APPLICATION OF MULTISTATE MARKOV MODEL IN ANALYZING THE TRANSITION OF HYPERTENSION AT HAWASSA UNIVERSITY COMPREHENSIVE SPECIALIZED HOSPITAL, ETHIOPIA

MSc. THESIS

BY

TAYESEW SHEGAW MOLTOT

NOVEMBER 2023

HAWASSA, ETHIOPIA

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A THESIS SUBMITTED TO COLLEGE OF NATURAL AND COMPUTATIONAL SCIENCE DEPARTMENT OF STATISTICS HAWASSA UNIVERSITY IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE IN STATISTICS

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APPROVAL SHEET 1

This is to certify that the thesis entitled "APPLICATION OF MULTISTATE MARKOV MODEL IN ANALYZING THE TRANSITION OF HYPERTENSION AT HAWASSA UNIVERSITY COMPREHENSIVE SPECIALIZED HOSPITAL, ETHIOPIA" submitted in partial fulfillment of the requirement for the degree of master of science in statistics with specialization of applied statistics of the graduate program of department of statistics, Hawassa university, and is an original work carried out by Tayesew Shegaw Moltot Id.No.GpApStR/0006/14 under supervision and no part of the thesis has been submitted for any other degree or diploma.

Daily acknowledgements have been made of the assistance and support received throughout the course of this study. I therefore suggested that it be approved as meeting the thesis requirements.

Approved by:

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APPROVAL SHEET 2

As members of the Board of Examiners for the final open defense of Tayesew Shegaw Moltot, we, the undersigned, have read, evaluated, and examined the candidate's thesis, “APPLICATION OF MULTISTATE MARKOV MODEL IN ANALYZING THE TRANSITION OF HYPERTENSION AT HAWASSA UNIVERSITY COMPREHENSIVE SPECIALIZED HOSPITAL, ETHIOPIA”. To confirm that the thesis has been approved in partial fulfillment of the criteria for the degree of Master of Science in Statistics (Specialization: Applied Statistics).

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Name of Internal Examiner I	Signature	Date
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DECLARATION

This thesis has been submitted to the School of Mathematical and Statistical Science at Hawassa University in partial fulfillment of the requirements for Master of Science degree in Statistics (Specialization: Applied Statistics). The full citation of all sources utilized in this thesis has been done in an appropriate manner. I certify that I have not submitted this thesis to any other organiz ation or location for the award of any academic degree, diploma, or certificate.

Name of Student	Signature	Date
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LIST OF ACRONYMS

WHO: World health organization

mm Hg: Millimeter of mercury

AIC: Akaike's information criterion

NCD: Non-communicable disease

CVD: Cardiovascular disease

BMI: Body mass index

BP: Blood pressure

ESC: European society of cardiology

ESH: European society of hypertension

LMIC: Low and middle-income country

DBP: Diastolic blood pressure

SBP: Systolic blood pressure

CHD: Coronary heart disease

MSM: Multi-state model

SRS: Simple random sampling

HR: Hazard ratio

FHTN: Family history of hypertension

HD: History of diabetes

CI: Confidence interval

LRT: Likelihood ratio test

HIV/ AIDS: Human Immunodeficiency Virus/Acquired immunodeficiency Syndrome

HU-CSH: Hawassa University Comprehensive Specialized Hospital

ABSTRACT

Background*: Hypertension is the primary cause of cardiovascular death as well as other serious conditions like heart attacks, strokes, chronic heart failure, and kidney failure. In Ethiopia, cardiovascular disease is by far the most common NCD-related cause of death, and hypertension is one of the main risk factors. this study aimed to model hypertension progression and identify factors determining the transition rate between different stages of hypertension among hypertensive patients under follow up at HU-CSH recorded between September 2017 to August 2022 using multistate Markov model by the European Society of Cardiology and the European S ociety of Hypertension's guidelines for blood pressure.*

Method*: Data for this study was obtained from Hawassa university comprehensive specialized Hospital, with a total of 210 hypertensive patients who were under follow up from September 2017 to August 2022 were included in the study. A twenty-four-month transition probability between prehypertension progression stages or state 1 (systolic <140 mm Hg & diast olic <90 mm Hg), grade 1 hypertension or state 2 (systolic 140-159 mm Hg & diastolic 90-99 mm Hg), grade 2 hypertension or state 3 (systolic 160-179 mm Hg diastolic 100-109 mm Hg) and grade 3 or state 4 hypertension (systolic ≥180 mm Hg & diastolic ≥110 mm Hg) and factors determining the rate of progression among patients was estimated.*

Result and Discussion*: Among the total number of patients included in the study, 56.7% were female and 43.3% were male. Among the total number of patients included in the study, 56.7% were female and 43.3% were male. Among them, 22.9% of patients were in state 1 at initial checkup, 36.2 in state 2, 23.8% in state 3 and 17.1% in state 4 hypertension. The estimated 24 m onths transition probability for the hypertensive patients was 15.1 % (95% CI: 0.108, 0.210) from state 1 to state 2, 1.4% (95% CI: 0.009, 0.023) from state 1 hypertension to state 3, 0.2 %(95% CI:0.001, 0.003) from state 1 to state 4, 12.8% (95% CI:0.091, 0.177) from state 2 hypertension to state 3, 2.6% (95% CI:0.017, 0.041) from state 2 hypertension to state 4, 20.5% (95%CI:0.137, 0.290) from state 3 to state 4 and 83.3% (95%CI: 0.768, 0.881), 72.6% (95%CI: 0.660, 0.778), 45.1% (95%CI: 0.368, 0.529) and 67.8% (95%CI: 0.577, 0.777) were the estimate probability of remaining at state 1, state 2, state 3 and state 4 respectively. The mean time a pati ent takes to transition from state to state was estimated and state 1 hypertension had the longest estimated time followed by state 2, while state 3 had the shortest estimated sojourn time. By comparing a likelihood ratio test statistic, the full model fits significantly better than the null model. The observed and expected plots does not have much deviations and assumption of homogeneity of transition rate through the specified time are satisfied.*

Conclusion*: The conditional probability of hypertensive patients from good states to the next worst state are decreasing over time except the first state of hypertension. Being male, older aged, living in urban, taking medication and treatments in the past, history of diabetes (between all states) had high risk of transition from state2 and state 3, state 3and state 4. Being female, younger age, living in rural, and not taking medication in the past between state 1 and state 2 were high risk of hypertension. Having family history of hypertension between state 1 to state 2, state 2 to state 3 and who were not family history of hypertension in state 3 to state 4 had high risk of transition of hypertension.*

Keywords: hypertension, multi state model, transition probabilities, transition intensities, ESC/ ESH

CHAPTER ONE

1. INTRODUCTION

1.1 BACKGROUND OF THE STUDY

The main cause of cardiovascular death as well as other severe disorders such as heart attack, chronic heart failure, stroke, and kidney failure is hypertension. According to Yang et al. (2020), hypertension is a substantial global cause of premature death. Compared to other diseases, hypertension or high blood pressure causes the most fatalities. Each year, uncontrolled high blood pressure kills about 10 million individuals globally. This figure exceeds the total number of fatalities from infectious diseases (WHO, 2022). Those with high blood pressure don't have any symptoms; only a blood pressure check can provide the response. The blood pressure is expressed as two separate numbers. The first number (systolic) represents the blood vessel pressure created when the heart contracts or beats. The second number or diastolic indicates the pressure in the vessels when the heart rests between beats. According to the World Health Organization (2023), persons who are not taking antihypertensive medication are considered to have hypertension if their systolic blood pressure is 140 mm Hg or higher and/or their diastolic blood pressure is 90 mm Hg or higher.

Worldwide, among the 1.28 billion adults between the ages of 30 and 79 who are projected to have hypertension, two thirds reside in low- and middle-income nations. The prevalence of hypertension varies by nation and region. Although hypertension is most common in the Region of Africa, it is least common in the Region of the Americas. In 2015, there were 1.13 billion adults worldwide who had hypertension, up from 594 million in 1975, mostly in low and middle-income nations. These individuals' increased risk of hypertension is mostly the reason for the rise of hypertension in the region (WHO, 2023).

In Ethiopia, cardiovascular disease is by far the most common NCD related cause of death, and hypertension is one of the main risk factors. Some evidence suggests that the magnitude of NCDs increased in Ethiopia between 1990 and 2015. Several factors, including changes in nutrition, socioeconomic status, demography, and epidemiology, have contributed to this expanding tendency. Furthermore, the available data on the incidence of non-communicable diseases (NCDs)

in Ethiopia is inconsistent and fragmented, with some studies suggesting comparatively higher rates of NCDs, while others reported this to be very low (Tesfay et al., 2022). The prevalence of hypertension and diabetes at HU-CSH was found high compared to reported prevalence from four institutional based cross-sectional studies from Addis Ababa police officer, Debre Berhan hospital, Gonder university hospital and Jimma university hospital (Kassa & Woldesemayat, 2019).

In prior studies, a number of risk factors, including genetic, environmental, and social factors, were discovered. Numerous studies indicate that behavioral risk factors, such as smoking, drinking too much alcohol, and not getting enough exercise, are to blame for the increased risk of hypertension. Additionally, family history of diabetes and hypertension, gender, age, and body mass index (BMI) were believed to be prognostic factors for hypertension (Yang et al., 2021). Modifiable risk factors and non-modifiable risk factors are two categories into which the WHO separated risk factors. Inactivity, cigarette and alcohol use, excessive salt intake, diets high in saturated and trans fats, eating insufficient amounts of fruits and vegetables, and being overweight or obese are some of the risk factors that can be altered. Age over 65, a family history of hypertension, and co-existing conditions like diabetes or kidney disease are examples of non-modifiable risk factors (WHO, 2023).

When values are associated with a higher risk of cardiovascular diseases, the measurement of blood pressure is classified based on either internationally accepted or arbitrary thresholds to determine the degree of severity and the necessary treatment (Boateng et al., 2021). Recent developments in the therapy of arterial hypertension by the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) have resulted in the development of new guidelines. The recorded score of blood pressure categorized based on the new for the management of arterial hypertension by the ESC/ESH (Williams et al., 2018) recognize BP groups: Optimal BP <120/80 mm Hg, normal BP 120-129/80-84mm Hg, high normal 130-139/85-89 mm Hg, grade 1 hypertension 140-159/90-99 mm Hg, grade 2 hypertension 160-179/100-109 mm Hg, and grade3 hypertension ≥180/≥110 mm Hg. This guideline is more related to world health classification of blood pressure (Chalmers, 1999). To estimate the transition probability between the most severe types of hypertension using ESC/ESH guideline, the researcher merges optimal, normal and high normal BP and assign as prehypertension stage to create four categories instead of six and used

prehypertension BP (state 1), grade 1 hypertension (state 2), grade 2 hypertension (state 3) and grade 3 hypertension (state 4).

1.2 STATEMENT OF PROBLEMS

Previous research on LMICs tried to evaluate the relationship between the various hypertension stages and determinant variables using random effects multinomial logistic regression, Cox proportional hazard and frailty models (Erango et al., 2019), Ergoye M. and Sultan H. (2017). However, the Cox and logistic regression models do not estimate the duration of a disease state, the probability of progressing from one stage to other stages, or the probability of returning to a healthy state of hypertension or recovering from the worst stage to the better hypertension stages. The Multi-state Markov model in continuous time provides several insights into the prevalence of hypertension. To show the complexity of diseases involving numerous states, the use of multis tate models gives a fresh statistical way to analyze the progression between the various phases or states of hypertension severity (Boateng et al., 2021), (Y. Wang et al., 2018), (Yang et al., 2020). However, all these studies use three stages of hypertension (normal, elevated, hypertensive) as a general. This may lead to misclassification errors of stages. This means that the model considers the possibility that individuals may be incorrectly classified into a certain state, leading to inaccurate estimates of transition probabilities (Jackson, 2022). To our knowledge, in Ethiopia, there has been only one previous study conducted on hypertension data using a multistate Markov model in 2016 at Haramaya University. This finding includes only two factors (gender and family history of hypertension) and three stages of hypertension. Using other factors and four stages of hypertension in Ethiopia is not well studied yet. To study the effect of other factors on transition intensity and to minimize misclassification in stage classification the researcher used residence, age, medication, and history of diabetes as additional factors and four stages of hypertension stages.

Therefore, this study aimed to model hypertension progression and identify factors determining the transition rate between different stages of hypertension among hypertensive patients under follow up at HU-CSH recorded between September 2017 to August 2022 using multistate Markov model.

1.3 Research Questions

The study aims to provide answers to the important questions about the transition of hypertensio n, such as:

- What is the conditional probability of hypertensive patients being in different states of hy pertension at a given time?
- What is the transition intensity of hypertensive patients to be in different states of hyperte nsion at a given time?
- How long does it take a patient to transition from one state to another?
- What were the factors determining the transition rate of hypertension among patients und er follow- up?

1.4 Objective of the Study

1.4.1 General Objective of the Study

- The general objective of this study was to anayze the transition of hypertension progr ession stages among hypertensive patients under follow up at Hawassa University Co mprehensive Specialized Hospital using the multistate Markov model.

1.4.2 Specific Objective

- To estimate the transition probabilities between the hypertension stages.
- To estimate the transition intensities from one hypertension stage to another.
- To estimate the mean sojourn time in each hypertension state.
- Identify the factors on the rate of transition from one stage to another.

1.5 Significance of the Study

This study is important for several reasons. First, focusing on a specific aspect of hypertension that has not previously received much attention, would have implications for health managers by giving pertinent data for planning purposes in the future and intervention to address hypertension progression. Second, the findings in this result would provide statistical information for the people who have hypertension threats, and clinicians, and it would be an input for other hospitals in

Ethiopia. Additionally, it may improve the financial and medical decisions made to reduce death from hypertension in Ethiopia. Finally, it would also be helpful as baseline data for those who are interested in carrying out further research in this regard and drive future research efforts.

1.6 Scope of the Study

This study focused on the application of the multistate Markov model in analyzing the transition of hypertension among hypertensive patients at Hawassa University Comprehensive Specialized Hospital registered between September 2017 and August 2022 in Sidama region, Hawassa, Ethio pia.

1.7 Operational Definition of Terms

The operational definition of terms is defined by the keywords used in the context of this study and ESC/ESH guidelines for each stage of hypertension.

- Blood pressure is created by the force of blood pushing against the walls of blood vessels (arteries) as it is pumped by the heart (WHO).
- Hypertension is defined as a systolic blood pressure of 140 mm Hg or greater and/or a diastolic pressure of 90 mm Hg or greater (WHO,1999).
- Prehypertension: SBP<140 and DBP<90 mm Hg.
- Grade 1 hypertension: SBP 140-159 and DBP 90-99 mmHg.
- Grade 2 hypertension: SBP 160-179 mm Hg and DBP 100-109 mm Hg.
- Grade 3 hypertension: SBP ≥180 mm Hg and DBP≥ 110 mm Hg.
- States/stages: refers to the different possible health or disease states that a patient can transition between over time.

1.8 Organization of the Thesis

The thesis is structured as follows. Chapter 2 provides the related literature review on hypertension, the multistate Markov model and risk factors of hypertension in Ethiopia as well as worldwide. Chapter 3 gives the methodology and data analysis methods. Chapters 4 and 5 highlight the results in line with the objective and discussions of the results including conclusion and recommendations are presented.

CHAPTER TWO

2. LITERATURE REVIEW

2.1. GENERAL OVERVIEW OF HYPERTENSION

A person is said to have hypertension if their systolic and diastolic blood pressure are both chronically elevated and greater than 90 mmHg and 140 mmHg, respectively. Numerous hypertension guidelines and blood pressure classifications characterize hypertension. Since the Joint National Committee advocated over 140/90 mmHg definition of hypertension in its guidelines in 1988, it has appeared to be an unquestionable dogma. Diastolic blood pressure (DBP) is the lowest level of blood pressure experienced during heart muscle relaxation between heartbeats, while systolic blood pressure (SBP) is the highest level experienced during a heart muscle contraction between heartbeats. Surprisingly, the American Heart Association, American College of Cardiology, and American Society of Hypertension produced a new hypertension guideline in 2017 that proposed defining hypertension as being higher than 130/80 mmHg.

According to international survey research on hypertension (Forouzanfar et al., 2017), 874 millio n adults out of the world's 3.5 billion adults had SBP readings of 140 mmHg or higher. The most frequent CVD risk factor is hypertension; thus, it needs to be addressed. Before starting medication, patients should be assessed utilizing their medical history, physical examination, and targeted testing (ETHNCD, 2016). According to the World Health Organization, one of the key CVD risk factors that can be modified is hypertension. Reduce the prevalence of hypertension by 33% between 2010 and 2030, one of the global goals for noncommunicable diseases (WHO, 2023).

2.2 REVIEW ON RISK FACTORS OF HYPERTENSION

A review of the literature on the causes of hypertension is included in this section based on research done on hypertension and other linked diseases in several nations, including Ethiopia. Hypertension is now more common, particularly in LMICs (poor and medium-income countries). Adults were more likely to have hypertension in LMICs than in high-income nations. Differences in the levels of hypertension risk factors, such as high salt and low potassium intake, obesity, alcohol consumption, physical inactivity, and unfavorable diet, may account for some of

the geographical heterogeneity in the incidence of hypertension. The risk factors of hypertension studied by many researchers are gender, place of residence, family history, BMI, alcohol consumption, Smoking, Level of education, Age, history of diabetes, taking antihypertensive medication, Marital status and any other factors (Boateng et al., 2021, Yang et al., 2020, Awol,2016 and others). Many researchers examined different outcomes in the world and our country Ethiopia on the risk of hypertension and blood pressure.

According to the study (Awol, 2016), of the total study of a cohort of 353 hypertensive patients obtained from Jimma University referral Hospital, the risk factors of hypertension he described in the paper were gender and hypertension history in their family. The patients were 172 girls and 181 men, with 152 having a family history of hypertension and 201 were not. According to the findings, female patients are 1.314 times more likely than male patients to transition from a healthy state (state 1) to an illness state (state 2) during their lifetime. Additionally, female patients are 2.437 and 1.199 times more likely than male patients to transition from an illness state (state 2) to a healthy state (state 1) and an absorbing state (state 3), respectively. Using the three stages of hypertension, females were more likely than males to transit from state 1 to state 3 hypertension, from state 2 to state 3, and to stay in state 3 (Boateng et al., 2021). But in all other state transitions, the probability of males was higher than females. In contrast to male participants, female participants have higher probabilities of moving from the elevated state to the hypertensive state, from normal to elevated and remaining at normal and hypertensive states. Zheng et al. (2022) found that female participants have lower probabilities of transitioning from the normal state to the hypertensive state and from elevated to normal state. The likelihood of female participants staying in the normal condition and returning to it over time is higher. In participants with similar blood pressure levels, men are more likely than women to go from the no hypertensive state to the hypertension state(Yang et al., 2020).

To investigate the impact of a family history of hypertension, individuals without such a history were 0.804 times more likely than those who did transition from state 1 to state 2. Contrarily, individuals who did not have a family history of hypertension were 0.899 and 1.115 times more likely to transition from state 2 to states 1 and 3, respectively, than those who did Awol (2016). A study by (Asresahegn et al., 2017) studied “Prevalence and associated factors of hypertension among adults in Ethiopia: a community-based cross-sectional study”, (Zelelew, 2020) studies on

“joint modeling of multivariate longitudinal blood pressure and blood glucose level with time to vascular complication of hypertensive diabetic patients”: a case study at Finoteselam general hospital: Amhara region Ethiopia and Erango et al(2019) on the title “Survival Time Analysis of Hypertension Patients Using Parametric Models” had demonstrated that a for the entire sample of study participants, having a family history of hypertension was strongly related with having hypertension. This could be explained by the fact that one-third to half of the risk of hypertension is caused by genetic factors. Numerous genes that can make someone more likely to have high blood pressure, heart disease, or stroke tend to be shared among blood relatives. Furthermore, this association may have been influenced by people's propensity to adopt their families' risky lifestyles. Research conducted by (Erango et al., 2019) on Survival Time Analysis of Hypertension Patients Using Parametric Models, concludes that the patient's initial age, family history of hypertension, intake of tobacco, blood cholesterol level, stage of hypertension disease, their adherence to therapy, and diseases that were related to their hypertension were all strongly linked to how long they lived.

Age is also another covariate affecting hypertension. Accordingly, age was a risk factor for developing prehypertension and hypertension. Between the three age cohorts examined (below 41 years,41–60 and 60 years), the transition probability from normal/elevated BP to stage 1 hypertension and from stage 1 to stage 2 hypertension was higher for those aged 41–60 years and those above 60 years, respectively. However, the probability of remaining at stage 2 hypertension was consistently higher for all age groups but highest among those above 60 years. The transitions from the no hypertensive state to the hypertension state are positively connected with the age of the participants. The hazard ratio rises with age, from normal to elevated state or from normal to hypertensive state by categorizing age as (18-24, 25-34, 35-44, 45-54). Increasing age was a risk factor for developing hypertension from the normal state or elevated state (Boateng et al., 2021), (Y. Wang et al., 2018), (Yang et al., 2020), (Zheng et al., 2022).

According to the study by (Boateng et al., 2021) in Ghana on “measuring hypertension progression with transition probabilities: estimates from the WHO sage longitudinal studies”, residents in rural areas had a higher likelihood of transitioning from normal/elevated BP to stage 1 hypertension than did urban areas. A higher likelihood of moving from stage 1 to stage 2 hypertension is connected with living in an urban area compared to a rural one. It is highly statistically significant

that respondents' place of residence is associated with both diabetes and hypertension. Compared to rural populations, urban residents have a higher prevalence of diabetes and hypertension. Urban respondents are more likely than those from rural locations to have diabetes and high blood pressure (Meitei & Ladusingh, 2019). A research study in Hawassa by(Getenet et al., 2019) on "Determinants of adherence to anti-hypertensive medications among adult hypertensive patients on follow-up in Hawassa Referral Hospital: A case-control study", patients with hypertension in urban regions were six times more likely to take their prescriptions consistently than those in rural areas.

World Health Organization Categories Diabetes, whether insulin-dependent or non-insulin-dependent, raises the risk of kidney disease, coronary heart disease (CHD), and ischemic stroke. Generally speaking, diabetes roughly triples the relative odds of dying from CHD and stroke. Additionally, among those without diabetes, it has been found that blood insulin and blood glucose levels are consistently and directly correlated with CHD risks. Compared to matched non diabetic, patients with diabetes mellitus have a 1.5 to 2 times higher prevalence of hypertension (Chalmers, 1999). Having high blood pressure is a typical symptom of both type 1 and type 2 diabetes. A primary goal for diabetic patients should be to drop their blood pressure to less than 140/80 mmHg while aiming for an SBP of 130 mmHg. Because of the advantages in preventing strokes, treated SBP levels of 130 mmHg should be taken into consideration, provided the treatment is well tolerated(Williams et al., 2018).

According to WHO (2023), one or more medications may be suggested by health professionals if a patient has high blood pressure. For most people, a blood pressure of less than 140/90 is the ideal level. There are several common blood pressure drugs. The World Health Organization advised not skipping or sharing medications, as well as managing other medical issues, as one of many lifestyle changes to lower blood pressure. By (2007/8), out of 1884 responders, 90% gave no comment, 2.1% responded no, and 7.9% said yes. But at the end of the study period 2014/15, 99% of the 1,884 respondents who were asked about medications or other treatments in the previous 12 months had no reaction, 0.4% had a negative response, and 5% had a positive response (Boateng et al., 2021). According to a study published in 2023 with the title "How Blood Pressure Predicts Frailty Transitions in Older Adults: A Multi-State Transition Model", in 2004, 2009, and 2014, a population-based cohort of older adults randomly selected from a population registry in

Switzerland had mean blood pressure readings of 137 (19)/79 (11) mmHg, and 37% of participants said they were taking antihypertensive medication.

2.3. Review of Markov and Multistate Model in Progression of Hypertension

Compared to cross-sectional data, which can only assess the prevalence of a disease at one particular moment in time, longitudinal data provide for a better estimation of the progression of the disease state (Boateng et al., 2021). The state transition dynamics of states in disease progression, such as HIV/AIDS and kidney failure progression, are analyzed using a multi-state Markov model. These models offer a useful resource for researching observations of a continuous-time process at any point. The use of transition probabilities in assessing the transition between stages of hypertension severity offers a more dependable approach than earlier models that aimed to forecast the possibility of being in either condition at a certain time point.

Awol (2016) used multi state transition models to examine state transition in Ethiopia using data on hypertension. In the studies by Solomon et al. (2018), Lintu et al. (2022), Zheng et al. (2022), and Ramezankhani et al. (2020), multistate modelling was applied to study the progression of HIV/AIDS disease. “A multistate Markov model for blood pressure transition in the elderly Chinese population: a quantitative longitudinal study”; “A multistate analysis of hypertension and mortality: Application of semi-Markov model in a longitudinal cohort study”; and “a multistate Markov model for the progression of kidney disease”. The multi-state survival model is widely applied in numerous fields. For exact time data, Anderson and Keiding (2002) Talk about several multi-state models that address event history analysis. Regarding the computing of multi-state Markov models using panel data, Jackson (2011) introduces the R package msm, which covers the fitting of hidden Markov models and a variety of multi-state models. Extensions and limitations of msm are also well discussed. For multi-state systems where states are not observed or are subject to incorrect state classification, hidden Markov models are employed.

Several studies try to express the average length of time an individual spends in a particular state of hypertension before transitioning to another state or exiting the model due to death. The mean sojourn time is an important parameter in understanding the natural history of hypertension. According to Awol (2016), sojourn times are predicted to be 0.94 and 1.49 months in healthy and illness states respectively. Each patient also experienced a total of 5.49 months of illness and 3.48

months of health. By using three states of hypertension (normotension, prehypertension, hypertension) on “prediction of transfer among multiple states of blood pressure based on Markov model: an 18-year cohort study” using Data from the China Health and Nutrition Survey from 1991 to 2009, in the study cohort, the duration of normotension and prehypertension states was 7.481and 6.929 years, respectively. In another study in Ghana by Boateng et al., 2021, from normal/high blood pressure to stage 1 hypertension, the average amount of time was 7.75 years, it takes 1.7 years to go from stage 1 to stage 2 hypertension, or to return to normal or high blood pressure, and 5.4 years from stage 2 hypertension to stage 1 hypertension. For multi-state systems where states may be misclassified or where states are not seen, hidden Markov models are employed.

CHAPTER THREE

3. DATA AND METHODOLOGY

3.1 STUDY AREA

The study was conducted at Hawassa University Comprehensive Specialized Hospital (HU-CSH) which is a public university hospital at the tertiary level. More than 15 million residents of the area choose it as their final referral location. The HU-CSH is located 275 kilometers south of Addis Ababa in the Sidama region of the Hawassa City Administration. Internal Medicine OPD, Surgical OPD, Pediatrics OPD, Obstetrics and Gynecology OPD, Special Clinics, and Eme rgency OPD are the six outpatient departments (OPD) that the Hospital has (Kassa & Woldesem ayat, 2019). We conducted this study mainly in departments at internal medicine OPD, specifical ly patients identified as hypertensive cases.

3.2 STUDY DESIGN

A retrospective cohort study design on patients who were under follow-up at Hawassa University comprehensive specialized Hospital between September 2017 and August 2022 were employed.

3.3 DESCRIPTION OF THE DATA

The data used for this study was based on secondary data obtained from Hawassa University comprehensive specialized Hospital. The data was taken from which the high blood pressure of subsequent patients has been recorded longitudinally. For the follow-up checkups, initially, individuals whose SBP reading was higher than 140 mmHg or DBP reading and greater than 90 mmHg were considered to have hypertension. The total population of hypertensive patients between the study period in hospital may exceed the number used in this study. For this study 210 hypertensive patients between the study period were used.

3.3.1 INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria

The study included all participants who had a minimum of two checkups (one initial checkup and a minimum of one follow-up) between 2017 and 2022 regardless of age, and a maximum of 24

months of follow-ups. The investigation included patients who had recorded variables on a history file card.

Exclusion Criteria

Patients whose basic information on sex, residence and age are missing, missing values (patients who had no initial checkup and one follow-up). Among the population of hypertensive patients identified for the study, most of hypertensive patients had follow ups less than two years, while some had more than two years follow up. To reduce this discrepancy of the data included in the study, recorded history for patients who had been treated above 24 months were discarded.

3.4 Sampling Design and Sampling Techniques

3.4.1 Sampling Design

In this study, the documented lists of those who started follow-ups at Hawassa University comprehensive specialized Hospital and who have a unique identification number were considered the sampling frame. Therefore, a simple random sampling procedure is applied.

3.4.2 Sample Size Determination

We always go through several phases when conducting research that requires selecting a sample size. Making decisions is beneficial, but selecting an excessively large sample suggests wasting money, and selecting too small of a sample reduces the value of the outcome. This study employed the appropriate sample size determination that satisfied the research objectives. The sample size determination formula (Cochran, 1977) for this research:

$$n_0 = (Z_{\frac{\alpha}{2}})^2(\frac{pq}{d^2}) \quad \text{.....3}$$

If then, $n_0 \div N \leq 5\%$ then $n_0 = n$,unless calculate "n" using the formula,

$$n = \frac{(Z_{\frac{\alpha}{2}})^2(\frac{pq}{d^2})}{1+\frac{1}{N}\left[(Z_{\frac{\alpha}{2}})^2(\frac{pq}{d^2})-1\right]} = \frac{n_0}{1+\frac{1}{N}(n_0-1)} \quad \text{.....3.1}$$

where,

- N=465 total number of hypertension patients at Hawassa university comprehensive specialized Hospital between study periods.
- $z\alpha_{/2}$ is the upper 2 appoints of standard normal distribution with α=0.05 significance level, which is $z\alpha_{/2}$ =1.96.
- "d" is the degree of precision (margin of error) that is mostly selected by the investigators
- The term p represents the proportion of prevalence of hypertension. It was obtained from the earlier equivalent study done by (Kassa & Woldesemayat, 2019) on data taken from Hawassa university comprehensive specialized Hospital, which is p=0.5.

$$n_0 = \frac{(1.96)^2(0.5)^2}{(0.05)^2} = 384.16$$

Now,$\frac{n_0}{N} = 0.83$ which is much greater than 5%, and then we have to apply the above formula (3.1). That is

$$\mathrm{n} = \frac{\mathrm{n_0}}{1 + \frac{(\mathrm{n_0} - 1)}{\mathrm{N}}} \cong 210$$

The prevalence of hypertension in this study refers to the number of patients whose average value of either systolic blood pressure 140 or above mmHg or diastolic blood pressure measured 90 mmHg or above among patients in internal medicine OPD. Out of the total 465 case records screened in the study periods, 210 patients were sampled for this study.

3.5 VARIABLE IN THE STUDY

3.5.1 DEPENDENT VARIABLE

The response variable of this study was the change in SBP and DBP in mmHg of the hypertensive patients' in the follow-up period since enrolled in the hospital (State 1: BP<140/90 mmHg, state 2: BP 140-159/90-99 mmHg, state 3: BP 160-179/100-109 mmHg, state 4: BP≥180/110 mmHg).

3.5.2. PREDICTOR VARIABLES

The explanatory variables that may have influence on the change in SBP and DBP in mmHg among patients are listed in the following Table 1. These variables were taken from the patient's history card registered at the Hospital.

Table 1: Summary of predictor variables with its respective codes

Variables	**Variable description**	**Categories**
Age	Age of patient at enrolment in years	0= <30 years, 1 = 30– 64 years, 2 = above 64 years
Sex	Sex of patient	0=female, 1=male
Residence	Residence place of the patients	0=rural, 1=urban
FHTN	The presence of Family history of hypertension	0=no, 1=yes
HD	History of diabetes	0=no, 1=yes
Medication	Medication or taking treatments in the past	0=no, 1= yes

3.6 STATISTICAL ANALYSIS

During the statistical evaluation, cross tabulated values were reported for descriptive analysis to analyze the percentage of each category and the multistate Markov model was built using the 'msm' library (version 1.7) under R software (version 4.2.3). Hazard ratios (HRs), 95% confiden ce intervals (CIs), transition probability, transition intensity and mean sojourn time were calculat ed.

3.6.1 MULTISTATE MARKOV MODELING

Multi-state model is a stochastic process model ($X(t)$, $t\epsilon T$) with a finite space, S = $\{s_1, s_2, s_3, s_4\}$. The process begins in one of these states and progresses systematically through each state. A step is a unit of movement. It doesn't matter which states the chain was in before to the present state if the process is currently in state s_i because it will move to state s_j at the following step with a probability denoted by p_{ij}.Transition probabilities are the probability p_{ij} which refers to the

probability of transitioning from state i to state j in a Markov chain. The process can remain in its current state, and this occurs with probability p_{ii}(KASHIHALWA, 2019).

There are ten possible transitions of blood pressure states of interest as shown below: Fig. 1 shows: state 1 → state1, state 1 → state 2, state 2 → state 1, state 2 → state 2, state 2 → state 3, state 3 → state 2, state 3 → state 4, state 3 → state 3, state 4 → state 3 and state 4 → state 4. A state transition can happen into its own state, into the previous state, or into the immediate next state. Transitions in both directions are permitted. An individual in a transient state has the option of remaining in it or moving on to the next state, but only after passing through the one that is right next to it. This is known as a two-step movement in which only one state at a time is possible for the respondent.

This study focused on a four-hypertension-states model with states labeled as state1 (prehypertension), state2 (grade 1 hypertension), state 3 (grade 2 hypertension) and state 4(grade 3 hypertension) having the state space S(t)= {1,2,3,4}. Thus, a person with prehypertensive state at time t = 0, may pass through the grade 1 hypertension state before ending in the grade 2 or grade 3 hypertension at time t = 24 months etc. The diagram below shows four hypertension stages with its possible transitions among these four states.

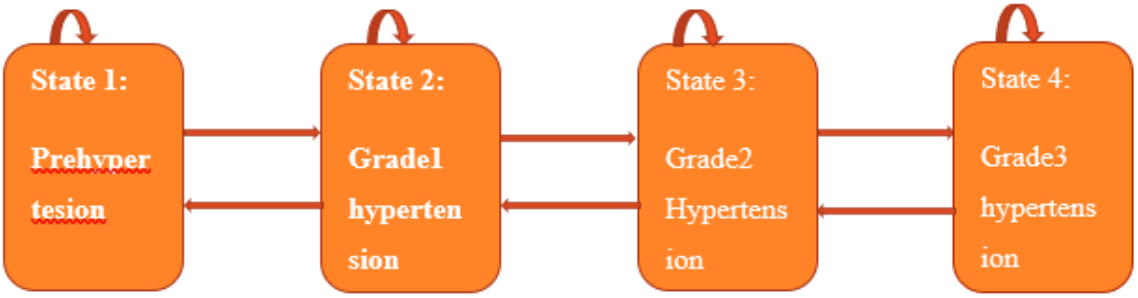

Figure 1 : Multi-state Markov chain model using ESH/ESC 2018 guideline

3.6.1.1 Assumption of Multistate Markov Model

The following are the assumptions that support the suggested multi-state Markov model:

- The future state depends on the current state and not on previous states;
- The transition intensities remain constant over time.

3.6.2 STOCHASTIC PROCESS

One might think of the progression of high blood pressure into hypertension as a Markovian stochastic process. A stochastic process is a collection of random variables X (t) that varies over time in an unpredictable way. A stochastic process model (that is, stochastic model) consists of five components: time t, number of observations n, state S, transition, and stochastic process. A state space S contains all of the potential random variables X (t) of the given stochastic process. where,

$$S = \{s_1, s_2, s_3, s_4\}. \quad \text{.....3.6.1}$$

If S is discrete, then the process is called a discrete-state stochastic process. Similarly, if S is continuous, then the process is called a continuous-state stochastic process. The stochastic process's collection of parameters, designated by the letter T, is usually a set of times. A discrete-time stochastic process is what is used when T is a countable set. The process is known as a continuous-time stochastic process if T is an interval of real values. If the Markov process is a continuous-time Markov process, then the transitions can occur at any point in time, with transition rates, whereas if the Markov process is a discrete-time Markov process, then the transitions occur at fixed points in time (Ibe, 2013). First-order Markov processes, or X (t), are stochastic processes in which knowledge about the process's future is only provided from its current state and not influenced by knowledge of its prior states. This means that the future state is independent of the past given the present state of the process (Ibe, 2013).

3.6.3 TRANSITION PROBABILITY

The transition probabilities are described by the multistate mode. The transition probability matrix (functions of time) is the 4x 4 matrix whose entry in row i and column j is the transition probability P (t) and is denoted by:

$$p_{ij}(\mathrm{t}) = \begin{bmatrix} p_{11} & \cdots & p_{14} \\ \vdots & \ddots & \vdots \\ p_{41} & \cdots & p_{44} \end{bmatrix} \text{.....3.6.2}$$

p_{ij} (t) denotes the transition probability that an individual in state i that will transit to state j at time t. p_{11} represents the probability of an individual staying in the prehypertension state at time t; p_{12}

represents the probability of patient progressing from prehypertension to grade 1 hypertension stage at time t, p_{13} represents the probability of hypertensive patient progressing from stage 1 to stage 3 hypertension, p_{14} represents the probability of a patient progressing from prehypertension state to the grade 3 hypertensive state. Similar definitions can be given for all other elements in the matrix. The probability of transitioning from state to state of hypertension is set to zero, given the hypertension state is the absorbing state. But in this study absorbing states were not considered. In the transition matrix P (t), rows represent now, or from X_t and the columns represent next, or to X_{t+1} and entry (i, j) is the conditional probability that next= j, given that now = i: the likelihood of moving from state i to state j.

$$p_{ij} = P\ (X_{t+1} = j | X_t = i) \quad \text{.....3.6.3}$$

The columns of P (t) do not in general sum to 1. Individuals' transition/movement probabilities through states are the entries in the probability transition matrix. The matrix P is time dependent and denoted by P (t). Each row in a transition probability matrix must sum to one and the probabilities in each must be larger than or equal to zero.

$$\sum_{j=1}^{4} p_{ij} = \sum_{j=1}^{4} \mathrm{P}(X_{t+1} = \mathrm{j} \mid X_t = \mathrm{i})$$

$$= \sum_{j=1}^{4} \mathrm{P}\{X_t\}(X_{t+1} = \mathrm{j}) = 1 \quad \text{.....3.6.4}$$

$$p_{ij} \geq 0 \ for\ all\ i, j \in \{1,2,3,4\} \quad \text{.....3.6.5}$$

3.6.4 TRANSITION INTENSITY

The intensity matrix represents the instantaneous risk of moving from state i to state j (Awol, 2016). The intensity between two states i and j, is the rate of change of the probability p_{ij} in a very small-time interval δt. This intensity may be influenced by the process's time t or more generally, by a group of unique, distinct explanatory variables z. The transition intensity matrix's elements in each row add up to zero, the off diagonal elements are non-negative, and the diagonal elements are negative for all values of i equal to j. This suggests that the patients in those states stay there while the off-diagonals represent the rates of patient's migration to other states of hypertension (KASHIHALWA, 2019), (Mafu, 2014a).

The state-to-state transitions are interval censored since it is presumed that they occurred prior to the subsequent evaluation because the precise timing of the change is not seen, but rather progresses continuously across time (Boateng et al., 2021). Therefore, the usual multistate model could not be applied since the precise transition time was unclear and the follow-up times for individual observation assessment were irregular. Instead, we used the time-homogeneous continuous-time Markov model, which is capable of accounting for these kinds of abnormalities, to compute transition probabilities and intensities. In the model, the patient is in state S(t) at time t. Transition intensities (i.e., the rate at which a person has the likelihood of moving from one state (i) to another one (j) at a given time (t)) determine movement into the next state (KASHIHALWA, 2019), (Boateng et al., 2021), (Yang et al., 2020).

Typically, an individual begins existence in one of the four states and, after staying in their current state for a certain amount of time, changes to a new state. The transition intensity matrix determines the next state into which an individual will transit and how long they will remain in the present state. Let x(t) = i represents the state of i at time t, and the transition intensity for the individual moving to state j during the interval (t, t + δt) is calculated as (Yang et al., 2020):

$$q_{ij}(t) = \lim_{\delta t \to 0} \frac{p(x(t+\delta t) = j | x(t) = i)}{\delta t} \qquad \text{(for i , j 1,2,3,4)} \ldots\ldots 3.6.6$$

Where, $q_{ij}(t)$is the instantaneous rate (risk) of moving from state i to state j at time t.

The transition intensity matrix is denoted as Q, given as:

$$Q = \begin{bmatrix} q_{11} & \cdots & q_{14} \\ \vdots & \ddots & \vdots \\ q_{41} & \cdots & q_{44} \end{bmatrix} \ldots\ldots 3.6.7$$

The rates at which individuals stay in their current condition and do not transition are represented by the diagonals of the matrix, while the rates at which individuals change into new states are represented by the off diagonals. That is, q_{11} represents the instantaneous rate of remaining in the prehypertension (state 1), q_{14} represents the instantaneous rate of transition from the prehypertension state to the grade 3 hypertension state (state 1 to state 4), similar definitions can be given for all other elements in Q which satisfy the following properties.

$$\sum_{j=1}^{4} q_{ij} = 0 \qquad \text{for all i} \ldots\ldots 3.6.8$$

$$q_{ii} = -\sum_{i \neq j} q_{ij} \quad for\ all\ i$$ ……..3.6.9

3.7 KOLMOGOROV EQUATIONS

How the transition intensity matrix Q and the transition probability matrix P are correlated is derived using the Kolmogorov equations. By resolving the Kolmogorov differential equation using the intensities as input, the transition probabilities may be computed. The Kolmogorov equations state that (Mafu, 2014a):

$$\frac{\partial}{\partial t} p(t) = p(t)Q, \quad \text{……...3.7}$$

With P (0) =I

3.8 DISTRIBUTION OF MEAN TIME LENGTH

The sojourn time measures how long a patient remains in a specific state at time t. Assume that there is a random distribution for the waiting time in a particular state. Sojourn time T_i in a time-homogeneous continuous Markov model has an exponential distribution with a rate of $-q_{ii}$(Yang et al., 2020). The term "mean sojourn times" refers to the typical length of a single stay in a state for processes that experience recovery and relapse cycles repeatedly. However, for a given set of covariate values, total duration of stay predicted the total amount of time spent in each transient condition between two future time points t_1 and t_2. This defaults to the expected duration of each state from the process's beginning (time 0, the present time) until the user's death or a specified future time. In this finding only, the average time of stay (Mean sojourn times) were discussed.

3.8.1 EXPONENTIAL DISTRIBUTION OF MEAN TIME LENGTH

As described above, sojourn times of a continuous-time Markov process in a state j are independent and exponential random variables with mean $-\frac{1}{q_{ii}}$ (Mafu, 2014). The hazard function is constant (corresponding to the Markov case) in exponential distribution. In contrast, in the case of a discrete Markov process, the sojourn times for a continuous-time Markov process in a state j are independent and geometrically distributed. The new state and the sojourn time only depend on state i; they are not dependent on the system's past before time t. The sojourn time and the new state are independent of one another as the current state is i. The time the patient spends in state i

before moving to state j (sojourn time) is (Mafu, 2014b) :

$$-\frac{1}{q_{ii}} \quad \text{.....3.8}$$

3.9 METHODS OF ESTIMATION

3.9.1 MAXIMUM LIKELIHOOD ESTIMATION

The model's unknown parameters can be calculated using the maximum likelihood estimation method. The number of transitions from state i to state j divided by the total number of transition s from state i to other states, as determined by the transition probability matrix, yields the maxim um likelihood estimate. The optimization method “bobyqa” from the minqa package from R was used for a fast derivative-free method (Jackson, 2022).

3.10 THE EFFECT OF COVARIATES ON THE TRANSITION RATE

Generalized regressions can be used to include explanatory variables at each level of the model and add covariates. When covariates are included in a model, the focus shifts from only the movement of subjects through various stages to the influence that these variables have on that movement (Mafu, 2014a). It is believed that transition intensity-related variables have a multiplicative effect. A unique collection of covariate effects may be present for each transition intensity. Through the transition intensities, these effects are incorporated into the model as covariates. The covariate effects on transition intensities were considered using the proportional hazards regression model. It used to describe how explanatory variables (covariate vector z) affect an individual's transition intensity at observation j.

$$q_{ij}(z_{ij}) = q_{ij}(0)\exp(\beta_{ij}{}^{T} Z_{ij}) \quad \text{.....3.10}$$

Where, $q_{ij}(0)$ represents the baseline intensity for a transition from state i to state j; $\exp(\beta_{ij}{}^{T} Z_{ij})$ refers to the hazard ratio for i^{th} individual’s j^{th} observation; β_{ij} is the vector of coefficients and z_{ij} represents the vector of covariates for i^{th} individual’s j^{th} observation.

3.11 MULTI-STATE MODEL ASSESSMENT

The assumptions underlying the Markov models need to be examined or verified. It is challenging to evaluate the Markov assumption. However, the assumption of homogeneity of transition rates over time and between subjects can be evaluated (Mafu, 2014). The assumption of constant transition rates was verified through visual checking (Anker et al., 2022), (Jackson, 2022), comparing observed against predicted number of individuals in each state over time. We would continue to use the time-homogeneous model, which has constant transition rates during the observation period, in cases where the assumption held, i.e., the proportions of observed and predicted states remained similar over time. Instead of comparing observed data with fitted or expected data under the model, it is sometimes difficult to tell how well a fitted multistate model describes an irregularly observed process using LRT. The fit of the expected numbers in each state or prevalence can be directly evaluated at those times if all persons were seen at those times. Assume that a person's state at time t was the same as it was at the time of their last observation. If the observation times are close together, then this might be fairly accurate (Jackson, 2022).

CHAPTER FOUR

4. RESULTS AND DISCUSSION

4.1 DESCRIPTIVE STATISTICS

A total of 210 hypertensive patients who were under follow up from September 2017 to June 2022 at Hawassa University Comprehensive Specialized Hospital were included in the study. Of these 56.7% were females and 43.3% were males. At the initial checkup there were 22.9% of patients in state 1 hypertension, 36.2% patients were in state 2 hypertension, 23.8% patients were in state 3 hypertension and 17.1% of patients were in state 4 hypertension. This shows that the majority of the patients were in the state 2 hypertensions during the first checkup.

As shown in age categories, 11.4% of patients were under 30, 72.9% were between 30-64 years old and the rest 15.7% were 64 years old and above. At initial checkup, 66.2% of patients were urban residents and 33.8% were from rural area, 31.4% had family history of hypertension, 53.8% of patients were taking medication or treatment in the past and 31.9% patients had family history of diabetes during the first checkups reports as registered in patient's history card.

Table 2: Descriptive statistics of variables used in assessing transitions in hypertension severity at initial checkups (t=0).

Variables	**Category**	**Number**	**Percent (%)**
States	State 1	48	22.9
	State 2	76	36.2
	State 3	50	23.8
	State 4	36	17.1
Age	<30	24	11.4
	30-64	153	72.9
	>64	33	15.7
Sex	Female	119	56.7
	Male	91	43.3
Residence	Urban	139	66.2
	Rural	71	33.8
Family history of hypertension	Yes	66	31.4
	No	144	68.6
Medication or taking treatments in the past	Yes	113	53.8
	No	97	46.2

History of diabetes	Yes	67	31.9
	No	143	68.1

4.2 TRANSITION FREQUENCY OF HYPERTENSION DISEASE

This study considered that blood pressure progression transits from one hypertension stage to other stages. Patient who started treatment under any stage has a likelihood to reach any other stage. If there is a decrease in mmHg, the patient has a recovery from the initial state and can transit to a better state, but if there is an increase in mmHg, the patient in crisis can transit to a worse state. The transition of hypertension in different states occurs at any time. A frequency table of successive state pairs is a helpful approach to summarize multi-state data. The Frequency table counts the number of times each patient had an observation of state i and then an observation of state j for each state i and j.

Table 3 shows the frequency of transition between the four hypertension stages from the beginning to the end according to the 24 months follow up. Transitions occurred between all four stages observed in this Table. Thus, there were 33 transitions from state 1 to state 2, 9 transited from state 1 to state 3, 8 transitioned from state 1 to state 4, 12 transitioned from state 2 to state 4, and 22 from state 3 to state 4. Similarly, 51 patients transited from state 2 to state 1, 34 patients transited from state 2 to state 3, 6 patients transited from state 3 to state 1,41 from state 3 to state 2 from a total patient sample for the current study 2, 14, 25 transitioned from state 4 to state 1, state 2 and state 3 respectively, while 119, 156, 71 and 87 patients remained at state 1, state2, state 3 and state 4 respectively.

Table 3 : Total number of transition frequency between hypertension states

From -to	State 1	State 2	State 3	State 4
State 1	119	33	9	8
State 2	51	156	34	12
State 3	6	41	71	22
State 4	2	14	25	87

4.3 TRANSITION INTENSITY

Table 4 shows the estimated transition intensity matrix of the maximum likelihood estimates (95% CI) over a 24 months period between the states of hypertension. The analysis results show a likely transition from state 1 to state 2 was 0.1978 and a recovery from state 2 to state 1 was 0.1567. The 95% confidence intervals for this transition were (0.134, 0.292) and (0.107, 0.230). The likelihood transition from state 2 to state 3 was 0.2374 and recovery from state 3 to state 2 was 0.5828. The 95% confidence intervals for this transition were (0.154, 0.366) and (0.393, 0.864). The likelihood transition from state 3 to state 4 was 0.3957 and the likelihood of transition from state 4 to state 3 was 0.4652. The 95% confidence interval for these transitions were (0.245, 0.640) and (0.291, 0.743).

The baseline intensity rate of remaining in state 1, state 2, state 3 and state 4 were- 0.1978, -0.3940, -0.9785 and -0.4652 respectively. Once in state 2, crisis (state 3) was more likely than recovery (state 1) and once in state 3, recovery (state 2) was more likely than crisis (state 4). According to the evaluated intensity, there was small rate of transition between the best and worst state between state 2, state 3 and state 4, but high from state 1 to state 2 compared to transition from worst to good state.

Table 4: Transition intensity matrixes for a multistate Markov model of the transition between state 1, state 2, state 3 and state 4 of hypertension at Hawassa university Comprehensive Specialized Hospital.

Transition states	**Baseline intensity**	**95% confidence interval**
state 1 - state 1	-0.1978	(-0.292, -0.134)
state 1 - state 2	0.1978	(0.134, 0.292)
state 2 - state 1	0.1567	(0.107, 0.230)
state 2 - state 2	-0.3940	(-0.532, -0.292)
state 2 - state 3	0.2374	(0.154, 0.366)
state 3 - state 2	0.5828	(0.393, 0.864)
state 3 - state 3	-0.9785	(-1.297, -0.738)
state 3 - state 4	0.3957	(0.244, 0.640)
state 4 - state 3	0.4652	(0.291, 0.743)
state 4 - state 4	-0.4652	(-0.743, -0.291)

4.4 TRANSITION PROBABILITY

Table 5 shows that a patient transitioning from state 1 enters to state 2, state 3 and state 4 with the probability of 0.151, 0.014, and 0.002, respectively. Patients transitioning from state 2 to state 3 and to state 4 with probability 0.128, 0.026 respectively. Probability of transitioning from state 3 to state 4 was 0.205. Moreover, the recovery probability of patients from state 4 to state 3, state 3 to state 2 and state 2 to state 1 were 0.241, 0.315, and 0.120 respectively. Patients recover from state 4 to state 2, from state 4 to state 1, from state 3 to state 1 with probability of 0.076, 0.004, and 0.028 respectively. The probability of staying in state 1 was 0.833, in state 2 was 0.726 and staying in state was with probability of 0.028. More precisely, the transition probability of recovery to a next good state were higher (0.315) compared to moving to next worst state (0.205) from state 3 and the transition probability of moving to the next worst state (0.128) were higher compared to moving to the next good state (0.12) from state 2.

Table 5: The transition probability matrix between hypertension states with 95% CI.

From - to	**State 1 Prob. (95% CI)**	**State 2 Prob. (95% CI)**	**State 3 Prob. (95% CI)**	**State 4 Prob. (95% CI)**
State 1	0.833 (0.768,0.881)	0.151 (0.108,0.210)	0.014 (0.009,0.023)	0.002 (0.001,0.003)
State 2	0.120 (0.085,0.167)	0.726 (0.660,0.778)	0.128 (0.091,0.177)	0.026 (0.017,0.041)
State 3	0.028 (0.018,0.043)	0.315 (0.234,0.406)	0.451 (0.368,0.529)	0.205 (0.137,0.290)
State 4	0.004 (0.002,0.008)	0.076 (0.048,0.112)	0.241 (0.167,0.325)	0.678 (0.577,0.777)

Table 5, indicates the probability of a patient starting from state i at time zero (initial checkup), made transition after one month to state j. For the hypertension data, the estimated transition probability matrices within a given time t = 6, t = 12, t=18, t = 24 and t=30 months are presented in Table 6. It shows the likelihood that a patient being at first visit in state i would be in state j after t months. The conditional probability of a patient starting from state 1 at time zero, and transiting to state 2, 3 and 4 after 6 months were 0.364, 0.107 and 0.064 respectively and remaining in the same state after 6 months with probability 0.464. Comparable interpretation of the other state at time t (6 months) in the Table. The conditional probability of a patient starting from state 4 at time zero, and transiting to state 3, 2 and 1 after 12 months were 0.179, 0.395 and 0.260 respectively. A patient being in state 4 at time zero, stays in the same state after 12 months with probability 0.167.

After 24 months, the probability of moving from state 1 to state 2 was 0.393, state 2 to state 3 was 0.160, and state 3 to state 4 was estimated to 0.137. Conversely the probability from state 2 to state 1, state 3 to state 2 and state 4 to state 3 respectively were estimated to be 0.311,0.393 and 0.162. The probabilities of transition from state 1 to state 2, state 3 and state 4 after 24 months are estimated to be 0.393, 0.159and 0.134 respectively and stay in the same state (state 1) after 24 months with 0.314 probability. Similar interpretation was applied for other probability with respect to the corresponding time.

Table 6: State occupation probabilities at t = 6, t = 12, t=18, t=24 and t = 30 months

Time in Month	From -to	State 1	State 2	State 3	State 4
t=6	state 1	0.464	0.364	0.107	0.064
	state 2	0.288	0.420	0.164	0.128
	state 3	0.209	0.402	0.197	0.192
	state 4	0.147	0.370	0.226	0.258
t=12	state 1	0.352	0.389	0.145	0.114
	state 2	0.308	0.394	0.161	0.137
	state 3	0.282	0.395	0.170	0.152
	state 4	0.260	0.395	0.179	0.167
t=18	state 1	0.323	0.392	0.156	0.130
	state 2	0.310	0.393	0.160	0.141
	state 3	0.303	0.393	0.163	0.141
	state 4	0.296	0.394	0.165	0.145
t=24	state 1	0.314	0.393	0.159	0.134
	state 2	0.311	0.393	0.160	0.136
	state 3	0.309	0.393	0.161	0.137
	state 4	0.307	0.393	0.162	0.138
t=30	State 1	0.312	0.393	0.160	0.136
	State 2	0.311	0.393	0.160	0.136
	State 3	0.310	0.393	0.160	0.136
	State 4	0.310	0.393	0.160	0.137

4.5 MEAN TIME LENGTH

Results in Table 7 shows the estimated average length of time a single staying in a state of hypertension, the standard error (SE), 95%CI for each of the transient states i. The patients spent 5.054, 2.538, 1.022, 2.150 months in state 1, state 2, state 3 and state 4 hypertension stages before transit to the other state. If an individual is in state 1, he/she spent 5.054 months in that state before

changing into other hypertensive states. Patients in prehypertension (state 1) have the highest mean length of stay and patients in state 3 had the shortest time of staying compared to others.

Table 7: Estimates of mean time length

Stages	Estimates	SE	95% CI
State 1	5.054	1.005	(3.423, 7.464)
State 2	2.538	0.389	(1.879, 3.428)
State 3	1.022	0.147	(0.771, 1.354)
State 4	2.150	0.514	(1.345, 3.435)

4.6 Effect of Covariates on the Transition Rates of Hypertension

The hazard ratios for gender, age, residence, FHTN, medication and history of Diabetes were estimated in Table 8. Consider a model with just one covariate, all transition intensities are modeled in terms of the variable and displays the estimated covariate effects (hazard ratios exp (β_{ij})) and their confidence intervals. In the hazard function the reference group was determined based on the ordering of the levels of the factor variable used in the model. The first level of the factor variable is considered as the reference group.

The hazard rate of transitions 0.309, 0.255, 0.961 and 0.585 for sex shows that males had less risk of hypertension to transit from state 1 to state 2, state 2 to state 1, state 3 to state 2 and state 4 to state 3 compared to females. Male patients had high risk of hypertension from state 2 to state 3 and from state 3 to state 4 than female patients. The hazard rate of transition between 30 to 64 years and 64 years and above were more than 1 in the transition from state 2 to state 3, state 3 to state 2, state 3 to state 4 and state 4 to state 3. This means patients in this age group had high risk of transition of hypertension backward and forward in these states compared to patients whose age was less than 30. But the forward and backward transition of hypertension between state 1 and state 2 of higher age category have less risk compared to under 30 age patients.

The estimated risk of transiting and 95% confidence interval for the residence effect were given in Table 8. Patients who were from urban place of residence were 1.242 times high risk of transition than the rural from state 2 to state 3, 1.539 times high risk of hypertension than rural from state 3 to state 2, 1.120 times high risk than rural from state 3 to state 4, 1.712 times high risk than from

state 4 to state 3. Patients who had family history of hypertension moving from state 1 to state 2, state 2 to state 1, state 2 to state 3 and state 3 to state 2 were about 1.544, 1.672, 1.093 and 1.051 times more risk of hypertension than these of patients who had not family history of hypertension respectively. Conversely, patients who had a family history of hypertensi on were 0.325 and 0.306 times less risk of hypertension to move from state 3 to state 4 and state 4 to state 3 than those who had no family history of hypertension.

The estimated risk of hypertensive patients who had taken medication or treatment of hypertensio n had hazard ratio less than one moving from state 1 to state 2, state 2 to state 1and state 4 to stat e 3. Patients who got treatments had less risk of hypertension compared to patients who did not g et medication or treatment in the past with HR of 0.516, 0.787 and 0.923 as shown below. Conve rsely, patients who had taken medication or treatments in the past had 1.202,1.361 and 1.563 time s more risk than those who did not get medications from state 2 to state 3, state 3 to state 2 and st ate 3 to state 4 respectively. Patients who had a history of diabetes had more risk of hypertension to transit from state 1 to state 2 (HR=1.398), from state 2 to state 3(HR=1.100) and from state 3 t o state 4(HR=1.033) than those who did not have diabetes history. The HR less than 1 shows that patients who had a history of diabetes had less risk of hypertension to transit from state 2 to state 1, state 3 to state 2 and state 4 to state 3 compared to those patients who did not have diabetes hi story respectively. Having a history of diabetes has a high risk of hypertension in all forward tran sitions of states and less risk in backward transitions of blood pressure states.

Table 8: The effects of each variable on transition intensity of hypertension.

Variables	**Transition**	**HR**	**95% CI**
Sex (0= Female (Ref),1= Male)	state 1 - state 2	0.309	(0.134, 0.711)
	state 2 - state 1	0.255	(0.111, 0.588)
	state 2 - state 3	1.031	(0.434, 2.446)
	state 3 - state 2	0.961	(0.423, 2.183)
	state 3 - state 4	1.607	(0.597, 4.327)
	state 4 - state 3	0.585	(0.221, 1.548)
Age	state1-state2	0.440	(0.181, 1.070)

(0= <30(Ref), 1= 30– 64, 2= > 64)	state 2-state1	0.529	(0.245, 1.144)
	state2-state3	3.190	(1.120, 9.091)
	state3-state2	2.628	(1.133, 6.094)
	state3-state4	1.586	(0.699, 3.595)
	state4-state3	2.061	(0.887, 4.790)
Residence (0=rural (Ref), 1=urban)	state1-state2	0.144	(0.023, 0.914)
	state2-state1	0.155	(0.022, 1.095)
	state2-state3	1.242	(0.535, 2.881)
	state3-state2	1.539	(0.693, 3.417)
	state3-state4	1.120	(0.428, 2.930)
	state4-state3	1.712	(0.655, 4.475)
FHTN (0=no (Ref), 1=yes)	state 1-state2	1.544	(0.665, 3.588)
	state2-state1	1.672	(0.729, 3.832)
	state2-state3	1.093	(0.442, 2.705)
	state3-state2	1.051	(0.462, 2.388)
	state3-state4	0.325	(0.103, 1.024)
	state4-state3	0.306	(0.102, 0.923)
Medication (0=no (Ref),1=yes	state1-state2	0.516	(0.151, 1.760)
	state2-state1	0.787	(0.245, 2.530)
	state2-state3	1.202	(0.499, 2.892)
	state3-state2	1.361	(0.609, 3.042)
	state3-state4	1.563	(0.581, 4.204)
	state4-state3	0.923	(0.353, 2.416)
HD (0=no (Ref),1=yes)	state1-state2	1.398	(0.528, 3.704)
	state2-state1	0.865	(0.313, 2.390)
	state2-state3	1.100	(0.415, 2.916)
	state3-state2	0.752	(0.303, 1.862)
	state3-state4	1.033	(0.381, 2.799)
	state4-state3	0.925	(0.357, 2.395)

4.7 Prediction of Survival Probability Based on the Multistate Markov Model

Predicting the probability of survival for patients in increasingly worse hypertension states for a future time t is a crucial use of multi-state models. Direct access to this is provided by the transition probability matrix P (t). Therefore, the survival probability for each subgroup may be inferred using the multistate Markov model, which might provide useful information to hypertensive patients in the future. The likelihood of not entering the absorbing state is represented by the survival probability, but in this study, there was no absorbing state and it represents the probability that a patient who begins at the initial time (t=0) and starts from state $i \in \{1,2,3,4\}$ would enter state $j \in \{1,2,3,4\}$ after month t. Survival probability curves over 60 months were given in Figures below.

Figure 2 shows the probability that a patient would start at time 0 in state 1 and go through stage $j \in \{1, 2, 3, 4\}$ after month t. The probability of remaining in state1 was high nearly 10 months before as compared to others then decreased and became constant as time increases. The probability of transition from state 1 to state 2 after 10 months was highest compared to other states and became constant as time increased. The survival probability of staying in state 1 and transiting to state 2 were high compared to transiting from state 1 to state 3 and state 4 of hypertension stages.

The transition probability starting from state 1 at time zero enters to state 3 was high compared to state 4 in the overall time interval of estimation. Transition probability from state 1 to state 3 becomes constant as time increases. The transition probability from state 1 to state 4 was the lowest compared to other states and became constant. Staying in state 1 and entering state 2 were the highest survival probability compared to bad state (state 3 and state 4).

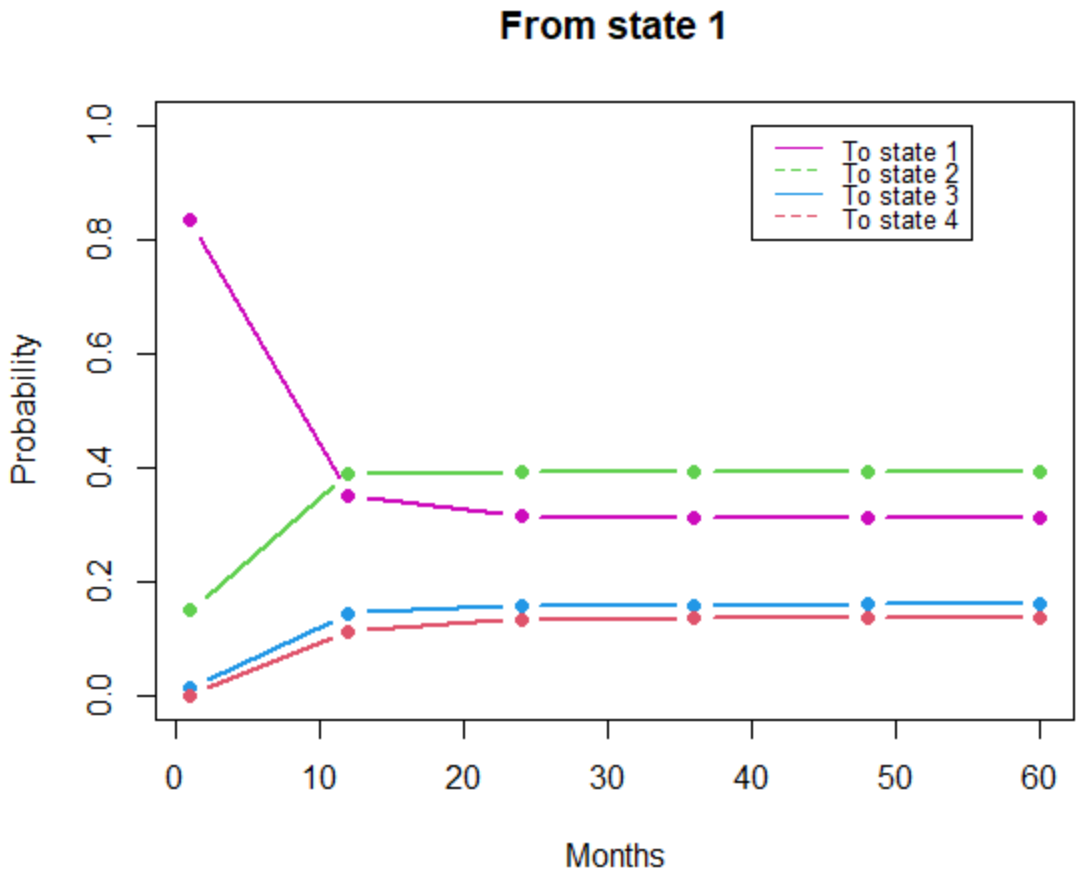

Figure 2:The probability that a patient at time 0 in state 1 and it will be in state j ∈ {1,2,3,4} after month t.

Figure 3 shows the probability of a patient entering stage $j \in \{1, 2, 3, 4\}$ after month t, starting fr om state 2 at time 0. The probability of remaining in state 2 was highest as compared to others in all months and decreases at the beginning and becomes constant as time increases. The probabilit y of patients starting from state 2 at time zero enters to state 1 was dramatically increased in the f irst few months and become constant as time increases. The transition probability of a patient star ting from state 2 at time zero enters to state 3 was high compared to state 4 in all months and bec ame constant. Again, the survival probability from state 2 to state 4 was the lowest probability co mpared to all other states and became constant as time increased.

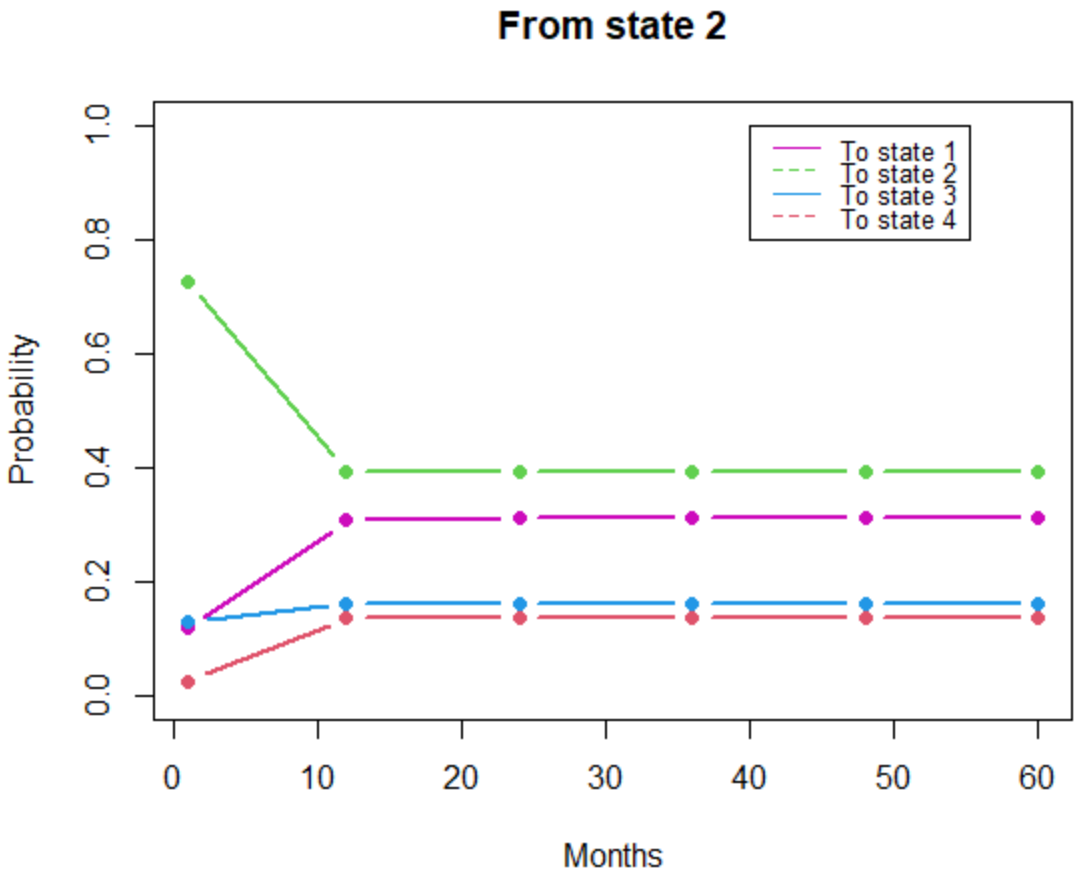

Figure 3: The probability that a patient at time 0 in state 2 will be in state j ∈ {1,2,3,4} after month t.

Figure 4 below shows the probability of a patient entering stage $j \in \{1, 2, 3, 4\}$ after month t, starting from state 3 at time 0. The probability of remaining in state 3 was high as compared to others in the beginning of the month, declined subsequently and became nearly constant after 25 months. The survival probability of a patient starting from state 3 at time zero enters state 2 was highest compared to other states after 2 months. While the survival probability from state 3 to state 4 were the lowest compared to other states and become constant as time increases. Transition probability from state 3 to state 2 was highest as time increased.

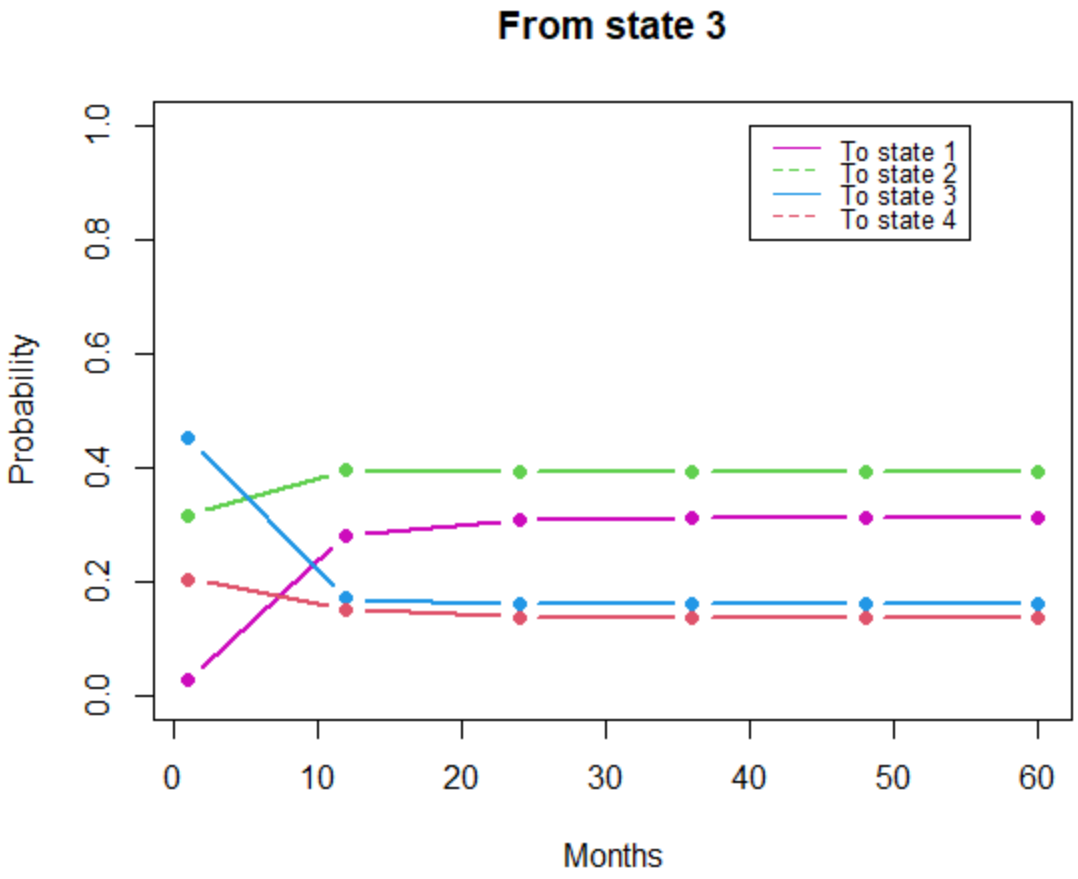

Figure 4: The probability that a patient at time 0 in state 3 will be in state j ∈ {1,2,3,4} after month t.

The probability that a patient would enter state $j \in \{1, 2, 3, 4\}$ after month t, beginning from state 4 at time 0 is shown in Figure 5. The probability of remaining in state 4 is high as compared to others for the first 4 months and declines until it becomes nearly constant as time increases. The survival probability from state 4 to state1 and state2 in the first 25 months was increasing. The probability of a patient starting from state 4 at time zero entering state 2 were highest and staying in state 4 was the lowest survival probability as time went on increasing.

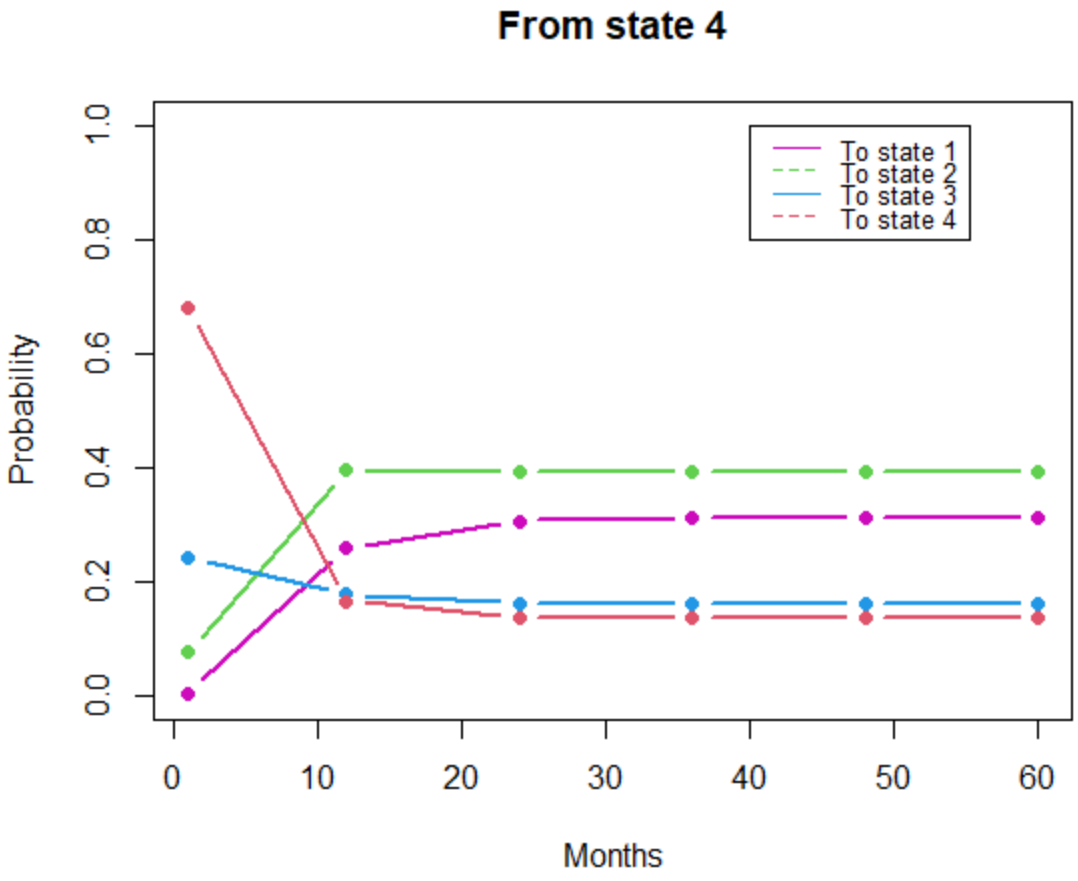

Figure 5: The probability that a patient at time 0 in state 4 will be in state j ∈ {1,2,3,4} after month t.

4.8 Model Comparison

In the analysis of multi-state models, distinct covariates in distinct transition hazards might be defined. Likelihood ratio tests between nested models fitted in msm can be performed using the function lrtest.msm to compare the model that were fitted. Therefore, it is necessary to compare the two models and select the proper one. The value of the $LRT = -2log_e(\frac{L_0(\theta)}{L_1(\theta)})$ where, $L_0(\theta)$ is the null model (without covariates) and $L_1(\theta)$ is the full model (with all covariates).

Comparing a likelihood ratio test statistic of 100.434 with 36 degrees of freedom shows that the model with covariates (full model) fits better than the base model with no covariates (null model).

Table 9: Model comparison using LRT

Model	-2logLikelihood	LR test statistics	Df	P-value
Null model	1582.771	-	-	-
Full model	1482.028	100.7434	36	4.81612e-08

4.9 MODEL ASSESSMENT

Estimating the observed prevalence at a sequence of sites using interpolation is the next step in determining the goodness of fit for prevalence counts. Figure 6 shows the observed and predicted prevalence of prehypertension (state 1), grade1 hypertension (state 2), grade2 hypertension (state 3) and grade 3 hypertension (state 4) in the follow-up time (from first month to 24 months). The prevalence vs time plots for the model fitted at a given time period in months, with sample size of 210 hypertensive patients.

Around 22% of patients were state 1 at the beginning of the study but as we moved away from zero to twenty months the percentage increased to around 31% of both expected and observed percentage. 36% of patients who were state 2 at the beginning of the study but as time goes to 20 months the observed and expected percentage changed to 34% and 39% respectively. 23% of patients who were state 3 at the beginning of the study and at month 20, the number decreased to around 12% and 16% of the observed and expected percentage respectively. Similarly,17% of patients who were at state 4 at initial time and at month 20 the observed and expected percentage of patients who were at state 4 were increased to nearly 21% and decreased to approximately 13% respectively.

The observed and expected plots do not have much deviations. Hence the assumption of homogeneity of transition rate through the specified time is satisfied. The difference between the predicted and observed prevalence is not substantial. The model had a good fit within all months and displayed a less deviation. Therefore, the model is a good fit.

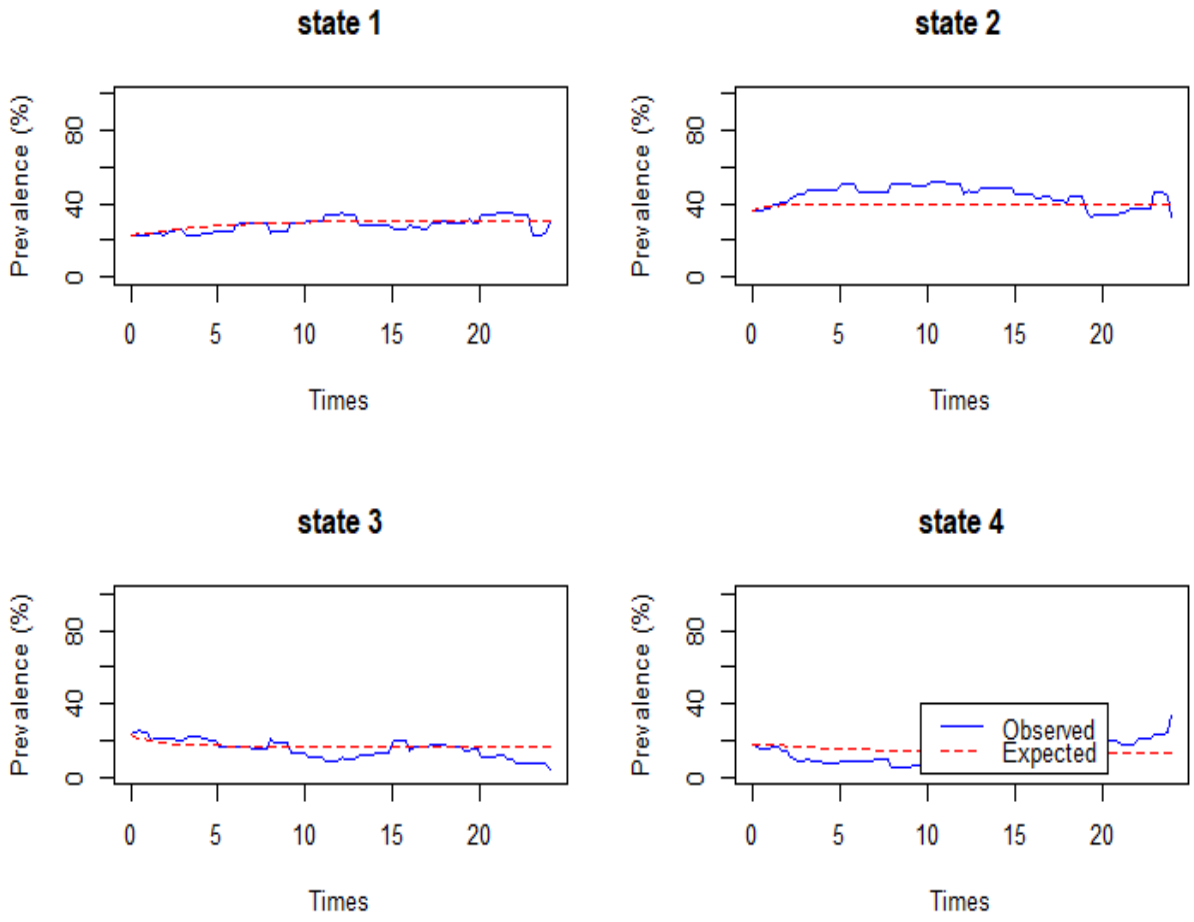

Figure 6: Prevalence vs time plots of hypertensive patients over 24 months follow up.

4.10 DISCUSSION

This study has estimated the transition probabilities between the stages of hypertension severity prehypertension BP, grade 1 hypertension, grade 2 hypertension, and grade 3 hypertension and the mean of time hypertensive patients might spend at a particular hypertension state. After the 24 months of transition, the probability of transition from state 1 to an adjacent state, that is, state 2 was 15%, greater than transition to a non-adjacent state, state 3 which was 1.4% and state 4 which was 0.2%. Again, the probability of transition from state 2 to an adjacent state, that is, state 3 was 12.8%, greater than transition to a non-adjacent state, state 4 which was 2.6%. This shows consistency of the findings with more recent studies in Ghana (Boateng et al., 2021). The probability of recovering from state 2 hypertension to state 1 (12%) was less than progressing to

state 3 (12.8%). Thus, a smaller number of patients recovered to a better health state than those who progressed to a worse stage. This may be due to low adherence of hypertension among the society in Hawassa (Getenet et al., 2019). While, the probability of recovering from state 3 to state 2 (31.5%) was greater than progressing to state 4(20.5%). However, once at state 2, state 3 and state 4, the probability of remaining at that stage after 24 months was much higher than recovering back to state 1, state 2 and state 3. The probability of remaining in stage 1 was the highest compared to the transition probability of staying in any other stages. The estimated transition probability within a given time t = 6, t = 12, t=18, t=24 and t = 30 months were presented. The probability of transition from good state to the next worst state decreases and becomes constant overtime except the transition from state 1 to state 2 which increases as time increases. This may be because of giving less attentions of controlling low blood pressure unless it harms their health. The transition probability from state 1 to state 3, state1 to state 4 and state 2 to state 4 were increased as time increased.

Another significant finding of this study was to answer how long it takes a patient to transit from state to state of hypertension. Hypertensive patient spends an average of 5 months at prehyperten sion stage before transitioning to grade 1 hypertension, 2.538 months at grade 1 hypertension stage before recover to prehypertension or transition to grade 2 hypertension state, 1.022 months at grade 2 hypertension stage before transition to grade 3 hypertension or recover to grade 1 hypertension state and 2.15 months at grade 3 hypertension stage before recover to grade 2 hypertensions. State 1 appears to have the longest estimated sojourn time followed by state 2. This is consistent with the findings studied in China, Ghana and contradicts with the study at Haramaya university (Zheng et al., 2022), (Awol, 2016), (Boateng et al., 2021). State 3 has the shortest estimated sojourn time.

The finding in this study relates the effect of covariates on the transition rate of hypertension using hazard ratio. Males were less likely to transit from state 1 to state 2 (consistency with Zheng et al., 2022), state 2 to state 1 (consistency with Yang et al., 2020, Y. Wang et al., 2018), state 3 to state 2 and state 4 to state 3 compared to female. But males were more likely to transit from state 2 to state 3 (consistency with Y. Wang et al., 2018, Yang et al., 2020, Meitei & Ladusingh, 2019) and from state 3 to state 4 than females. The hazard ratios of patients between 30 to 64 years and 64 years and above were at high risk of transiting from state 2 to state 3, state 3 to state 2, state 3 to state 4 and state 4 to state 3 compared to patients whose age were less than 30. As age increased

the risk of transition of hypertension was high. This is consistent with the research by (Zheng et al., 2022), (Chalmers, 1999), (Boateng et al., 2021). But the forward and backward transition of hypertension between state 1 and state 2 of higher age category have less risk compared to under 30 age patients. Living in urban areas had less risk of hypertension compared to rural areas when blood pressure was moved between the first and second stage of hypertension. Patients living in urban areas had higher risk of hypertension than rural ones when the transition states were state 2-state3, state 3-state2, state 3-state 4and state4-state3. Urban residence was associated with high risk of progressing to a more severe form of hypertension. This is in line with the finding of (Boateng et al., 2021) in Ghana.

The estimated hazard ratio shows patients who had a family history of hypertension were at higher risk of hypertension than those who had no family history of hypertension moving from state 1 to state 2, state 2 to state 1, state 2 to state 3 and state 3 to state 2. Conversely, patients who have a family history of hypertension were less likely to move from state 3 to state 4 and state 4 to state 3 than those who had no family history of hypertension. The risk of hypertension who were taking medication or treatment of hypertension before were high compared to patients who were not taking treatment. Patients transition from state 2 to state 3, state 3 to state 2 and state 3 to state 4(HR: 1.202,1.361, 1.563). Conversely, patients who got treatments had less risk of hypertension compared to patients who did not get medication or treatment in the recent past with HR of 0.516, 0.787 and 0.923 in the transition from state 1 to state 2, state 2 to state 1and state 4 to state 3 respectively. This might be due to the fact that patients did not take medication or treatment properly. According to Getenet et al., (2019) conducted in Hawassa referral hospital on Determinants of adherence to anti-hypertensive medications among adult hypertensive patients, rate of medication adherence was found to be very low. Patients who had a history of diabetes were more likely to transit from state 1 to state 2 (HR=1.398), from state 2 to state 3(HR=1.1) and from state 3 to state 4(HR=1.033) than those who did not have diabetes history. Patients who have a history of diabetes were less likely to transit from state 2 to state 1, state 3 to state 2 and state 4 to state 3 compared to those patients who did not have diabetes history respectively. Having a history of diabetes has high risk of hypertension in all forward transition and less risk in backward transition of blood pressure states.

The survival probability of each hypertension states was predicted using probability vs time in months and become constant after time t increases. Comparing a likelihood ratio test statistic, the full model fits better than the base model (null model). The observed and expected plots do not have much deviation and assumption of homogeneity of transition rate through the specified time are satisfied. Therefore, the model is a good fit.

CHAPTER FIVE

5. CONCLUSIONS AND RECOMMENDATIONS

5.1 CONCLUSIONS

This research assessed the transition of hypertension based on longitudinally measured blood pressure of hypertensive patients under follow up at Hawassa university comprehensive specialized hospital using multistate Markov model. The finding shows that most of the patients moved to the next worst state were at grade 3 hypertension stages(state3) with probability 0.205. The conditional probability of hypertensive patients from good states to the next worst state are decreasing over time except the first state of hypertension. State 1 hypertension had the longest estimated mean length of time followed by state 2, while state 3 had the shortest estimated mean length of time. The factor associated with higher risk of hypertension severity from good state to worst state was being males, older age, living in urban areas, taking medication or treatments in the past and history of diabetes between state 2,3,4 of hypertension and all states for HD. Being female, living in a rural area, younger age, not taking medication in the past between state 1 and state 2 were also factors having high risk of hypertension.

5.2 RECOMMENDATIONS

Based on the findings of the study, the following recommendations are made for health policy makers, clinicians and others.

- More attention should be given to the progression from grade 2 hypertension state to grade 3 hypertension states which have the highest transition probability of hypertension to the next worst state.
- Awareness should be given for people who are older, living in urban areas and have low adherence to medication about hypertension which are at risk of hypertension.
- The progression of hypertension stages should be evaluated in different hospitals in the region and might be used as an input to control transition of hypertension severity in Ethiopia.

- The Ethiopian government should pay particular attention to the distribution of hypertens ion to reduce the hypertension transition rate. It is important to inform, checking and cont rolling blood pressure is mandatory to manage hypertension severity.

5.3 LIMITATION OF THE STUDY

This study has some limitations. The first drawback is that patient heterogeneity was not considered when analyzing data from just one center at Hawassa University Comprehensive Specialized Hospital. In order to ensure accurate generalization, a suitable sample size must be determined, considering the socioeconomic and demographic diversity of the patients. This sample size must also be significant enough to support future multistate analysis and provide a complete picture of hypertension in Ethiopia. The second limitation is the incomplete patient records during the follow-up of clinical appointments, specifically with regard to data on clinical parameters. This forces us to discard some data. Third, patients are observed at pre-specified assessment times and their states are determined only at these times. Patients did not start follow ups at the same time and in similar blood pressure states. Therefore, there were missing states. In complete case analysis might lead to biased results, and so invalid inferences. Fourth, although many literatures show the interest of applying semi-Markov models for disease progression, this study used Markov models. Finally, some significant covariates, such as diet, smoking, exercise, BMI, alcohol consumption, were not covered in the current study. Therefore, in future research, the model should be improved by incorporating more frequently collected data and more covariates.

6. REFERENCE

Anker, D., Carmeli, C., Zwahlen, M., Rodondi, N., Santschi, V., Henchoz, Y., Wolfson, C., & Chiolero, A. (2022). How blood pressure predicts frailty transitions in older adults in a population-based cohort study: A multi-state transition model. *International Journal of Epidemiology*, *51*(4), 1167–1177. https://doi.org/10.1093/ije/dyab210

Asena, T. (2021). *Semi-Markov Modelling of HIV / AIDS Disease Progression*.

Asresahegn, H., Tadesse, F., & Beyene, E. (2017). Prevalence and associated factors of hypertension among adults in Ethiopia: a community-based cross - sectional study. *BMC Research Notes*, 1–8. https://doi.org/10.1186/s13104-017-2966-1

Awol, S. (2016). Journal of Biostatistics and Epidemiology. *J Biostat Epidemiol.*, *1*(1), 37–44.

Boateng, G. O., Lartey, S. T., Baiden, P., Si, L., Biritwum, R. B., Kowal, P., Magnussen, C. G., Ben Taleb, Z., Palmer, A. J., & Luginaah, I. (2021). Measuring Hypertension Progression with Transition Probabilities: Estimates from the WHO SAGE Longitudinal Study. *Frontiers in Public Health*, *9*(April), 1–12. https://doi.org/10.3389/fpubh.2021.571110

Chalmers, J. (1999). 1999 World Health Organization-International Society of Hypertension guidelines for the management of hypertension. *Clinical and Experimental Hypertension*, *21*(5–6), 1009–1060. https://doi.org/10.3109/10641969909061028

Cochran. (1977). *Cochran_1977_Sampling_Techniques_Third_Edition.pdf*.

Erango, M. A., Gergiso, K. T., & Hebo, S. H. (2019). Survival Time Analysis of Hypertension Patients Using Parametric Models. *Advances in Research*, *October*, 1–10. https://doi.org/10.9734/air/2019/v20i230155

Getenet, A., Tesfa, M., & Ferede, A. (2019). *Determinants of adherence to anti-hypertensive medications among adult hypertensive patients on follow-up in Hawassa Referral Hospital: A case – control study*. https://doi.org/10.1177/2048004019892758

Ibe, O. (2009). *Markov Process for Stochastic Modeling*.

Jackson, C. (2022). Multi-state modelling with R: the msm package. *Cambridge, UK*, 1–53.

KASHIHALWA, S. P. (2019). *MODELLING PROGRESSION OF HIV/AIDS DISEASE USING HOMOGENOUS SEMIMARKOV PROCESSES: COHORT STUDY, NA*. *April*.

Kassa, A., & Woldesemayat, E. M. (2019). Hypertension and Diabetes Mellitus among Patients at Hawassa University Comprehensive Specialized Hospital, Hawassa, Southern Ethiopia. *International Journal of Chronic Diseases*, *2019*, 1–8. https://doi.org/10.1155/2019/2509242

Lintu, M. K., Shreyas, K. M., & Kamath, A. (2022). A multi-state model for kidney disease progression. *Clinical Epidemiology and Global Health*, *13*(December 2021), 100946. https://doi.org/10.1016/j.cegh.2021.100946

Mafu, T. J. (2014a). *Modelling of Multi-State Panel Data: The Importance of the Model Assumptions by*. *December*.

Mafu, T. J. (2014b). *Modelling of Multi-State Panel Data: The Importance of the Model Assumptions by*. *December*.

Meitei, W. B., & Ladusingh, L. (2019). Transition Specific Risk Factors Affecting the Lifestyle Disease Progression from Diabetes to Hypertension in India. *Health*, *11*(08), 1055–1071. https://doi.org/10.4236/health.2019.118083

SOLOMON, K. M., GEBREGEWERGIS, A. G., TILAHUN, F., & CHERU, A. (2018). Application of Multi-State Semi-Markov Models on HIV/Aids Disease Progression. *I-Manager's Journal on Mathematics*, *7*(3), 30. https://doi.org/10.26634/jmat.7.3.14988

Tesfay, F. H., Zorbas, C., Alston, L., Backholer, K., Bowe, S. J., & Bennett, C. M. (2022). Prevalence of chronic non-communicable diseases in Ethiopia: A systematic review and meta-analysis of evidence. *Frontiers in Public Health*, *10*. https://doi.org/10.3389/fpubh.2022.936482

Wang, W. (2022). *Multi-state Markov models with fixed and random effects*.

Wang, Y., Ma, Z., Xu, C., Wang, Z., & Yang, X. (2018). Prediction of transfer among multiple states of blood pressure based on Markov model: An 18-year cohort study. *Journal of Hypertension*, *36*(7), 1506–1513. https://doi.org/10.1097/HJH.0000000000001722

Williams, B., Giuseppe Mancia* , Wilko Spiering , Michel Azizi, M. B. (Switzerland), Denis L. Clement (Belgium), Antonio Coca (Spain), G. de S. (Italy), Anna Dominiczak (UK), Thomas Kahan (Sweden), F. M. (Germany), Josep Redon (Spain), Luis Ruilope (Spain), Alberto Zanchetti† (Italy), M. K., (Ireland), Sverre E. Kjeldsen (Norway), R. K. (Germany), Stephane Laurent (France), Gregory Y. H. Lip (UK), R. M. (UK), Krzysztof Narkiewicz (Poland), F. R. (Switzerland), Roland E. Schmieder (Germany), Evgeny Shlyakhto (Russia), C. T., (Greece), Victor Aboyans (France), I. D. (France), Stephane Laurent (France), Gregory Y. H. Lip (UK), R. M. (UK), Krzysztof Narkiewicz (Poland), F. R. (Switzerland), Roland E. Schmieder (Germany), Evgeny Shlyakhto (Russia), C. T., & (Greece), Victor Aboyans (France), I. D. (France). (2018). Interpretation of the 2018 ESC/ESH Guidelines for the Management of Arterial Hypertension. In *Chinese General Practice* (Vol. 22, Issue 21). https://doi.org/10.12114/j.issn.1007-9572.2019.00.224

Yang, J., Liu, F., Wang, B., Chen, C., Church, T., Dukes, L., & Smith, J. O. (2020). Blood Pressure States Transition Inference Based on Multi-State Markov Model. *IEEE Journal of Biomedical and Health Informatics*, *25*(1), 237–246. https://doi.org/10.1109/JBHI.2020.3006217

Zelelew, N. (2020). *Joint Modeling of Multivariate Longitudinal Measures of Hypertension and Time to Develop Cardiovascular Disease Complication among Hypertensive Outpatients Treated at DebreTabor General Hospital, Ethiopia.*

Zheng, X., Xiong, J., Zhang, Y., Xu, L., Zhou, L., Zhao, B., & Wang, Y. (2022). Multistate Markov model application for blood pressure transition among the Chinese elderly population: a quantitative longitudinal study. *BMJ Open*, *12*(7), 1–8. https://doi.org/10.1136/bmjopen-2021-059805

7. APPENDIX

APPENDIX 1: MODELS WITH COVARIATE

Base line intensity with covariate Sex

Call:

msm (formula = state ~ Months, subject = ID, data = data. Frame (TEMP, qmatrix = Q, covariates = ~Sex, opt. method = "bobyqa")

Maximum likelihood estimates
Baselines are with covariates set to their means
Transition intensities with hazard ratios for each covariate

	Baseline	Sex
state 1 - state 1	-0.1972 (-0.3012, -0.1291)	
state 1 - state 2	0.1972 (0.1291, 0.3012)	0.3089 (0.1342,0.7111)
state 2 - state 1	0.1592 (0.1036, 0.2445)	0.2552 (0.1108,0.5877)
state 2 - state 2	-0.3925 (-0.5317, -0.2897)	
state 2 - state 3	0.2333 (0.1516, 0.3588)	1.0308 (0.4344,2.4457)
state 3 - state 2	0.5650 (0.3790, 0.8422)	0.9613 (0.4232,2.1833)
state 3 - state 3	-0.9895 (-1.3288, -0.7369)	
state 3 - state 4	0.4246 (0.2574, 0.7001)	1.6071 (0.5968,4.3273)
state 4 - state 3	0.5540 (0.3396, 0.9037)	0.5848 (0.2210,1.5476)
state 4 - state 4	-0.5540 (-0.9037, -0.3396)	

-2 * log-likelihood: 1558.919

Base line intensity with covariate age

Call:
msm (formula = state ~ Months, subject = ID, data = data. Frame (TEMP), qmatrix = Q, covariates = ~Age, opt. method = "bobyqa")
Maximum likelihood estimates
Baselines are with covariates set to their means
Transition intensities with hazard ratios for each covariate

	Baseline	Age

state 1 - state 1 -0.2034 (-0.3009, -0.1375)

state 1 - state 2 0.2034 (0.1375, 0.3009) 0.4398 (0.1808,1.070)

state 2 - state 1 0.1655 (0.1116, 0.2455) 0.5289 (0.2445,1.144)

state 2 - state 2 -0.4194 (-0.5859, -0.3003)

state 2 - state 3 0.2539 (0.1560, 0.4133) 3.1901 (1.1195,9.091)

state 3 - state 2 0.6489 (0.4155, 1.0134) 2.6275 (1.1329,6.094)

state 3 - state 3 -1.0152 (-1.3784, -0.7477)

state 3 - state 4 0.3663 (0.2266, 0.5920) 1.5858 (0.6995,3.595)

state 4 - state 3 0.4108 (0.2571, 0.6564) 2.0608 (0.8867,4.790)

state 4 - state 4 -0.4108 (-0.6564, -0.2571)

-2 * log-likelihood: 1570.47

Base line intensity with covariate residence

Call:

msm (formula = state ~ Months, subject = ID, data = data. frame (TEMP), qmatrix = Q, covariate s = ~Residence, opt. method = "bobyqa")

Maximum likelihood estimates

Baselines are with covariates set to their means

Transition intensities with hazard ratios for each covariate

	Baseline	Residence
state 1 - state 1	-0.2595 (-0.4981, -0.1352)	
state 1 - state 2	0.2595 (0.1352, 0.4981)	0.1441 (0.02272,0.9138)
state 2 - state 1	0.2235 (0.1142, 0.4372)	0.1553 (0.02202,1.0954)
state 2 - state 2	-0.4535 (-0.6657, -0.3089)	
state 2 - state 3	0.2300 (0.1509, 0.3505)	1.2415 (0.53505,2.8805)
state 3 - state 2	0.5609 (0.3821, 0.8232)	1.5385 (0.69265,3.4174)
state 3 - state 3	-0.9611 (-1.2725, -0.7260)	
state 3 - state 4	0.4003 (0.2467, 0.6495)	1.1195 (0.42780,2.9297)
state 4 - state 3	0.4763 (0.2968, 0.7645)	1.7115 (0.65466,4.4747)
state 4 - state 4	-0.4763 (-0.7645, -0.2968)	

-2 * log-likelihood: 1570.058

Base line intensity with covariate Family history of hypertension

Call:

msm (formula = state ~ Months, subject = ID, data = data. frame (TEMP), qmatrix = Q, covariate s = ~FHTN, opt. method = "bobyqa")

Maximum likelihood estimates

Baselines are with covariates set to their means

Transition intensities with hazard ratios for each covariate

	Baseline	FHTN
state 1 - state 1	-0.1964 (-0.2889, -0.1335)	
state 1 - state 2	0.1964 (0.1335, 0.2889)	1.5443 (0.6647,3.5875)
state 2 - state 1	0.1549 (0.1055, 0.2274)	1.6715 (0.7292,3.8317)
state 2 - state 2	-0.3921 (-0.5297, -0.2902)	
state 2 - state 3	0.2372 (0.1541, 0.3652)	1.0932 (0.4419,2.7048)
state 3 - state 2	0.5757 (0.3877, 0.8549)	1.0505 (0.4621,2.3880)
state 3 - state 3	-1.0300 (-1.4158, -0.7493)	
state 3 - state 4	0.4543 (0.2474, 0.8340)	0.3255 (0.1035,1.0237)
state 4 - state 3	0.5539 (0.3003, 1.0216)	0.3062 (0.1016,0.9227)
state 4 - state 4	-0.5539 (-1.0216, -0.3003)	

-2 * log-likelihood: 1575.781

Base line intensity with covariate medication and taking treatments in the past

Call:

msm (formula = state ~ Months, subject = ID, data = data. frame (TEMP), qmatrix = Q, covariate s = ~Medication, opt. method = "bobyqa")

Maximum likelihood estimates

Baselines are with covariates set to their means

Transition intensities with hazard ratios for each covariate

	Baseline	Medication
state 1 - state 1	-0.2358 (-0.4232, -0.1314)	
state 1 - state 2	0.2358 (0.1314, 0.4232)	0.5156 (0.1511,1.760)

state 2 - state 1 0.1804 (0.1032, 0.3154) 0.7867 (0.2446,2.530)

state 2 - state 2 -0.4158 (-0.5814, -0.2973)

state 2 - state 3 0.2354 (0.1515, 0.3657) 1.2017 (0.4994,2.892)

state 3 - state 2 0.5891 (0.3924, 0.8846) 1.3609 (0.6088,3.042)

state 3 - state 3 -1.0048 (-1.3395, -0.7537)

state 3 - state 4 0.4156 (0.2520, 0.6855) 1.5626 (0.5808,4.204)

state 4 - state 3 0.4830 (0.2976, 0.7837) 0.9233 (0.3529,2.416)

state 4 - state 4 -0.4830 (-0.7837, -0.2976)

-2 * log-likelihood: 1576.976

Base line intensity with covariate history of diabetes

Call:

msm (formula = state ~ Months, subject = ID, data = data. frame (TEMP), qmatrix = Q, covariate s = ~HD, opt. method = "bobyqa")

Maximum likelihood estimates

Baselines are with covariates set to their means

Transition intensities with hazard ratios for each covariate

	Baseline	HD
state 1 - state 1	-0.2035 (-0.3063, -0.1352)	
state 1 - state 2	0.2035 (0.1352, 0.3063)	1.3985 (0.5281,3.704)
state 2 - state 1	0.1583 (0.1050, 0.2387)	0.8649 (0.3130,2.390)
state 2 - state 2	-0.3945 (-0.5352, -0.2908)	
state 2 - state 3	0.2362 (0.1523, 0.3662)	1.0998 (0.4147,2.916)
state 3 - state 2	0.5848 (0.3926, 0.8712)	0.7515 (0.3033,1.862)
state 3 - state 3	-0.9857 (-1.3162, -0.7382)	
state 3 - state 4	0.4009 (0.2407, 0.6676)	1.0325 (0.3809,2.799)
state 4 - state 3	0.4780 (0.2856, 0.8001)	0.9245 (0.3569,2.395)
state 4 - state 4	-0.4780 (-0.8001, -0.2856)	

-2 * log-likelihood: 1576.998

APPENDIX 2: MODEL ASSESSMENT

The observed and expected numbers and percentage

$Observed

State 1	State 2	State 3	State 4	Total
0	48	76	50	36	210
2	43	79	44	28	194
4	36	68	34	13	151
6	38	60	23	14	135
8	28	59	24	6	117
10	32	52	13	7	104
12	38	42	9	9	98
14	22	39	11	8	80
16	20	32	10	8	70
18	17	25	9	5	56
20	15	16	6	10	47
22	15	14	3	8	40
24	7	8	1	8	24

$Expected

	state 1	state 2	state 3	state 4	Total
0	48.000	76.000	50.000	36.000	210
2	49.104	76.032	35.857	33.007	194
4	41.113	59.547	26.354	23.986	151
6	38.521	53.227	22.875	20.377	135
8	34.406	46.089	19.446	17.058	117
10	31.185	40.935	17.065	14.815	104
12	29.761	38.549	15.943	13.747	98
14	24.496	31.455	12.941	11.107	80
16	21.550	27.515	11.281	9.653	70

18	17.302	22.008	9.003	7.688	56
20	14.555	18.468	7.544	6.433	47
22	12.406	15.716	6.413	5.465	40
24	7.451	9.429	3.845	3.275	24

$`Observed percentages`

	State 1	State 2	State 3	State 4
0	22.86	36.19	23.810	17.143
2	22.16	40.72	22.680	14.433
4	23.84	45.03	22.517	8.609
6	28.15	44.44	17.037	10.370
8	23.93	50.43	20.513	5.128
10	30.77	50.00	12.500	6.731
12	38.78	42.86	9.184	9.184
14	27.50	48.75	13.750	10.000
16	28.57	45.71	14.286	11.429
18	30.36	44.64	16.071	8.929
20	31.91	34.04	12.766	21.277
22	37.50	35.00	7.500	20.000
24	29.17	33.33	4.167	33.333

$`Expected percentages`

	state 1	state 2	state 3	state 4
0	22.86	36.19	23.81	17.14
2	25.31	39.19	18.48	17.01
4	27.23	39.44	17.45	15.88
6	28.53	39.43	16.94	15.09
8	29.41	39.39	16.62	14.58
10	29.99	39.36	16.41	14.25
12	30.37	39.34	16.27	14.03

14	30.62	39.32	16.18	13.88
16	30.79	39.31	16.12	13.79
18	30.90	39.30	16.08	13.73
20	30.97	39.29	16.05	13.69
22	31.01	39.29	16.03	13.66
24	31.05	39.29	16.02	13.64