTRACT

Background: Stroke is the second leading cause of death and the third leading cause of disability-adjusted life-years worldwide. It remains a disease of immense public health significance despite the advances in understanding its epidemiology, quality of life, and pathophysiology. It is a complex condition occurring in heterogeneous populations with a variety of mechanisms each having a different prognosis. Developing risk score helps clinicians to properly manage stroke.

Objective: To develop and validate risk score for in-hospital mortality of stroke at Felege Hiwot comprehensive specialized hospital, Bahir Dar, North West Ethiopia 2021.

Methods: A retrospective cohort study was conducted from March 11 to April 10 among stroke patients admitted at Felege Hiwot comprehensive specialized hospital from September 11/2018 to March 7 /2021. Patient medical records were selected by Computer-generated simple random sampling technique and data were extracted by structured checklists. Data entry was done using Epi data 3.1, and data processing, and analysis were done by SPSS version 26 and R programming language version 4.0.4. Both descriptive and multivariable binary logistic regression analysis were done to identify predictors of in-hospital mortality. Internal validation of the model was performed using the bootstrap technique and simplified risk scores were established from the beta (β) coefficients of predictors of the final reduced model.

Results: Among 912 stroke patients enrolled in study 132 (14.5%) patients died during a hospital stay. The risk prediction model was developed from eight routine prognostic predictors (age, sex, type of stroke, diabetes mellitus, temperature, Glasgow Coma Scale, and Pneumonia. The area under the curve of the model was 0.895 (95% confidence interval: 0.859-0.932 for the original model and was the same for the bootstrapped model. The area under the curve of simplified risk score was 0.893 (95% confidence interval: 0.856–0.929). The model calibration test was p-value 0.225. The developed risk score had a possible range of 0-14.

Conclusion and recommendation: The in-hospital mortality risk prediction score developed from eight predictors (age, sex, type of stroke, diabetes mellitus, temperature, Glasgow Coma Scale, and Pneumonia) had a good discrimination ability. It is simple, easily memorable, and helps clinicians to identify the risk of patients and manage properly. Additional prospective studies in different populations and settings are required to externally validate the risk score.

Keywords: stroke, in-hospital mortality, risk score, Felege Hiwot, Ethiopia

ABBREVIATIONS AND ACRONYMS

AUC	Area under the curve
BUN	Blood Urea Nitrogen
C-Statistics	Consistency Statistics
DALYs	Disability Adjusted Life years
GCS	Glasgow Coma Scale
HICs	High-Income Countries
HS	Hemorrhagic Stroke
ICH	Intra Cerebral Hemorrhages
IQR	Inter Quartile Range
IS	Ischemic Stroke
LMICs	Low and Middle-Income Countries
NIHSS	National Institute of Health and Stroke Scale
ROC	Receiver Operating Characteristics Curve

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1. INTRODUCTION

1.1 Background

According to World Health Organization, “stroke is rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer, or leading to death, with no apparent cause other than of vascular origin”(1).

Stroke called brain attack is the second leading cause of death and the third leading cause of disability-adjusted life-years worldwide. It occurs when a blood clot blocks a blood vessel that carries blood from the heart to the body or a tube through which the blood moves through the body breaks, interrupting blood flow to an area of the brain. Strokes can be classified broadly as ischemic and hemorrhagic. In both the developed and developing world, ischemic stroke is currently the predominant stroke type which accounts for 80% of strokes, and hemorrhagic stroke accounts for only 20% of total strokes(2-4). Ischemic stroke is usually caused by a blockage of a blood vessel (artery) in the brain: there are two types of ischemic strokes called thrombotic strokes and embolic strokes. Strokes caused by the breakage or "blowout" of a blood vessel in the brain are called hemorrhagic strokes. There are two types of hemorrhagic stroke: subarachnoid and intracerebral. An intracerebral hemorrhage, bleeding occurs from vessels within the brain itself (2).

Stroke is a disease of immense public health importance with serious economic and social consequences. The public health burden of stroke is set to rise over future decades because of demographic transitions of populations, particularly in developing countries(4). The prognosis of stroke depends on the quick diagnosis of the type, followed by appropriate and fast management(3)

1.2. Statement of the Problem

Stroke remains a disease of immense public health significance despite the advances in understanding its epidemiology, quality of life, and pathophysiology (4). Although stroke incidence, prevalence, mortality, and disability-adjusted life years (DALY) rates declined from 1990 to 2017, the absolute number of people who developed new stroke, died, survived, or remained disabled from stroke has almost doubled. In 2017, there were 11.9 million incidents,

104.2 million prevalent, 6.2 million fatal cases of stroke, and 132.1 million stroke-related DALYs worldwide(5).

The global burden of stroke was increasing dramatically due to the growing size and aging of the world's population, with marked differences between high- and low-income countries. Primary prevention had contributed to a decrease in stroke incidence in high-income countries (HICs) but the epidemiological transition had led to an increase in incidence in low to middle-income countries (LMIC). LMICs had a high burden of the stroke where 80% of all incident strokes, 77% of all stroke survivors, 87% of all deaths from stroke, and 89% of all stroke-related DALYs) happened in 2017 (5-7).

Of all prevalent strokes, 82.4 million were ischemic strokes, 17.9 million were intracerebral hemorrhages, and 9.3 million were subarachnoid hemorrhages. From 11,931,000 incident stroke cases Ischemic stroke (IS) constituted 64.9%, primary intracerebral hemorrhage (PICH) 26.2% and subarachnoid hemorrhage (SAH) 8.9% worldwide, the corresponding stroke pathological type proportions in HICs were 66.6%, 19.1%, 14.3%, and in LMIC 64.4%,28.1% and 7.6%, respectively (4, 5).The annual mortality rate of stroke is around 5.5 million worldwide (4). From the total fatal cases of stroke 2.7 million people died of ischemic stroke, 3.0 million died of intracerebral hemorrhage, and 0.4 million died of subarachnoid hemorrhage (5, 8).

Globally, between 1990 and 2013, there were significant increases in prevalent cases, total deaths, and DALYs of stroke in younger adults (aged 20 to 64 years). In 2013, in younger adults the global prevalence of HS was 3.7 million cases, and IS was 7.3 million cases. There were 1.5 million stroke deaths globally among younger adults. From 1990 to 2017, in high-income countries, there was a significant 6% increase in stroke incidence rates in people aged 15–49 but no significant changes in stroke prevalence (1% increase); and significant (47%) reductions in stroke mortality and 39% reduction DALY rates. In LMICs there was a small but significant increase in stroke prevalence (4%), although stroke incidence, mortality, and DALY rates have significantly declined (5, 9).

A systematic review and meta-analysis conducted in Africa found a high and increasing burden of stroke in Africa. In 2009, there were an estimated 483 thousand new stroke cases among people aged 15 years or more in Africa, equivalent to 81.2 /100,000 person-years. An estimated

1.89 million stroke survivors among people, with a prevalence of 317.3 /100000 population. Comparable figures for the year 2013 based on the same rates would amount to 535 thousand new stroke cases and 2.09 million stroke survivors, suggesting an increase of 10.8% and 9.6% of incident stroke cases and stroke survivors respectively, attributable to population growth and aging between 2009 and 2013(10).

Although the overall age-adjusted stroke mortality rates decreased by 1% (increased by 9% for ischemic stroke and decreased by 10% for hemorrhagic stroke), the number of deaths from stroke in Sub Saharan Africa (SSA) nearly doubled from 1990 to 2013. The increase in the number of stroke deaths particularly noticeable for ischemic stroke (104% increases in 2013 compared to 1990). Although the majority of deaths from stroke in SSA in 1990 were due to hemorrhagic strokes (55%), in 2013 the proportional frequency of deaths from hemorrhagic stroke was slightly lower (49.6%) than that from ischemic stroke. Compared to GBD 2010 stroke mortality estimates, the mean age at death from stroke in SSA was the lowest among all LMIC (11).

In Ethiopia stroke was the second leading cause of death caused an estimated 32859.5 deaths among all ages and both gender groups in 2016. Death from stroke also has contributed to 30% of the total cardiovascular deaths (109499.7) estimated to have occurred in the year 2016. The total death from stroke was estimated to have increased by 23.8 % between 2000 and 2016(12). A systematic review and meta-analysis done in Ethiopia showed that nearly one-fifth (18%) of stroke patients have died during hospitalization. It indicated that there was a regional difference in the in-hospital mortality rate of stroke ranges from 10.7% in the Tigray region to 35.2%) in Southern Nation's Nationalities and Peoples Region (SNNPR). The Magnitude of the in-hospital mortality rate is increasing (15.1% until 2016 and it becomes 19.6% after 2016). The in-hospital mortality rate of the Amhara region was 14.7 %(13).

Several factors have been identified as predictors for in-hospital mortality including age, localization of ischemia, Glasgow Coma Scale (GCS) , stroke severity measured by the National Institutes of Health Stroke Scale, posterior circulation stroke syndrome, non-lacunar stroke cause, pre-stroke functional disability (modified Rankin Scale >0), preexisting heart disease, having coma, cerebral edema, atrial fibrillation, diabetes mellitus, hypertension, tobacco smoking, alcohol, dyslipidemia, and family history of stroke (14-17).

Previous studies focused on explaining the cause for in-hospital mortality of stroke but Stroke is a complex condition occurring in heterogeneous populations with a variety of mechanisms, each having a different prognosis (18), nowadays, the focus shifted to prediction researches to determine the risk of an individual patient to die during hospital stay by combining multivariable prognostic predictors. Worldwide several risk prediction models have been developed previously to predict the in-hospital mortality stroke but they were complex, need special training to measure predictors, need an invasive procedure, and do not incorporate all types of strokes. The GET-with Guidelines stroke is the only valid model which includes both types of stroke but applicable with the aid of Web-based computational support (19-21) made them not applicable in a resource-limited setup like Ethiopia. Although studies indicated high in-hospital mortality of stroke there was no clinical developed prediction model in Ethiopia. Predicting the probability of in-hospital mortality in stroke patients is important for proper management and plan by applying the available evidence at the bedside. The study aimed to develop and validate a risk score for in-hospital mortality of stroke using information routinely available to clinicians at hospital admission such as demographic characteristics, clinical presentation, risk factors and complications, and biochemical characteristics.

1.3 Significance of the Study

The result of this study will use for the patient and their families directly or indirectly to determine the cost and benefit of the management given for the patient and to decide in order to expose for invasive management. The study will help health professionals in the management of stroke and also help to guide supportive care plans, to coordinate appropriate rehabilitation services, to facilitate patient and/or family counseling or discussions about the end of life decisions. Policymakers will use it in conducting fair comparisons when evaluating stroke fatality among different facilities for hospital outcomes and performance assessment. Furthermore, it will be used as baseline information for researchers who investigate for in-hospital mortality of stroke.

2. LITERATURE REVIEW

2.1 Overview of Stroke in Hospital Mortality

The different studies showed that overall in-hospital mortality of stroke patients vary across countries worldwide .Stroke mortality rates also diverse across several African studies and ranges from 6.2% in Benin (16) to 34.8% in Sierra Leone (22), reflecting the differences in access to quality healthcare systems, absence of national health insurance schemes, lack of trained medical workforce, lack of diagnostic imaging, inappropriate treatment, and absence of in- hospitals stroke units(22).

Stroke was the third leading cause of non-communicable medical admissions in Uganda responsible for 13.4% of non-communicable admissions (62%) and had a case fatality rate of 26.8% (23). A study done in Kenya found that mortality of stroke decreased with the increase in follow-up time with high mortality record in the first 3 months of follow-up (18.4% by day 10, 10.4% by day 28, and 10.3% by month 3, respectively (24), it is also supported by another study conducted in Serra Leone indicated that majority of the deaths occurring in the first week of in-hospital stay(22) and inpatients had approximately four (3.9) fold increased risk of death compared to out-Patients (24).

2.2 Predictors of Stroke in Hospital mortality

2.2.1 Sociodemographic characteristics

Socio-demographic characteristics were identified as a risk of stroke and its mortality worldwide. A hospital-based study of acute ischemic stroke conducted in eight states in the USA showed that inpatient mortality was significantly higher (67% increased risk) in patients living in low-income areas than in those in high-income areas(25). A study conducted in Gondar university hospital indicated that more than half (55.4%) of patients were from urban residence (26) and another study conducted in Felege Hiwot referral hospital also found that 56.7% of the patients from urban residents (27) in contrary to this a study conducted in Jimma and Debre Markos found that majority of stroke patients were rural residents which accounted for 72.4% and 53.7% respectively (28) (29). According to studies, there was a difference in the proportion of affected and in-hospital mortality between males and females. Most found that stroke was more common

in males (28, 30-33), but in contrast others indicated females were highly affected (24, 26). Many studies found in hospital mortality of stroke was higher in women (22, 30, 34, 35) but others indicated it was higher in males(24, 36).

Globally most studies indicated that increasing /old age had increased risk of in-hospital mortality. A study conducted in the Tabriz stroke registry of Iran showed that elderly (≥ 65 years) patients were 1.6 times more likely to die during hospitalization (19, 34, 36-39).

2.2.2 Clinical presentation characteristics

Studies showed that globally there was a variation in the burden of morbidity and mortality among types of stroke, Ischemic stroke was the most commonly diagnosed and Hemorrhagic stroke was the most deadly type of stroke among admitted patients (21, 40) but some found hemorrhagic stroke was the most commonly diagnosed type (41). The Get with guidelines study found that out of the total diagnosed strokes IS, 82.4%; ICH, 11.2%; SAH, 2.6%, and uncertain type accounted for 3.8% of strokes and from total in-hospital deaths IS, 5.5%; ICH, 27.2%; SAH, 25.1%, and unknown type accounted for 6.0% (19). Several studies found that patients diagnosed with hemorrhagic stroke had a higher risk of in-hospital mortality than patients diagnosed with ischemic stroke. The risk of in-hospital mortality of patients having a hemorrhagic stroke was three times higher in a study conducted in Serra Leone, around six (5.65) times higher in a study conducted at Cameron and about four times higher (3.85) in the study conducted in Hawassa, Ethiopia than patients having an ischemic stroke (20, 22, 33, 40, 42).

Time to admission plays a central role in acute stroke management, with early thrombolysis treatment minimizing damage to the brain and improving chances of recovery. A study conducted in Hawassa showed that most stroke patients (69%) were admitted more than 24 hours after stroke onset (40) and a Study conducted at Ayder referral hospital in northern Ethiopia found less than 10% arrived at the hospital within 3 hours of stroke onset; nearly half (47.9%) were delayed over 24 hours(43). Studies found that hemiplegia was the most common clinical presentation of admitted stroke patients (17, 26, 32, 42, 43). Increased temperature/fever at admission was a significant predictor of in-hospital mortality of stroke (16, 44).

Level of consciousness was an independent predictor of in-hospital mortality of stroke, Patients who had a lower admission (GCS<8) were more likely to die. A hospital-based study conducted in southwestern Saudi Arabia found that Patients having a low level of consciousness had 7 times higher risk to die at the hospital, a similar study conducted in Serra Leone indicated 6 times higher, a study done in Cameron also found 2 times higher and another study conducted in Hawassa, Ethiopia found approximately four (RR 3.8) times higher risk of in-hospital death than patients having higher GCS(>8) (16, 22, 33, 36, 39, 40).

2.2.3 Risk factors/complications

Several modifiable or non-modifiable risk factors have been linked to a higher risk of developing stroke. Non-modifiable risk factors include a positive family history of strokes, age, male gender, and black or Hispanic races. Modifiable risk factors contributed to 80% of strokes which can be modified with behavioral changes. Hypertension remains the leading risk factor of stroke in both developed and developing countries despite the racial differences in the risk factors of stroke(4, 45).Hypertension was found the most common risk factor of stroke worldwide. A hospital-based study conducted in southwestern Saudi Arabia showed that patients having pre-stroke hypertension had approximately two times higher risk of in-hospital mortality than those who do not have. According to systematic review and meta-analysis result in Ethiopia hypertension was the most common risk factor found in 47% of hospitalized stroke patients (13, 16, 17, 22, 26, 32, 36, 43, 46).

Both neurologic and medical complications were common in the majority of stroke patients. Aspiration pneumonia was also an independent predictor of in-hospital mortality of stroke. A study conducted in Tabriz Iran found that patients who had aspiration pneumonia had a 1.5 times higher risk of in-hospital mortality of stroke. Aspiration pneumonia was found in 19.8% of stroke patients admitted stroke unit of Jimma university medical center (39, 47)

A study conducted in Hawassa showed that patients who had seizures were approximately four times higher (RR 3.7) risk of in-hospital mortality than those who did not have(40). Another study conducted in Nigeria showed that the odds of one-month in-hospital mortality of stroke were two times higher in patients who had seizures (48).

Evidence from systematic review and meta-analysis in Ethiopia showed Urinary incontinence found in 28.4% of admitted stroke patients and was found an independent predictor of in-hospital mortality of stroke(13). The study conducted in Jimma Ethiopia found that patients who had urinary incontinence were 3.5 times higher at risk of in-hospital death (47, 49). A study conducted in Sierra Leone showed that the previous stroke increases the odds of in-hospital mortality of stroke two times(AOR = 2.31)(22); A Study conducted in St. Paul's Teaching Hospital, Addis Ababa, Ethiopia also found that a previous history of stroke had significantly associated with in-hospital mortality of stroke (41).

2.2.4 Biochemical characteristics

Basic laboratory tests of stroke including Hemoglobin, blood urea nitrogen, and creatinine were identified as predictors of in-hospital mortality of stroke. Creatinine levels were independently associated with in-hospital mortality of stroke .one unit increase in creatinine level had a 1.8 times higher risk of stroke in-hospital mortality (50), elevated serum creatinine increases the risk of in-hospital mortality of stroke patients nine times than patients having normal creatinine level(51).

2.3 Predicting in-hospital mortality of stroke

Globally, there were many prognostic models which were developed to predict in-hospital mortality of stroke. The Get With The Guidelines-Stroke (GWTG-Stroke) risk score developed based on administrative data in Japan predicted the overall in-hospital mortality of stroke had c statistic of 0.78 from predictors of age, stroke type, method of arrival at the hospital, history of atrial fibrillation, previous stroke, coronary artery disease, carotid stenosis, diabetes, peripheral vascular disease, hypertension, dyslipidemia, smoking, and weekend or night admission as significant independent predictors of mortality (19).

Different models were developed to predict mortality of acute ischemic stroke (AIS). The PREMISE score was developed in Austrian for early stroke unit mortality (7days) with predictors Age, stroke severity measured by the National Institutes of Health Stroke Scale, pre-stroke functional disability (modified Rankin Scale >0), preexisting heart disease, diabetes mellitus, posterior circulation stroke syndrome, and non-lacunar stroke with the area under the

curve of the score 0.879 and 0.884 in the derivation cohort and validation sample respectively (52). Another risk score was also developed in Canada for AIS early death (30 days) after hospitalization showed that c statistic was 0.850, 0.851 for the derivation and internal validation cohort respectively. Predictors were older age, male sex, severe stroke, no lacunar stroke subtype, glucose greater than or equal to 7.5 mmol/L (135 mg/dL), history of atrial fibrillation, coronary artery disease, congestive heart failure, cancer, dementia, kidney disease on dialysis, and dependency before the stroke(38)(39).

A study conducted in Japan developed three acute ischemic stroke mortality models for 7 days, 30 days in-hospital mortality, and overall in-hospital mortality from administrative data. The C-statistics for derivation and validation data were 0.906 and 0.901, 0.893 and 0.872 and 0.883 and 0.876 for the 7-day, 30-day, and overall in-hospital mortality prediction models respectively. Independent variables included were patient age (as a continuous variable), sex, comorbidities upon admission, patient consciousness and disability levels, and arrival period. Comorbidities included acute myocardial infarction, atrial fibrillation, dyslipidemia, hypertension, peripheral vascular disease, chronic pulmonary disease, connective tissue disease, liver disease, renal disease, and cancer(20).

The model developed for in-hospital mortality of elderly acute stroke patients indicated that age, smoking, congestive heart failure, warfarin use, Glasgow Coma Scale, mean arterial pressure less than 60 mm Hg, admission white blood cell count (WBC), and creatinine levels were independent predictors of mortality with the area under the curve of 0.83(50).

The PLAN score was also developed as a bedside prediction rule for death and severe disability following AIS addresses issues of practicality and efficiency by only requiring basic information such as preadmission comorbidities, LOC, age, and neurologic focal deficit, which are all established risk factors that can be evaluated by non-specialist clinicians with a c-statistics 0.88(53).

3. CONCEPTUAL FRAMEWORK

Candidate prognostic factors for in-hospital mortality of stroke patients including sociodemographic, clinical presentation, comorbidities, and biochemical characteristics.

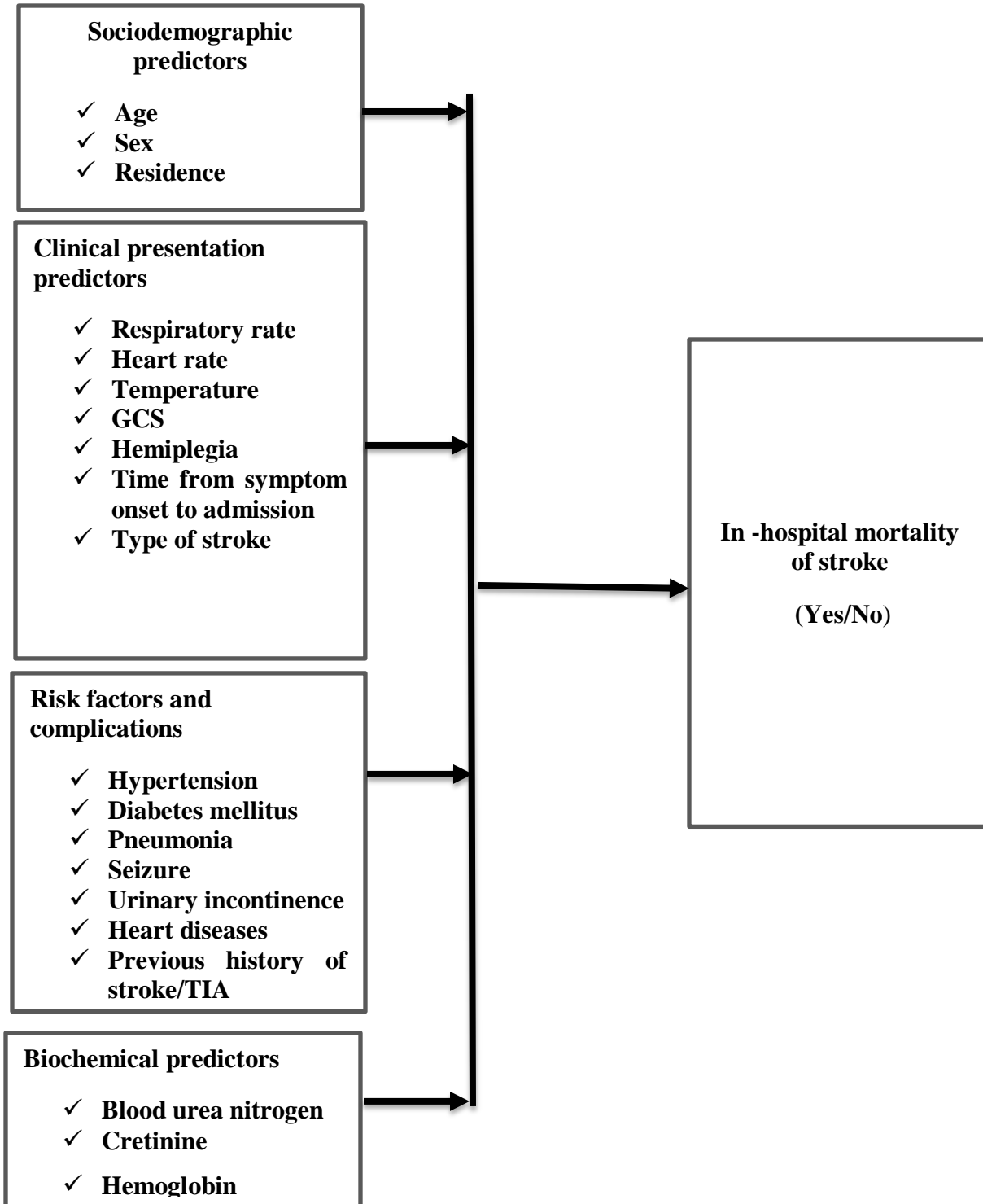


Figure 1. Conceptual Framework, showing the predictors of in-hospital mortality of stroke

4. OBJECTIVE

4.1 General Objective

To develop and validate risk score for in-hospital mortality of stroke among patients admitted to Felege Hiwot comprehensive specialized hospital, Bahir Dar, North West, Ethiopia 2021

4.2 Specific Objectives

To develop a risk prediction model for in-hospital mortality of stroke among patients admitted to Felege Hiwot comprehensive specialized hospital, Bahir Dar, Northwest, Ethiopia 2021

To develop a risk score for in-hospital mortality of stroke among patients admitted to Felege Hiwot comprehensive specialized hospital, Bahir Dar, Northwest, Ethiopia 2021

5. METHODS

5.1 Study Setting

The study was conducted in Felege Hiwot comprehensive specialized hospital (FHCSH) which is found in Bahir Dar City, the capital of Amhara National Regional State, northwest Ethiopia 575 Kilometer far from Addis Ababa, the capital city of Ethiopia. It provides health care service for more than 10 million people coming from Bahir Dar city, west Gojjam zone, east Gojjam zone, awe zone, north and south Wello zones, south and north Gondar zones partial part of Benshangul Gomez and Oromia region. The hospital has currently a total of 1431 human power in each discipline and 500 formal beds. The medical ward is one of the 13 wards in FHCSH where stroke patients are hospitalized in the stroke unit having twenty-four beds and four rooms. Stroke was the first leading cause of admission at a hospital in 2012 E.C. The hospital has a Computed Tomography (CT) scan and functional 24 hours daily but it has no magnetic resonance imaging (MRI). MRI is available at a private clinic in Bahir Dar city(54).

5.2 Study Design and Period

A retrospective cohort study was conducted from September 11, 2018 to March 7, 2021 and extracted since March 11- April 10, 2021.

5.3 Population

5.3.1 Study domain

All stroke patients admitted to the medical ward at Felege Hiwot comprehensive specialized hospital

5.3.2 Study population

All stroke patients admitted to medical ward at Felege Hiwot comprehensive specialized hospital during the period from September 11, 2018 to March 7, 2021.

5.4 Eligibility Criteria

5.4.1 Inclusion criteria

All medical records of stroke patients admitted to the medical ward at FHCSH from September 11, 2018, to March 7, 2021.

5.5 Sample Size Determination and Sampling Procedure

The sample size was determined by a rule of thumb assumption of 10 events per predictor variable (55) with twenty predictors and incidence of in-hospital mortality of stroke 21.6% (49) gives ($N=n*10/\text{rate of the event}$). Where N =sample size calculated, and n =number of predictors eligible for the model). So, produce a sample size of 926. The data were extracted by using computer-generated simple random samples of patient records.

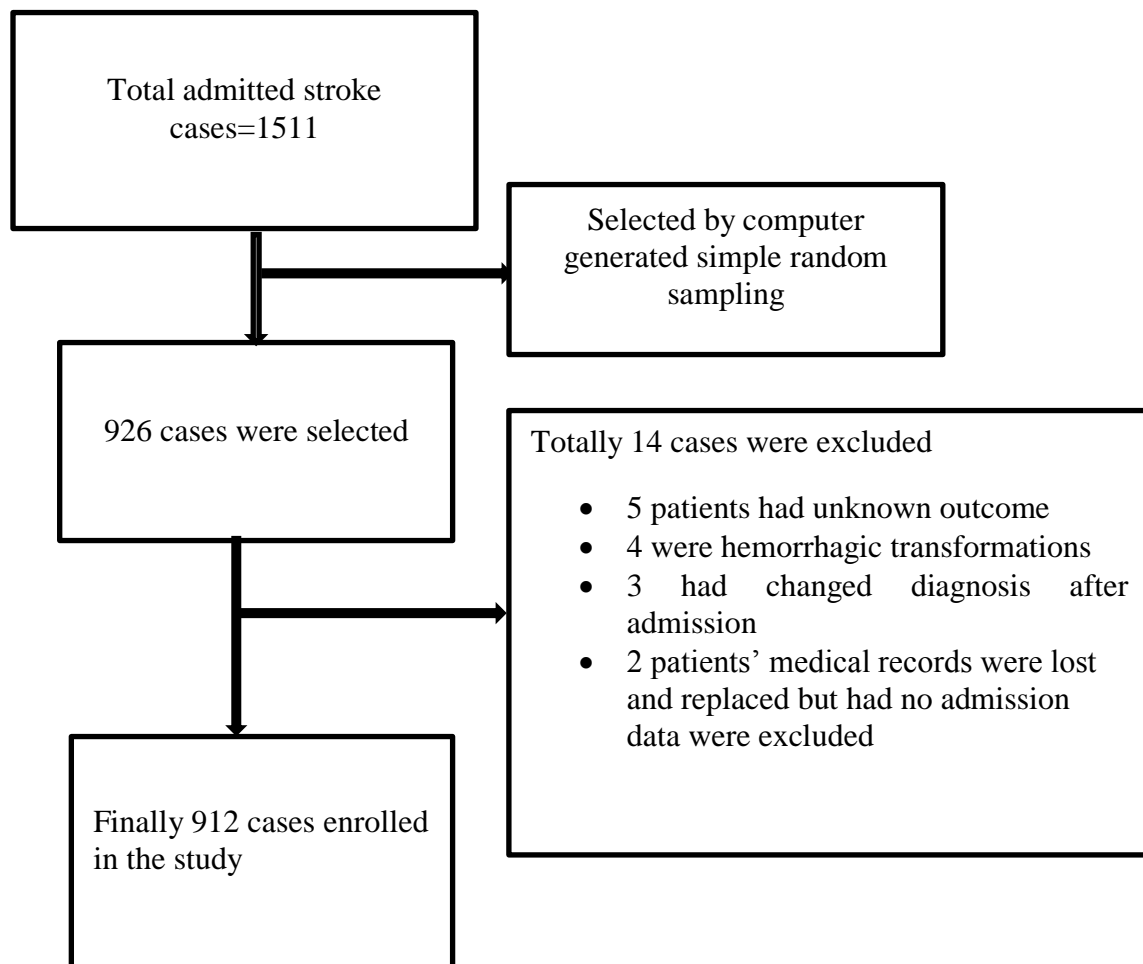


Figure 2. The flow chart shows the Sampling procedure

5.6 Study Variables

5.6.1 Dependent variable

In-hospital mortality of stroke (Yes /No)

5.6.2 Candidate Predictor variables

Socio-demographic predictors: Age, Sex, Residence

Clinical presentation predictors: Respiratory rate, Heart rate, Temperature, Hemiplegia, GCS at admission, time from symptom onset to admission, type of stroke.

Risk factors or complications - Hypertension, Diabetes mellitus, Pneumonia, Seizure, Urinary incontinence, Heart diseases, previous history of stroke.

Biochemical characteristics –Hemoglobin, Blood urea nitrogen (BUN), and Creatinine.

5.7 Definition of Terms

Hypertension- when a Patient had a history of antihypertensive treatment before admission or systolic blood pressure greater than or equal to 140 mm Hg or diastolic blood pressure greater than or equal to 90 mm Hg during admission(56).

Diabetes mellitus –when a Patient had a medical history of diabetes mellitus or had admission random blood sugar of greater than 200mg/dl or fasting blood sugar of greater than or equal to 126 mg/dl(56).

5.8 Data Collection Tools and Techniques

Data were extracted by structured checklists after the identification of medical registration numbers from the inpatient registration abstract. The questionnaire contains socio-demographic characteristics, risk factors, and complications, clinical presentations, biochemical characteristics, and outcomes. The data were collected by two public health, one BSc and one comprehensive nurse professionals, and supervised by one public health professional. Printed questionnaires, Paper, pencil, rubber, pen, and patient card records were used to collect data.

5.9. Data Quality Controls

The data collectors were given training on how to extract data and data were checked for completeness on the same day of the extraction. Pretest was done in 5% of patients at Felege Hiwot comprehensive specialized hospital which was not included in the final study. The data collection format was further modified after a pretest was conducted. Pre-existing knowledge of data collectors and supervisors about the predictors used in the patient record and where predictors recorded helped the data to be extracted with great quality. In addition, the questions were prepared by category according to variables.

5.10. Data Analysis and Management

Data were entered into Epi-data version 3.1, exported to SPSS Version 26 for data cleaning and management. Data were assumed missing at random, missing data of predictors were replaced by multiple imputations chained equations approach. The analysis was done by SPSS version 26 and R-software version 4.0.4. Categorical variables were described by percentage and frequency and continuous variables were described by median and interquartile range. Bivariable binary logistic analysis was done to select candidate predictors for multivariable binary logistic regression analysis. The variables with a p-value <0.25 were entered in to multivariable analysis to identify independent predictors of in-hospital mortality of stroke, predictors having p-value of <0.05 in the reduced model were used to develop risk score for in-hospital mortality of stroke.

The area under the ROC curve (discrimination) and calibration plot (calibration) were computed to check accuracy of the model. An AUC less than or equal to 0.5 is considered to represent a non-discriminative model whereas an AUC equal to or greater than 0.7 is considered as fair discriminative ability, an AUC equal to or greater than 0.8 is considered to represent good discriminative ability, and an AUC equal to or greater than 0.9, excellent discriminative ability (57).

To make internal validation, 1000 random bootstrap samples with a replacement on all predictors in the data set were computed. The model's predictive performance after bootstrapping was considered as the performance that can be expected when the model is applied to future stroke patients admitted to Felege Hiwot comprehensive specialized hospital. Mortality prediction

scores were established by transforming each coefficient from the model to a rounded number by dividing it by the lowest coefficient. The number of points was subsequently rounded to the nearest integer. Then the total score for each stroke case was determined by assigning the points for each variable and adding them up.

5.11 Ethical Consideration

The research proposal was approved by the Ethical Review Board of Bahir Dar University, College of Medicine and Health Sciences, and ethical clearance was obtained from the board. Ethical clearance and supporting letter were submitted and written informed consent was obtained from the hospital management. To ensure confidentiality of the patients' information, the name and address of the patients were not recorded during the data collection. No one other than the investigator had access to the collected data. Investigator used the collected data only to answer the stated objectives.

6. RESULTS

6.1 Baseline Patient Characteristics

6.1.1 Socio-demographic characteristics

A total of 912 stroke patients were enrolled in the study. The median age of patients was 65, with an interquartile range (55, 65) and ranges from 20 to 115 years. Over half (58.2%) of patients were male and 53.4% of patients were urban dwellers. Of the total in-hospital deaths, 94(71.2%) had the age of ≥ 65 years and Females accounted for 67(50.8%) of in-hospital deaths. More than half of deaths (55.3%) occurred among urban residents (**Table1**).

Table1. Sociodemographic characteristics of stroke patients admitted to Felege Hiwot comprehensive specialized hospital from September 11, 2018, to March 7, 2021(n=912).

Sociodemographic predictors	Category	Frequency	Percent
Age	<65	394	43.2
	≥ 65	518	56.8
Sex	Female	381	41.8
	Male	531	58.2
Residence	Rural	425	46.6
	Urban	487	53.4

6.1.2 Clinical presentation characteristics

Ischemic stroke was the most common type of stroke accounted for 617(67.7%) of admitted stroke patients. One hundred forty (15.4%) patients were comatose at admission and the median time to admission was 24hours with inter quartile range of (12, 24). Hemiplegia was one of the clinical presentations in 271(29.7%) of admitted stroke patients. Five hundred fifty-nine (71.2%) in-hospital deaths were comatose during admission (**Table2**).

Table 2. Clinical presentation characteristics of stroke patients admitted to medical ward of Felege Hiwot comprehensive specialized hospital from September 11, 2018, to March 7, 2021(n=912).

Clinical presentation	Category	Frequency	Percent
Hemiplegia	Yes	271	29.7
	No	641	70.3
GCS	3-8	140	15.4
	9-15	772	84.6
Time to admission (hrs.)	>24	348	38.2
	≤ 24	564	61.8
Heartrate (beats/min)	≤100	716	78.5
	>100	196	21.5
Respiratory rate (breath/min)	>20	752	82.5
	12-20	160	17.5
Temperature (degree Celsius)	>37.5	71	7.8
	≤37.5	841	92.2
Type of stroke	Hemorrhagic	295	32.3
	Ischemic	617	67.7

GCS- Glasgow Coma Scale

6.1.3 Risk factors and complications

Hypertension was the most common risk factor found in 462(50.7%) of stroke patients. Sixty-three (6.9%) patients had comorbidity of diabetes mellitus and seizure was found only in 42(4.6%) of stroke patients. About Fifteen percent (14.9%) of patients had a previous history of stroke or transient ischemic attack (**Table 3**)

Table 3. Risk factors and complications of stroke patients admitted to medical ward of Felege Hiwot comprehensive specialized hospital September 11, 2018, to March 7, 2021(n=912).

Risk factors /complications	Category	Frequency	Percent
Hypertension	Yes	462	50.7
	No	450	49.3
Diabetes mellitus	Yes	63	6.9
	No	849	93.1
Pneumonia	Yes	267	29.3
	No	645	70.7
Seizure	Yes	42	4.6
	No	870	95.4
Urinary in continence	Yes	93	10.2
	No	819	89.8
Heart diseases	Yes	186	20.4
	No	726	79.6
Previous Hx of stroke or TIA	Yes	136	14.9
	No	776	85.1

Hx-history, TIA-transient ischemic attack

6.1.3 Biochemical characteristics

Biochemical characteristics were not normally distributed when distribution was checked by the Shapiro-Wilk normality test. The median hemoglobin level was 13.8 g/dl with IQR (12.5, 13.8). The median blood urea nitrogen of stroke patients was 36 mg/dl IQR (20, 36) and the median creatinine was 0.854 mg/d IQR (0.68, 0.85) (**Table 4**).

Table 4. Biochemical characteristics of 912 stroke patients admitted to the medical ward of

Biochemical characteristics	Category	Frequency	Percent
Hemoglobin (mg/dl)	≥ 12	764	83.8
	< 12	148	16.2
BUN(mg/dl)	≤ 18	201	22.0
	> 18	711	78.0
Cretinine(mg/dl)	≤ 1.2	681	74.7
	>1.2	231	25.3

Felege Hiwot comprehensive specialized hospital from September 11, 2018, to March 7, 2021.

BUN-Blood Urea Nitrogen

6.2. Development and Validation of a Prediction Model

Out of 912 admitted stroke patients finally enrolled in the study 132 (14.5%) patients were died during the hospital stay. There were 223 (24.5%) blood urea nitrogen, 155 (17%) creatinine, 120 (13.2%) hemoglobin, 12 (1.32%) temperature and 1(0.1%) GCS missing values. To predict in-hospital mortality, 20 socio-demographic, risk factors/complications, clinical and biochemical characteristics predictors were included in this study. The bivariable logistic regression analysis identified 15 candidate predictors for the multivariable prediction model. To be liberal p-value of 0.25 as a cut-off value was used to enter into multivariable regression. Accordingly, variables were Age, Sex, Type of stroke, Heart rate, Respiratory rate, Temperature, Hemiplegia, Level of consciousness/GCS, Hypertension, Diabetes mellitus, Pneumonia, Seizure, Urinary incontinence, BUN, Creatinine. Finally, 8 variables, were remained in the final reduced model with a p-value of <0.05 (**Table 5**).

Table 5. Coefficients of both bivariable and multivariable binary logistic regression analysis (n=912)

Characteristic	Category	Bivariable analysis		Multivariable analysis	
		β [95% CI]	p-value	β [95%CI]	p-value
Age	≥ 65	.731(.329 ,1.133)	<0.001	0.692(0.122,1.282)	0.019**
	<65	1			
Sex	Female	.425(.055, .795)	0.024	0.616 (0.081-1.157)	0.024**
	Male	1			
Hemiplegia	Yes	.433 (.0487, .818)	0.027	0.246(-0.309, 0.793)	0.380
	No	1			
GCS	3-8	3.676(3.195,4.156)	<0.001	3.100(2.546 , 3.681)	<0.001**
	9-15	1			
Heartrate (beats/min)	>100	.640 (.234, 1.047)	0.002	0.540(-0.073,1.147)	0.081
	≤ 100	1			
Respiratory rate (breath/min)	>20	.663 (.081,1.246)	0.026	0.241(-0.507 1.052)	0.543
	12-20	1			
Temperature (degree Celsius))	>37.5	1.599 (1.083,2.12)	<0.001	1.032(0.267, 1.791)	0.008**
	≤ 37.5	1			
Type of stroke	Hemorrhagic	1.024 (.649,1.399)	<0.001	0.800(0.247 , 1.357)	0.005**
	Ischemic	1			
Hypertension	Yes	.326 (-.047, .698)	0.086	0.152(-0.403,0.710)	0.592
	No	1			
Diabetes mellitus	Yes	1.034 (.461,1.607)	<0.001	1.076(0.233 ,1.882)	0.010**
	No	1			
Pneumonia	Yes	2.112(1.707,2.527)	<0.001	0.949(0.381 ,1.513)	<0.001**
	No	1			
Seizure	Yes	.348 (-.446 ,1.141)	<0.001	-0.533(-1.743, 0.575)	0.366
	No	1			
Urinary in continence	Yes	.621 (.095,1.146)	0.021	-0.158(-1.009, 0.654)	0.710
	No	1			
BUN(mg/dl)	≤ 18	1			
	>18	.663 (.139 , 1.187)	0.013	0.789(0.226 ,1.351)	0.396
Creatinine(mg/dl)	≤ 1.2	1			
	>1.2	1.164 (.782, 1.546)	<0.001	0.789(0.226 , 1.351)	0.006**

BUN-Blood Urea Nitrogen, GCS- Glasgow Coma Scale, TIA-transient ischemic attack. ** indicates variables used in the development of score, creatinine, and BUN measured (mg/dl)

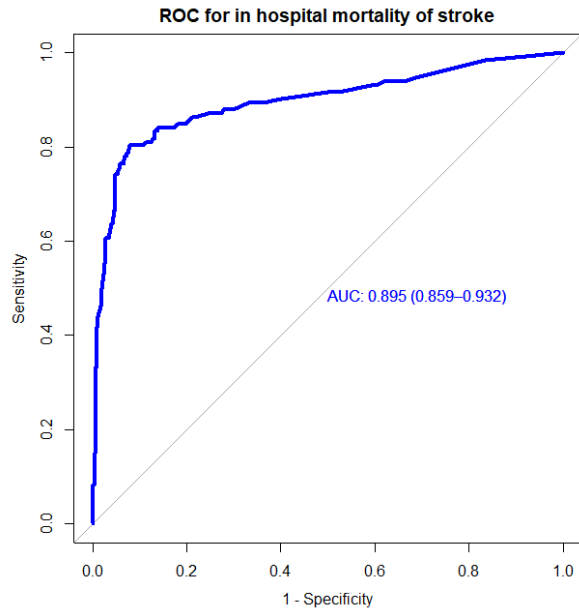
The accuracy of the AUC of the final reduced model was 0.895 (95% confidence interval: 0.859-0.932). Internal validation was performed using the bootstrap technique; the validated model resulted in an optimism coefficient of 0.079, however it had the same AUC as the development model (**Figure3**). In addition to the discrimination test (ROC) analysis to accuracy and validity of the model, a calibration plot between predicted probabilities and observed probabilities was done using a calibration belt, this produced a p-value of 0.225, showing that there is no difference between the two sets of probabilities, and indicating that the model doesn't miss represents the data (**Figure 4**).

Based on the optimal cut off point (Youden index) the predicted risk cutoff point of β coefficients of predicted a probability of 0.1792, the model has accuracy: 0.905(95% CI: 0.884, 0.923); with a sensitivity of 0.7955, Specificity: 0.9231, positive predictive value: 0.6364, and negative predictive value of 0.9639.

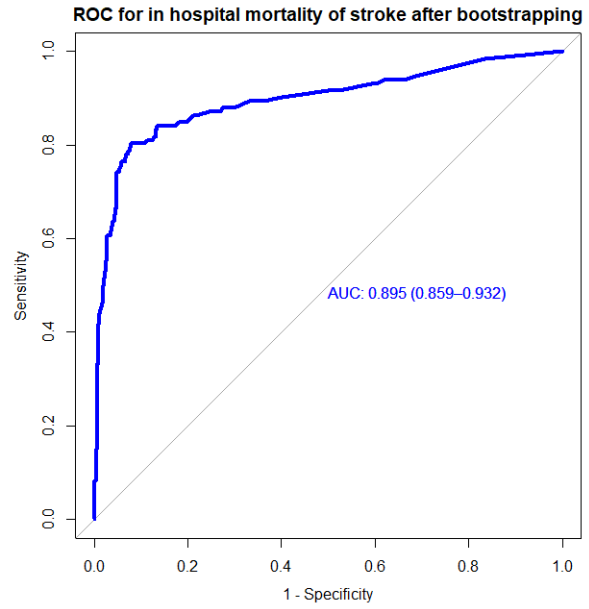
The linear relationship of the original model is shown as:

Log odds of $y = \alpha + \beta x_1 + \beta x_2 + \beta x_3 + \beta x_4 + \beta x_5 + \beta x_6 + \beta x_7 + \beta x_8$

Log odds of in hospital mortality of stroke = $-4.649 + 0.722 \text{ age} + 0.642 \text{ sex} + 1.128 \text{ temperature} + 0.817 \text{ type of stroke} + 2.908 \text{ GCS} + 0.914 \text{ pneumonia} + 1.061 \text{ diabetes mellitus} + 0.790 \text{ creatinine}$



(A)



(B)

Figure 3. Receiver operating characteristics curve of model for prediction of in-hospital mortality of stroke for development (A) and Validation (B) (N=912)

model calibration

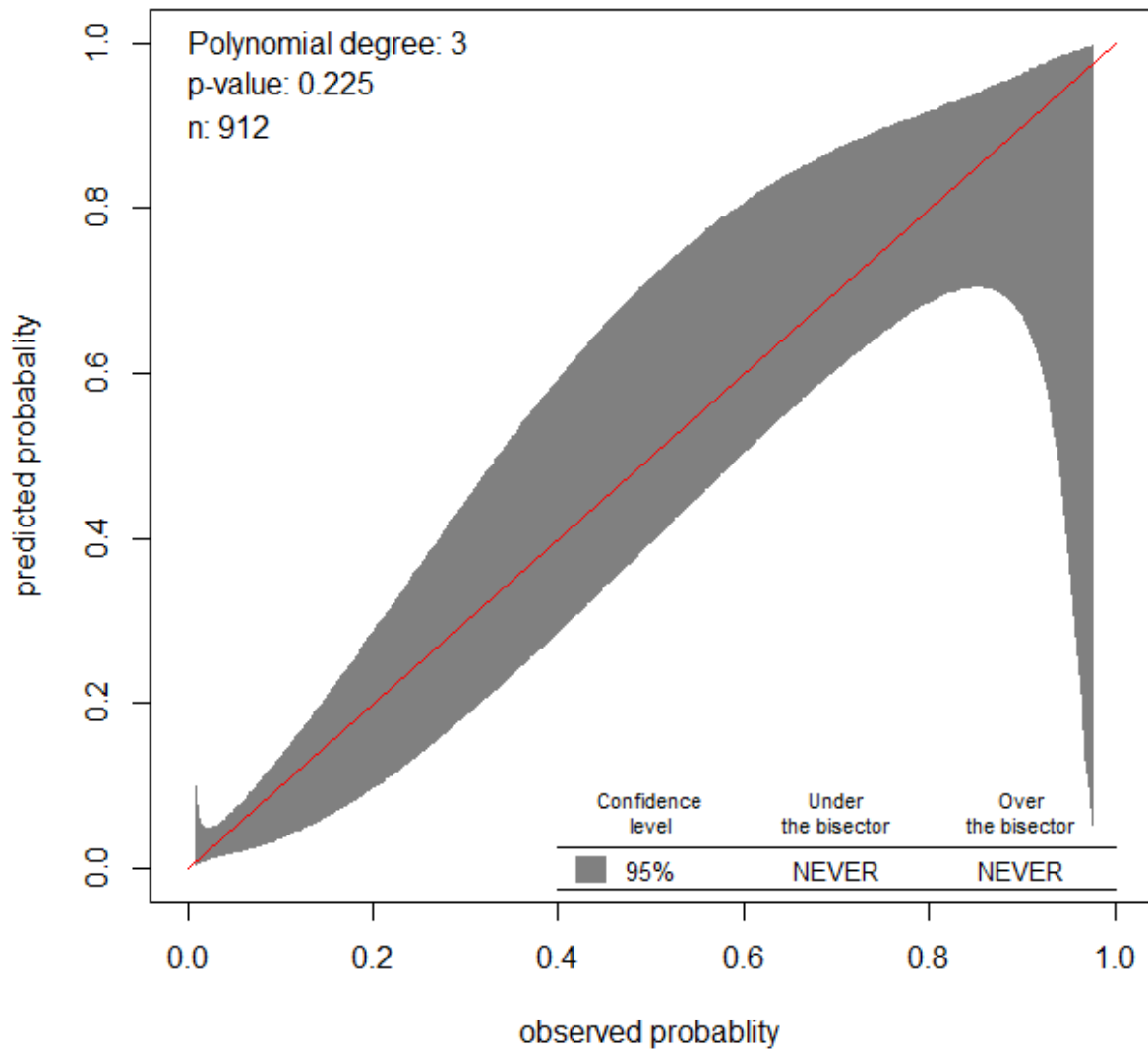


Figure 4. Calibration plot of observed versus predicted probability of in-hospital mortality of 912 stroke patients admitted to Felege Hiwot comprehensive specialized hospital, 2021

6.3 Risk Score Development

For practical utility, a simplified risk score was developed from eight variables (age in years, sex, temperature, type of stroke, diabetes mellitus, pneumonia, level of consciousness and creatinine). Each variable score was assigned by dividing its corrected β coefficient with the least coefficient in the model (beta coefficient of sex) and rounding to the nearest integer score (**Table 6**).

One point was assigned for each age ≥ 65 years, Female sex, hemorrhagic type of stroke, Creatinine >1.2 mg/dl, and pneumonia, 2 points were assigned for temperature $>37.5^{\circ}\text{C}$ and Diabetes mellitus, and 6 points were assigned for coma level of consciousness ($\text{GCS} \leq 8$) but for patients having age <65 , male sex, ischemic stroke, temperature $\leq 37.5^{\circ}\text{C}$, no comorbidity of diabetes mellitus, pneumonia, and patients having admission GCS 9-15 was given each score zero. The simplified score had an AUC of 0.893 (95%CI: 0.856–0.929). The possible minimum and maximum scores a stroke patient can have are 0 and 14, respectively. Bias of β coefficients was corrected after internal validation.

Table 6. Prognostic predictors and prognostic index scores derived from 912 stroke patients admitted to the medical ward of Felege Hiwot comprehensive specialized hospital from September 11, 2018, to March 7, 2021.

Predictors	β coefficients after corrected	Risk Score
Age >65	0.722	1
Sex (Female)	0.642	1
Creatinine(>1.2 mg/dl)	0.790	1
Temperature $>37.5^{\circ}\text{C}$	1.128	2
Hemorrhagic stroke	0.817	1
GCS(3-8)	2.908	5
Diabetes mellitus (Yes)	1.061	2
Pneumonia (Yes)	0.914	1

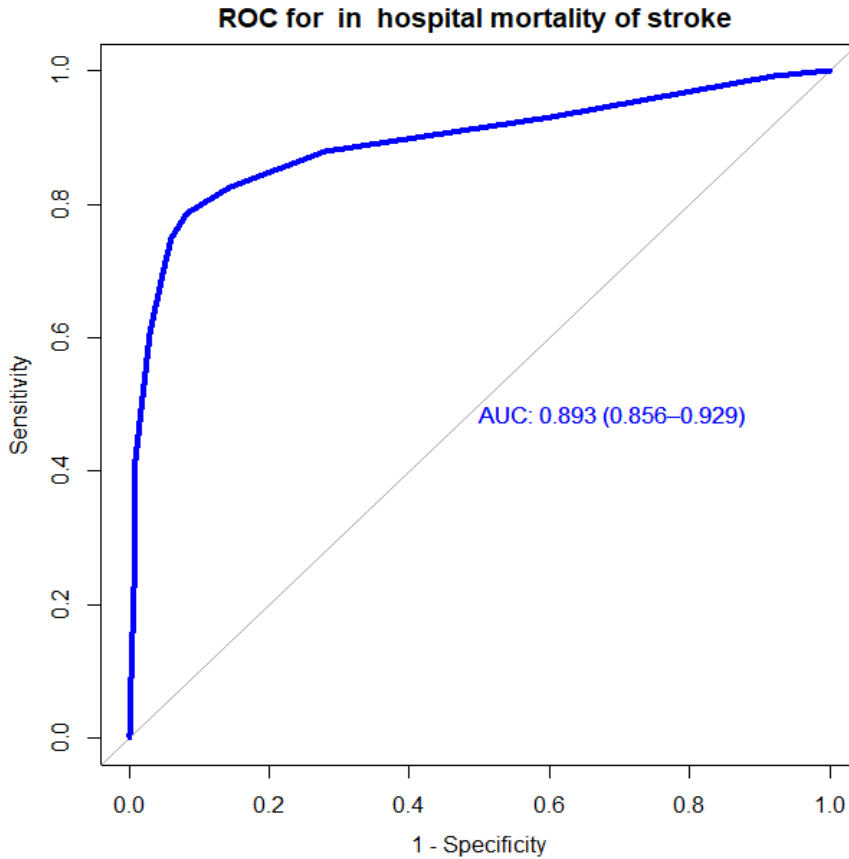


Figure 5 . ROC curve of the score for in-hospital mortality of stroke (n=912)

The risk of in-hospital mortality of a patient was dichotomized by using the Youden index to high risk (>5) and low risk (≤ 5) based on the risk score, 146 (16 %) were categorized as high risk and 766 (84%) as low risk for in-hospital mortality of stroke. Using the cut point >5 the score had a sensitivity of 78.79% and a specificity of 91.67 %.

Score of individual patient= Age+ Sex +Pneumonia + 2 * Diabetes mellitus + 5 * GCS + 2 * temperature + type of stroke + Creatinine

Table 7. Risk classification of in-hospital mortality of stroke using simplified prediction score

Risk category	Number of stroke patients (%)	Number of patients who died in hospital (%)
Low risk(≤ 5)	766 (84.0)	33(25.0)
High risk(>5)	146(16.0)	99(75)
Total	912(100)	132(100)

7. DISCUSSION

This study aimed to develop and validate risk scores for in-hospital mortality of stroke. Therefore a prediction model was developed using socio-demographic, clinical presentation, risk factors /complications, and biochemical test variables. In the present study, the model developed with eight predictors (age, sex, stroke type, temperature, level of consciousness, creatinine, and presence of comorbidity of pneumonia and Diabetes mellitus) with the area under the Receiver operating characteristics curve showed good discriminative accuracy; suggesting that the sensitivity and specificity of the model appear robust enough to be an aid in the clinical judgment of stroke patients. The calibration test also showed the agreement of observed and predicted probabilities. The model helps to identify stroke patients having a higher risk of in-hospital mortality at admission and helps clinicians to early focus on potentially modifiable risk factors to prevent further progression of the high-risk patient population. Level of consciousness was the strongest determinant of in-hospital mortality of stroke.

Previously the Get With The Guidelines stroke mortality(GWTG) score using predictor variables: age, stroke type, method of arrival at the hospital, history of atrial fibrillation, previous stroke, coronary artery disease, carotid stenosis, diabetes, peripheral vascular disease, hypertension, dyslipidemia, smoking, and weekend or night admission was the first developed and validated model for all types of stroke. It had fair discrimination (19). The model developed in this study is better than the previous since the model is simple and easily applicable in clinical setup, developed from a fewer number of predictors, having good discrimination ability, but the GWTG mortality score had fair discrimination ability without including the National Institute of health and stroke scale (NIHSS) had good discrimination only NIHSS was included in the risk model. It also has limited clinical practicability because the score is difficult to calculate with points ranging from 0 to 204 and its application needs the aid of Web-based computational support. In contrary to the previous score the current score was developed in a single hospital and is the only prediction score developed for in-hospital mortality of stroke in Ethiopia.

A risk prediction model developed for in-hospital mortality of elderly acute stroke patients indicated that age, smoking, congestive heart failure, warfarin use, Glasgow Coma Scale, mean arterial pressure less than 60 mm Hg, admission white blood cell count (WBC), and creatinine levels were independent predictors of mortality with good discrimination ability (50). Even if the

model had good discrimination ability the current model had higher discriminating power and includes all patients than including elders only.

The PREMISE score developed for early stroke unit mortality (7days) with predictors Age, stroke severity measured by the National Institutes of Health Stroke Scale, pre-stroke functional disability (modified Rankin Scale >0), preexisting heart disease, diabetes mellitus, posterior circulation stroke syndrome, and non-lacunar stroke (52). It had good accuracy similar to the current model but the predictors NIHSS and modified Rankin scale require special training and were not applicable in developing countries like Ethiopia. In addition, it considers only ischemic stroke patients.

A study conducted in Japan also developed three acute ischemic stroke mortality models for 7 days, 30 days in-hospital mortality, and overall in-hospital mortality from administrative data. From independent predictors age (as a continuous variable), sex, comorbidities upon admission, patient consciousness, and disability levels, and arrival period. Comorbidities included acute myocardial infarction, atrial fibrillation, dyslipidemia, hypertension, peripheral vascular disease, chronic pulmonary disease, connective tissue disease, liver disease, renal disease, and cancer, having good to excellent discriminatory power (20). The model developed in this study had comparable discriminatory power with the previous models. The current model has fewer predictors which were easily memorable and applicable in clinical setup compared to the previous models. In addition, the models had no simplified risk scores developed

The PLAN score developed as a bedside prediction rule for death and severe disability following AIS addresses issues of practicality and efficiency by only requiring basic information such as preadmission comorbidities, LOC, age, and neurologic focal deficit (53). It is simple and all established risk factors that can be evaluated by non-specialist clinicians and had good discrimination comparable to the current score developed in this study. But it only included ischemic stroke patients and only included the verbal component of GCS.

The risk score developed in this study was developed from predictors which were previously identified as predictors of in-hospital mortality of stroke.

8. LIMITATION OF THE STUDY

The outcome may be affected by the effect of treatment and other behavioral factors that contributed to mortality which were not included in the study. It was a single-center study that cannot be applicable in other hospitals without external validation.

9. CONCLUSION

In the study, a risk prediction model for in-hospital mortality of stroke was developed from eight routine and non-invasive prognostic predictors (age, sex, type of stroke, diabetes mellitus, and temperature, level of consciousness, pneumonia, and creatinine). A simplified risk score from the reduced model was developed for easy use of the result for routine patient management purposes in hospitals. The risk score has good accuracy (discrimination AUC of 0.893) for ROC curve and calibration p-value much higher than 0.05 of perdition of in-hospital mortality from stroke. The score produced a sensitivity of 78.8%, and 91.7% specificity accuracy level prediction, showing that the model has a very good ability to reduce false-positive and false-negative cases. The model was internally validated with bootstrapping technique to insure applicable to predict in other data.

10. RECOMMENDATION

Researchers' further investigation is required to externally validate the risk score in different populations and settings

Health professionals' acceptance and application of developed risk score is may be necessary at the bedside

Health Policymakers may incorporate the developed risk score in stroke management and follow up of its application and judge it.

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12. ANNEXES

Annex I Consent Form

My name is Tiruayehu Getinet. I am a post-graduate student in Bahir Dar University College of Medicine and Health Sciences Department of Epidemiology and Biostatistics. Now I would like to conduct my thesis work in Felege Hiwot comprehensive specialized hospital among stroke patients admitted in the medical ward from 2018-2020 by reviewing medical records of patients. I need your support and permission for my work to be conducted as needed.

Would you give me informed consent?

Signature _____

Annex II English version Questionnaire

MRN_____

I.SOCIODEMOGRAPHIC CHARACTERISTICS

101. Age in years (yrs.)? ____

102. Sex 1. Male 2. Female

103. Residence 1.Rural 2. Urban

II. Diagnosis and outcome of stroke

201. Date of admission (dd/mm/yyyy) _____

202. Date of Discharge (dd/ mm/yyyy) _____.

203. How long the patient stayed in hospital (day/s)? _____

204. What type of stroke was diagnosed? 1. Ischemic stroke 2. Hemorrhagic stroke

205. What was the condition of patient at discharge?

1. Death 2. Improved 3. Deteriorated
4. The same 5. Referred 6. Left against medical advice

206. How long was the time from symptom onset to admission (hour/s)? _____.

207. Did the patient have a previous history of stroke/transient ischemic attack? 1. Yes
2.No

III. CLINICAL PRESENTATION CHARACTERISTICS OF STROKE PATIENTS

Clinical presentation predictors fill 0= NO 1=YES		At admission	During hospital stay(recent to the outcome)
301. Did the patient have hemiplegia?			
302. Did the patient have aphasia?			
Put the actual number of measurement for the next variables			
303. Blood pressure(mmHg)	Systolic		
	Diastolic		
304. Heart rate of the patient (beat/minute)?			

305. Respiratory rate of the patient (breath/minute)?		
306. The temperature of the patient (degree Celsius)?		
307. Glasgow Coma Scale of the patient?		

IV. Risk factors /complications of a stroke in hospital mortality predictors

Comorbidity predictors ,Put 0 = No , 1 = Yes	At admission	During hospital stay near to discharge
401. Did the patient have hypertension?		
402. Did the patient have diabetes mellitus?		
403. Did the patient have Pneumonia?		
404. Did the patient have a seizure?		
405. Did the patient have Urinary incontinence?		
406. Did the patient have heart disease?		

V. Laboratory predictors

Laboratory predictors	Reference range	At admission	During hospital stay recent to discharge
501. Hemoglobin(mg/dl)			
502. Blood Urea Nitrogen(mg/dL)			
503. Cretinine(mg/dL)			
504. Random blood sugar(mg/dL)			

600. Treatments given to treat stroke_____