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ORIGINAL RESEARCH

Joint Modeling of Blood Pressure Measurements and Survival Time to Cardiovascular Disease Complication among Hypertension Patients Follow-up at DebreTabor Hospital, Ethiopia

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Introduction: Hypertension is also referred to as a silent killer and a leading factor for cardiovascular disease complication in the world today. This study aimed to identify the factors that affect longitudinal outcomes and survival time for cardiovascular disease complications among patients with hypertension.

Methods: A retrospective cohort study was conducted among a randomly selected sample of 178 outpatients with hypertension at the Debre Tabor Specialized Hospital between September 2017 and December 2019. Three different models were used to analyze the data: the bivariate mixed-effects model, Cox proportional hazard model, and bivariate joint model for longitudinal and survival sub-models linked by shared random effects.

Results: Bivariate mixed-effects and Cox proportional hazards survival sub-models were jointly preferred based on the minimum Akaike Information Criterion value. The estimated values of the association parameters were 0.0655 ($p = 0.0270$) and 0.963 ($p = 0.0387$), indicating that the association between systolic and diastolic blood pressure with time to event was guaranteed. The joint bivariate mixed-effects model analysis showed that patients with hypertension with a family history of hypertension and clinical stage II hypertension have a high chance of developing cardiovascular disease complications and have high average systolic and diastolic blood pressure compared to their counterparts. Patients with hypertension and diabetes have higher systolic and diastolic blood pressure than their counterparts.

Conclusion: Generally, systolic and diastolic blood pressure stabilized over the follow-up period of treatment, while sex and residence were statistically insignificant to the survival time of cardiovascular disease complication. Health professionals and concerned bodies should therefore focus on patients with comorbidities, older age, and poor adherence to hypertension control and cardiovascular disease complications using technology, such as text messaging, and mobile application to promote cardiovascular health at early stage. It is important to provide early interventions for these groups of people, especially for those with family history.

Keywords: joint model, multiple longitudinal assessments, time to event outcome

Introduction

Hypertension is a silent killer among non-communicable chronic diseases and the leading risk factor for cardiovascular disease complications, such as heart disease (eg, coronary artery disease, congestive heart failure, and heart attack), stroke (eg, cerebral infarction and cerebral hemorrhage), kidney disease, and impaired vision.[1–3] It is also called high blood pressure (BP), a situation in which the arterial vessel pressure is elevated, requiring the heart to work beyond normal levels to circulate blood through blood vessels.[4] BP was defined using two measurement quantities: (systolic blood pressure [SBP] and diastolic blood pressure [DBP]). Clinically, a person is said to be hypertensive if their SBP is greater than 140 mmHg and/or DBP is greater than 90 mmHg and if they are already under medication.[5,6]

Non-communicable diseases (NCDs) are a major cause of death worldwide and are one of the health challenges of the 21st century.[7] According to the World Health Organization (WHO, 2020), NCDs account for 80% of the global disease burden. Seven

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out of every ten deaths in developing countries are caused by NCDs, and about half of these deaths are in people younger than 70 years.[8]

A study conducted in, 2017 in 195 countries showed hypertension is a major public health problem. For example, among 1.13 billion deaths globally, 12.8% of these deaths were attributed to hypertension.[9,10] A similar study conducted in Africa revealed 46% of the adult population had hypertension which has the highest in the world.[10,11] According to a WHO report, hypertension is responsible for at least 45% of global deaths due to heart disease and 51% of deaths due to stroke.[12] Another study conducted in Australia on 6083 hypertension patients showed that 373 participants developed heart failure.[13]

Non-communicable diseases, such as hypertension and vascular diseases, have the highest burden of morbidity and mortality in Africa.[14] In the first half of the 20th century, hypertension was almost non-existent in Africa, but currently, estimates show that in Africa, more than 40% of adults have hypertension.[10] It is estimated that the number of hypertensive patients in sub-Saharan Africa will rise to 150 million by 2025 because of demographic and epidemiologic transitions.[15,16]

Current disease assessments in sub-Saharan Africa suggest that there is a wide imbalance (0.4–47.5%) in the prevalence of hypertension, with Ethiopia considered to share a similar high profile of hypertension in sub-Saharan Africa.[17,18] According to WHO report revealed that 34% of all deaths in Ethiopia were due to non-communicable diseases (NCDs), of which 12% contribute to cardiovascular disease. Available scholarly information shows that because of economic development and rapid urbanization, non-communicable diseases and their associated risk factors have risen and become a double burden in Ethiopia.[19]

Given the interdependence of these determinants on the onset of hypertension, jointly evaluating these interrelated factors that may alter the rate of change in cardio metabolic outcomes could be useful in developing appropriate public health interventions.[20] In addition, many researchers have conducted studies using a cross-sectional study design, which does not show the progression of the disease over time, or used multiple linear regression or logistic regression to identify determinant factors without considering the correlations within the multiple outcomes and subject-specific random effects.[21–23]

Some studies[5,24] have been conducted on hypertension and the risk factors that lead to the development of cardiovascular disease complications to determine survival time and longitudinal outcomes separately. These analysis methods do not consider the dependencies or interrelationships between different data types such as longitudinal and time-to-event data types. Consequently, separate analyses may not be appropriate when repeated measurements and time-to-event data are correlated and fail to consider all available information in an integrated manner.

In many clinical studies, longitudinal biomarkers and the event time of interest have been collected simultaneously to explore their association.[25–27] This study applied a joint modeling framework because the main significance of this study was the reduced bias associated with measurement errors and missing data. The survival model with time-dependent covariates may be measured with an error or may be missing and to reduce possible bias associated with informative dropouts because longitudinal data record with informative dropout, we need to model time to dropouts (ie, to detect the survival probability of hypertension patients under follow-up). This study aimed to assess the association between SBP, DBP, and survival time to cardiovascular disease complications among outpatients with hypertension.

Materials and Methods

Study Design, Study Area and Sampling Procedure

Hospital-based retrospective studies were conducted among adult outpatients with hypertension attending a hypertension (HTN) clinic between September 2017 and December 2019 at the Debre Tabor Specialized Hospital (DTSH). DebreTabor Hospital is the only specialized hospital in the southern Gondar zone. It is located 666 and 107 km from Addis Ababa, the capital city of Ethiopia, and Bahir Dar, the capital city of Amhara regional state, respectively.

The study considered patients with hypertension aged greater than 18 years based on the patient's identification number. Patients who were pregnant or complicated before the study period were not included in the study. In this study, the sample size was calculated using the Schoenfeld formula to obtain statistically significant results.[28] The research was conducted at the University of Gondar; the study's results showed that individuals with hypertension had a 1.39 (95% CI) chance of getting a heart disease, and we used 80% power of the test and 5% level of significance from the standard normal distribution table.[24,29] Therefore, a total of 178 outpatients were randomly selected using simple random selection from all the HTN outpatients registered at the Debre Tabor Hospital from September 2017 to December 2019 and all of them met the inclusion criteria.

Operational Definitions

If a person's SBP is higher than 140 mmHg and/or their DBP is higher than 90 mmHg while they are already taking medication, they are said to have HTN. The British Heart Foundation (BHF) states that there are three stages of HTN:[30,31] pre-stage, which is when the blood pressure is between 120/80 mmHg and 140/90 mmHg in the clinic; Stage I: This is when the blood pressure is between 140/90 mmHg and 160/100 mmHg. Stage II: This is a severe stage, and the blood pressure was greater than 160/100 mmHg.

Adherence to medication can be defined as the extent to which the medication-taking behavior of the patient corresponds with the prescribed antihypertensive medication. In accordance with the Morisky Medication Adherence Scale, medication adherence was assessed using a validated eight-item, five-point Likert response scale, with scores of <6, 6 to <8, and 8 reflecting poor, fair, and good adherence, respectively.[32,33]

Study Variables

Two longitudinal and one survival outcome variables were considered in this study. These were SBP and DBP in mmHg for the longitudinal and time to develop cardiovascular disease complication in months from September 2017 to December 2019. The time to develop cardiovascular disease complications among hypertensive outpatients under follow-up at the DTSH was coded as censored (0) or event (1). The predictors included in this study were sociodemographic and clinical characteristics. Detailed descriptions of predictors are presented in Tables 1–3.

Data Analyses

In this study, both descriptive and inferential statistical analyses were used. Three different models were used: the linear mixed-effects model for bivariate longitudinal measurements of hypertension,[5,6] Cox proportional hazard model for time to develop cardiovascular disease complications,[34] and bivariate joint model for longitudinal and survival sub-models linked by shared random effects.[35]

Let $Y_{ik}(t_{ijk})$ denote the j^{th} observed value of the k^{th} longitudinal outcome for subject i, measured at time t_{ijk}, for $i = 1, \ldots, N$; $k = 1, \ldots, K$, and $j = 1, \ldots, nik$. A bivariate linear mixed model (BLMM) is a common approach, where measurements for different outcomes can be recorded at different times between patients and outcomes and is given by

$$\mathrm{Y_{ik}}\left(\mathrm{t_{ijk}}\right) = \mathrm{X_{ik}}^{\mathrm{T}}\left(\mathrm{t_{ijk}}\right)\beta_{\mathrm{k}} + \mathrm{Z_{ik}}^{\mathrm{T}}\left(\mathrm{t_{ijk}}\right)\mathrm{b_{ik}} + \varepsilon_{\mathrm{ik}}$$

where $\mathrm{X_{ik}}^{\mathrm{T}}\left(\mathrm{t_{ijk}}\right)$ and $\mathrm{Z_{ik}}^{\mathrm{T}}\left(\mathrm{t_{ijk}}\right)$ are row vectors of covariates for subject i, associated with fixed and random effects, respectively, which can vary by outcome; β_k is a vector of fixed effect parameters for the k^{th} outcome; and b_{ik} is a vector of subject-specific random effects for the k^{th}, outcome. We denote the vector of subject-specific random effects for all K outcomes by $\mathrm{b_{ik}} = (\mathrm{b_{i1}}, \mathrm{b_{i2}}, \mathrm{b_{i3}})\mathrm{T}\sim\mathrm{N}(0, \sum)$. The $\varepsilon_{\mathrm{ik}}$ is the corresponding measurement error term such that, $\varepsilon_{\mathrm{ik}}\sim\mathrm{BVN}(0, \psi)$. Assume that the measurement errors of different longitudinal outcomes are independent of each other and that they are also independent of random effects b_{ik}.

For survival outcome, we consider the Cox proportional hazard model,[34] given as:

$$h_i(t) = h_o(t)exp(\alpha_i{}^T X_i(t) + \gamma_i(t))$$

Where $\mathrm{X_i}$ represents the vector of baseline covariates with the corresponding parameter estimates α_i; $h_0(t)$ denotes the baseline hazard function, and $\gamma_i(t)$ is the latent process that captures the association structure between the measurement and event processes.

The data were coded and entered into a statistical package for social science (SPSS) version 26 and R version 4.0.0, with joineRML package was used for analysis. Statistical decisions were made at 5% level of significance.

Results

Descriptive Statistics

In this study, 178 hypertensive patients age greater than 18 years were recruited. Among the patients considered in the studies, 52 (29.2%) developed cardiovascular disease, whereas 126 (70.8%) were censored. The median

survival time of the patients was 15 months and the mean survival time was 14 months. The proportion of female patients who developed cardiovascular disease complications was 32 (17.9%), which was greater than the proportion of male patients 20 (11.3%).

In addition, the majority of HTN patients 94 (52.8%) resided in urban areas. Among them, 31 (17.4%) were developing cardiovascular disease complications, while 84 (47.2%) lived in rural area, among which 21 (11.8%) were developing cardiovascular disease complications. From the total participants, 75 (42.2%) had diabetes; among these, the proportion of cardiovascular disease complications was 31 (17.4%), which was greater than in patients without diabetes. Of the 178 participants, 50 (28.1%) of hypertensive patients had a family history of hypertension; among these, the proportion of cardiovascular disease complications was 29 (16.3%), which was greater than that of patients who had no family history of hypertension.

Patients with clinical Stage-II accounted for large proportion 23 (12.9%) of cardiovascular disease complications compared to pre-stage 10 (5.6%) and Stage-I 19 (10.8%), respectively. Patients who had a history of cardiac disease from their family accounted large proportion 28 (15.7%) of developing cardiovascular disease compared those without a history of cardiac disease from their family. Among 178 participants identified as having high blood pressure, 56 (31.4%) and 55 (30.9%) patients were adhering poorly and fairly, with proportions of developing cardiovascular disease of 24 (13.5%) and 20 (11.3%), respectively.

Table 1 Distribution of Important Socio-Demographic and Clinical Characteristics of Hypertensive Patients Follow-up at DebreTabor Hospital

Variables	Categories	Status (n=178)	
		Censored: n (%)	Event: n (%)
Sex	Female	72 (69.2)	32 (30.8)
	Male	54 (73)	20 (27)
Residence	Rural	63 (75)	21 (25)
	Urban	31 (51.7)	29 (48.3)
FHHTN	No	105 (82)	23 (18)
	Yes	31 (51.7)	29 (48.3)
Diabetic disease	No	82 (79.6)	21 (20.4)
	Yes	44 (85.7)	31 (41.3)
SHTN	Pre stage	53 (84.1)	10 (15.9)
	Stage I	49 (72.1)	19 (27.9)
	Stage II	34 (59.6)	23 (40.4)
FHCVD	No	116 (82.9)	24 (17.1)
	Yes	10 (26.3)	28 (73.7)
Adherence status	Poor	32 (57.1)	24 (42.9)
	Fair	35 (63.6)	20 (36.4)
	Good	59 (88.1)	8 (11.9)

Note: n, sample outpatients.
Abbreviations: FHHTN, family history of hypertension; FHCVD, family history of cardiovascular disease; SHTN, WHO clinical stage of hypertension.

Non-Parametric Analysis for Survival Data

The plots in Figure 1 indicate the Kaplan–Meier (KM) survival functions of HTN patients for different categories of variables. Patients with diabetes had higher survival times than those without diabetes, and patients residing in urban areas had higher survival times than those residing in rural areas. Patients without a history of cardiovascular disease in their families had a longer survival time than those with cardiovascular disease in their families.

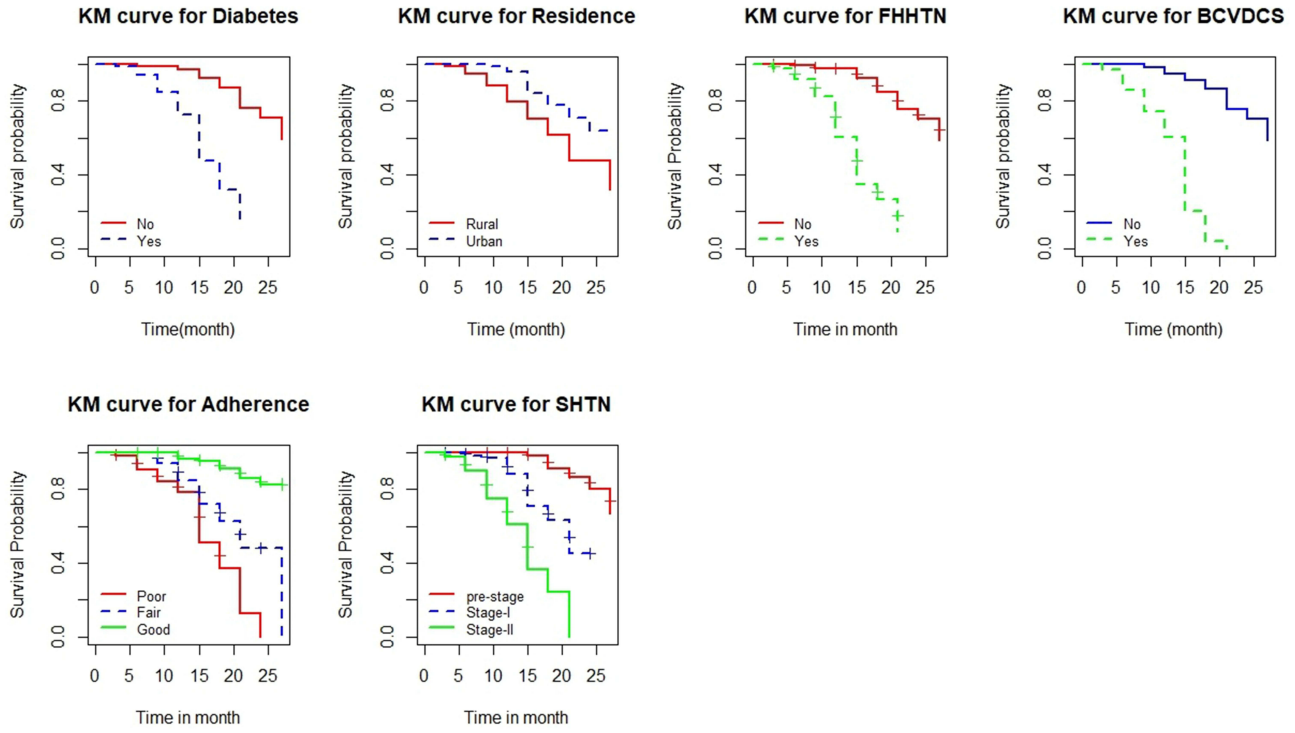

Figure 1 Kaplan–Meier survival estimates of different groups of hypertensive patients at DebreTabor Hospital, Ethiopia.

Table 2 shows the Log rank test of each categorical variable and reveals that family history of hypertension, diabetes, residence, clinical stage of hypertension, and family history of cardiovascular disease were statistically significant at the 5% level.

Table 2 Results of the Log Rank Test for the Significant Categorical Variables of HTN Patients Follow-up at DebreTabor Hospital

Predictors	Categories	DF	Chi-square Statistic	P-value
Sex	Female	1	26.37	0.0001
	Male			
Residence	Rural	1	13.27	0.0003
	Urban			
FHHTN	No	1	36.64	0.0001
	Yes			
Diabetic disease	No	1	76.74	0.0001
	Yes			

(*Continued*)

Table 2 (Continued).

Predictors	Categories	DF	Chi-square Statistic	P-value
SHTN	Pre stage	2	102.74	0.0001
	Stage I			
	Stage II			
FHCVD	No	1	34.42	0.0001
	Yes			
Adherence status	Poor	2	56.86	0.084
	Fair			
	Good			

Abbreviations: FHHTN, family history of hypertension; FHCVD, family history of cardiovascular disease; SHTN, WHO clinical stage of hypertension.

Scaled Schoenfeld residual tests and plots are commonly used to verify proportionality assumptions before fitting the Cox Proportional Hazard (PH) model. According to Table 3 of the global test, each predictor variable and the global test are not statistically significant at the 5% level.

Table 3 Results of Proportionality Assumption for the Significant Categorical Variables of HTN Patients Follow-up at DebreTabor Hospital

Variables	Categories	rho	Chi-Square Statistic	p-value
Age		−0.17029	2.06291	0.151
Sex (ref= Female)	Male	−0.03453	0.06737	0.795
FHHTN (ref=No)	Yes	−0.06311	0.16370	0.686
Diabetic disease (ref=No)	Yes	−0.09774	0.58520	0.444
SHTN (ref= Pre stage)	Stage I	−0.11181	0.60931	0.435
	Stage II	−0.1548	1.16853	0.280
FHCVD (ref=No)	Yes	−0.00465	0.00143	0.907
Adherence status (ref= Poor)	Fair	−0.0216	0.03082	0.861
	Good	−0.11851	1.04430	0.307
Global			5.01631	0.890

Similarly, the Schoenfeld residual plot in Figure 2 also revealed that the resulting curve was parallel and did not show any pattern with time in the covariates of age, sex, clinical stage of hypertension, family history of hypertension, and family history of cardiovascular disease since the proportionality assumption was met.

Cox Proportional Hazards Regression Analysis

A univariate analysis with a 25% level of significance was first performed to identify the variables associated with survival time to cardiovascular disease complication. In the multivariate analysis, variables that were significant at this

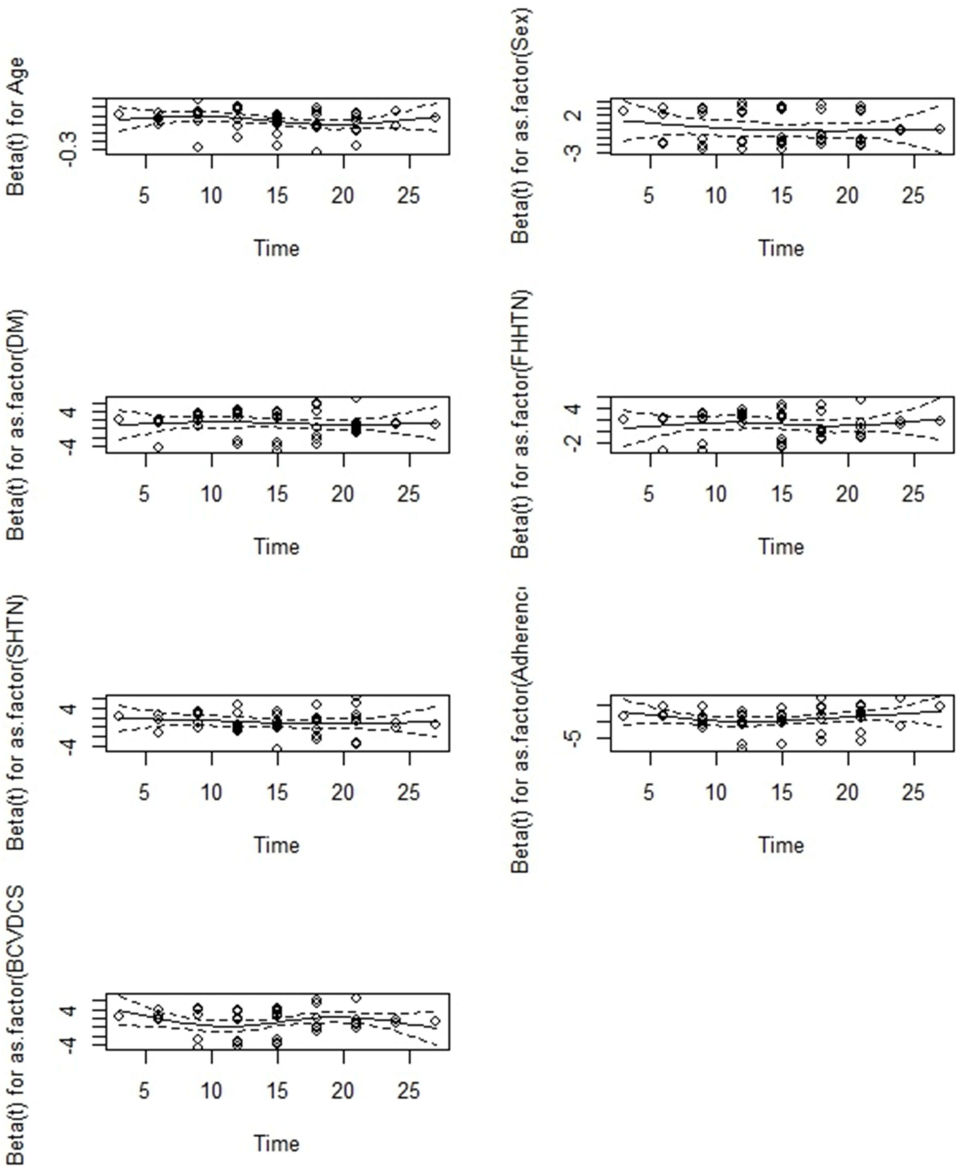

Figure 2 Schonfildes residual plot for significant categorical variables of HTN patients follow-up at DebreTabor Hospital.

level were incorporated. At a 5% level of significance, residence, diabetes, family history of hypertension, stage of hypertension, and family history of cardiovascular disease were statistically significant predictors of survival time to cardiovascular disease complication (Table 4).

Table 4 Cox Proportional Hazards Regression Analysis of Time to CVDC of Hypertensive Patients Follow-up at DebreTabor Hospital

Predictors	Categories	Estimates	Std error	HR	95% CI (L-U)	P-value
Age		0.00465	0.3200	1.0046	0.985–1.024	0.03711
Sex (ref=female)	Male	0.1665	0.3404	1.1812	0.606–2.302	0.62463
Residence (ref=Urban)	Rural	−0.7718	0.3200	0.4621	0.246–0.865	0.0158

(*Continued*)

Table 4 (Continued).

Predictors	Categories	Estimates	Std error	HR	95% CI (L-U)	P-value
Diabetes (ref=No)	Yes	1.394	0.1419	4.033	2.212–9.466	0.0002
FHTN (ref=No)	Yes	1.2932	0.4641	3.644	1.467–9.0521	0.00534
SHTN (ref=pre-stage)	Stage I	1.5449	0.1425	0.6659	1.286–2.242	0.01734
	Stage II	−0.4064	0.1708	1.2089	0.5049–1.573	0.1831
FHCVD (ref=No)	Yes	1.8791	0.1443	6.5480	2.823–10.602	0.0001
Adherence (ref=Good)	Fair	0.2723	0.3779	1.3129	0.626–2.754	0.4712
	Poor	−0.5305	0.4156	0.5882	0.260–1.328	0.20185

Note: ref, reference category of the categorical variable.
Abbreviations: HR, hazard ratio; CI, confidence interval.

Longitudinal Data Analysis

An individual profile plot was obtained to gain insights into the data over time. The individual profile plot shows that there was variability within and between subjects over time in the systolic and diastolic blood pressure of individual patients with HTN. Furthermore, the loess smoothing plots indicated that the average systolic and diastolic blood pressure declined linearly over time (Figure 3). As shown in Figure 4, patients with higher systolic and diastolic blood pressures tended to have a higher risk of cardiovascular disease complications. The blue and red curves represent the mean blood pressure profiles for the cardiovascular disease complication (event) and censored groups, respectively. The mean systolic and diastolic blood pressures were higher in

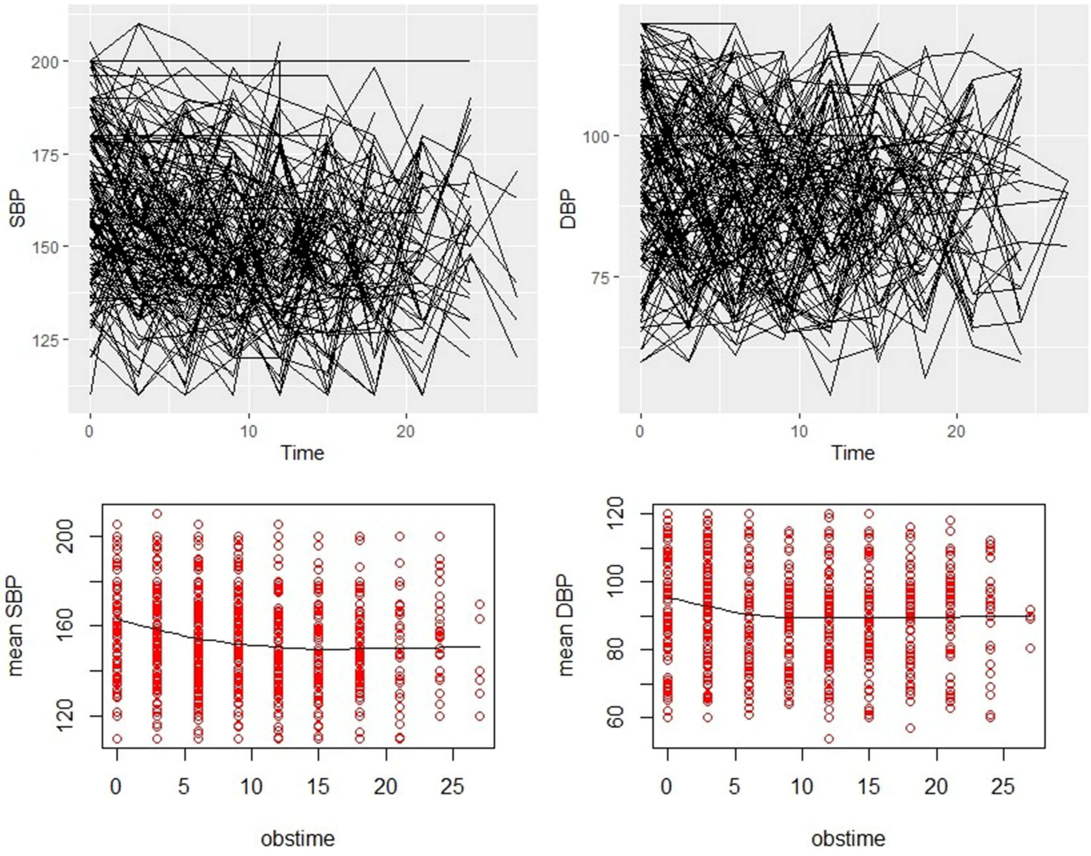

Figure 3 Individual and mean profile plots of the SBP and DBP of HTN patients.

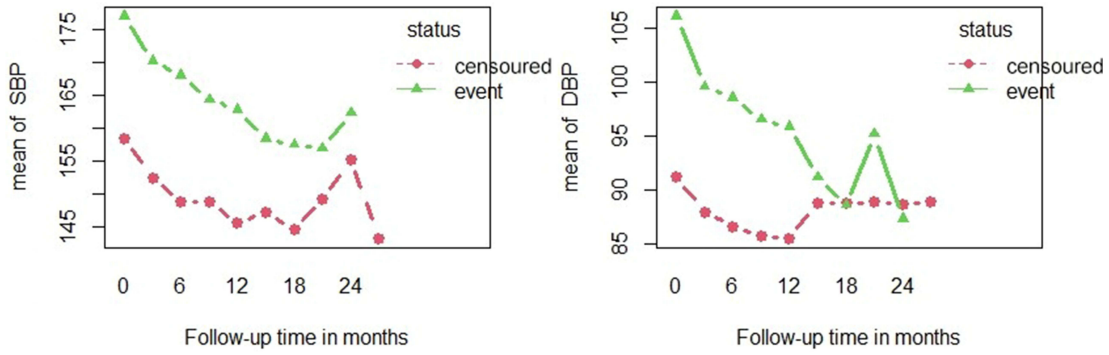

Figure 4 Average trend line of SBP, and DBP over time with cardiovascular disease complication status at DebreTabor Hospital, Ethiopia.

the event group than in the censored group, indicating an association between the risk of cardiovascular disease complications and higher systolic and diastolic blood pressure.

Analysis of Bivariate Longitudinal Mixed Effect Model

Before fitting the joint model, the bivariate longitudinal mixed effects model was fitted using different covariance structures. The model with unstructured (UN) covariance matrices showed that it was significantly better with smaller Akaike information criteria (AIC) and Bayesian information criteria (BIC), which indicates that the model with random intercept and random slope was a better fit for bivariate longitudinal outcomes. The bivariate-mixed effects model showed that age, baseline systolic blood pressure, diabetes, residence, family history of hypertension, clinical stage of hypertension, interaction between baseline systolic blood pressure and stage of hypertension, and observation time were significantly associated with SBP, whereas baseline diastolic blood pressure, diabetes, stage of hypertension, adherence, and observation time were significantly associated with DBP (Table 5).

Table 5 Bivariate Random Mixed-Effects Model for SBP and DBP of HTN Outpatients Follow-up at Debre Tabor Hospital, Ethiopia

Predictors	Categories	SBP		DBP	
		Estimates (se)	p-value	Estimates (se)	p-value
Intercept		120.83(9.98)	0.0001	80.17(6.70)	0.0001
Age		0.129(0.073)	0.0388	0.022(0.039)	0.544
BSBP		0.194(0.072)	0.0007	0.017(0.039)	0.116
BDBP		−0.109(0.089)	0.2202	0.181(0.049)	0.0002
Sex (ref=Female)	Male	−2.966(2.483)	0.2324	−0.844(1.977)	0.67
Diabetes (ref=No)	Yes	8.085(2.661)	0.0001	4.356(1.842)	0.0004
Residence (ref=Urban)	Rural	4.478(2.118)	0.0345	1.059(1.234)	0.391
FHHTN (ref=No)	Yes	7.625(2.837)	0.0072	2.39(1.648)	0.147
SHTN (ref=pre-stage)	Stage I	27.03(14.22)	0.1054	1.361(1.861)	0.464
	Stage II	41.39(12.81)	0.0021	5.843(1.88)	0.002
Adherence (ref=good)	Fair	0.409(1.963)	0.8348	−5.249(1.505)	0.001
	Poor	0.813(1.984)	0.6819	−6.24 (1.441)	0.0001
Time		−0.581(0.131)	0.0001	−0.187(0.066)	0.001

(*Continued*)

Table 5 (Continued).

Predictors	Categories	SBP		DBP	
		Estimates (se)	p-value	Estimates (se)	p-value
Variance covariance estimates		**Intercept for SBP**	**Time for SBP**	**Intercept for DBP**	**Time for DBP**
SBP	Intercept for SBP	178.46	−6.618	41.929	−1.962
	Time for SBP		0.868	0.298	0.453
DBP	Intercept for DBP			86.45	−3.797
	Time for DBP				0.524
Standard deviation		13.88	0.8683	9.29	0.524
Residual standard error					
Sigma2 for SBP	15.30				
Sigma2 for DBP	10.32				

Abbreviations: BSBP, baseline systolic blood pressure; BDBP, baseline diastolic blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; FHHTN, family history of hypertension; FHCVD, family history of cardiovascular disease; SHTN, clinical stage of hypertension.

Joint Model Analysis of SBP & DBP with Time to Cardiovascular Diseases Complication

In this subsection, longitudinal SBP, DBP, and time to cardiovascular disease complications are fitted together. The association between repeated measures of SBP and DBP with survival time to cardiovascular disease complications among hypertensive outpatients using a linear mixed-effects sub-model and a Cox proportional hazards survival sub-model was jointly addressed.

The estimated association parameter (γ) was significantly different from zero ($p < 0.05$), indicating a positive association between SBP, DBP, and survival time with cardiovascular disease complications. The results indicated that the slopes of the SBP and DBP measurements were positively associated with cardiovascular disease complications. A unit increase in SBP and DBP increased the risk of cardiovascular complications.

Comparison of Separate and Joint Models

When evaluating the overall performance of the separate and joint models in terms of model parsimony and goodness of fit, the joint model was preferred because it had smaller AIC and BIC than the separate model. Moreover, the statistical significance of the association parameters provides evidence that the joint model is better than separate models. As Table 6 shows, the estimates of the association parameters in the survival sub-model analysis under the joint model were significantly different

Table 6 Joint Model of Longitudinal SBP & DBP with Survival Time to Cardiovascular Disease Complication

Predictors	Categories	Longitudinal Sub Model				Survival Sub Model		
		SBP		DBP		Estimate (se)	HR	P-value
		Estimate (se)	P-value	Estimate (se)	P-value			
Intercept		120.123 (11.849)	0.0001	78.37(5.311)	0.0001			
Age		0.143(0.068)	0.035			0.003 (0.018)	1.39	0.022
BDBP		0.129(0.083)	0.123	0.189(0.045)	0.0001			

(*Continued*)

Table 6 (Continued).

Predictors	Categories	Longitudinal Sub Model				Survival Sub Model		
		SBP		DBP		Estimate (se)	HR	P-value
		Estimate (se)	P-value	Estimate (se)	P-value			
BSBP		0.359(0.13)	0.006	0.048(0.033)	0.143			
Sex (ref=Female)	Male	−2.243(2.286)	0.327			0.086 (0.607)	1.090	0.887
Residence (ref=Urban)	Rural	3.747(2.275)	0.0996			−1.207 (0.606)	0.299	0.046
Diabetes (ref=No)	Yes	7.037(2.314)	0.002			1.686 (0.716)	5.400	0.0002
FHHTN (ref=No)	Yes	7.929(2.488)	0.001	2.863(1.358)	0.035	1.252 (0.732)	3.496	0.017
SHTN (ref=pre-stage)	Stage I	27.95(14.487)	0.054	1.71(1.862)	0.359	−0.901(1.038)	0.403	0.185
	Stage II	41.03(14.083)	0.004	5.134(1.883)	0.014	0.657 (0.884)	1.93	0.037
FHCVD (ref=No)	Yes					2.253 (0.617)	9.511	0.0003
Adherence (ref=good)	Fair			−5.877(1.307)	0.0001	−1.066(0.778)	0.344	0.642
	Poor			−6.346(1.408)	0.0001	0.286 (0.615)	1.33	0.17
Time		−0.601(0.114)	0.0001	−0.154(0.078)	0.04			
Random effects variance covariance matrix								
	Intercept (SBP)	Time (SBP)	Intercept (DBP)	Time (DBP)				
Intercept (SBP)	180.64	−6.025	46.226	−2.66				
Time (SBP)		0.431	0.298	0.006				
Intercept (DBP)			92.213	−3.647				
Time (DBP)				0.274				
Standard deviation	13.44	0.656	9.603	0.523				
Residuals standard errors								
SBP $-\sigma_1$	15.25							
DBP $-\sigma_2$	10.33							
Association								
SBP $-\gamma_1$						0.65 (0.028)		0.027
DBP $-\gamma_2$						0.963 (0.044)		0.039

Abbreviations: BSBP, baseline systolic blood pressure; BDBP, baseline diastolic blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; FHHTN, family history of hypertension; FHCVD, family history of cardiovascular disease; SHTN, clinical stage of hypertension.

from zero, indicating that the three outcomes were correlated. Therefore, the joint model was preferable for fitting the data better than the separate model.

For a one-year increment in age, the average SBP of the patients significantly increased by 0.1372 mmHg (s. e. = 0.0690), keeping all variables constant.

The average SBP of patients with diabetes was significantly increased by 7.197 mmHg (s.e = 2.2942) compared to patients without diabetes, keeping all other variables constant, which means that patients with diabetes had a higher SBP than patients without diabetes. The average SBP of patients who had a history of hypertension with their family was significantly increased by 9.5498 mmHg (p = 0.0001) compared to patients who had no history of hypertension with their

family. On average, patients who said yes (had a family history of HTN) had higher SBP than patients who did not have a family history of hypertension, keeping all other variables constant.

The parameter estimates of 2.5774 mmHg corresponding to the standard error of 1.2945 for DBP indicated that the average DBP of patients who had a history of hypertension with their family was 2.577 times higher than that of patients who did not have a history of hypertension with their family, with other variables being constant.

The estimated hazard ratio of cardiovascular disease complications in diabetic hypertension patients relative to non-diabetic hypertension patients was 4.984, indicating that the risk of cardiovascular complications among diabetic hypertension patients was 4.984 ($p = 0.0001$) times higher than that among non-diabetic hypertension patients, keeping all other variables constant.

Other variables being constant, the risk of cardiovascular disease complication for patients who had a history of cardiovascular disease with their family were (HR=7.76, p-value = 0.0094) times higher than the risk of developing cardiovascular disease complication for patients who had no history of cardiac disease with their family. Other factors being constant, the risk of cardiovascular disease complications in stage II patients was ($HR = 6.359$, $p = 0.006$) times higher than that in patients whose clinical stage was pre-stage.

Discussion

This study assessed predictors associated with hypertension measurements (SPB and DBP) and survival time to cardiovascular disease complications among outpatients with HTN at DTSH in Ethiopia. Our study identified factors associated with the longitudinal and survival sub-models. The longitudinal sub-model showed that age was an important sociodemographic predictor of SBP, suggesting that average SBP increases with age. According to a study done at Jimma University Specialized Hospital in Ethiopia, showed that an increase in age of one year was linked to a typical rise in SBP in mmHg.[5,36] The noted findings show an age-dependent risk of SBP over time, indicating that an older person has a higher systolic pressure and a higher risk of arterial stiffness due to aging.

The current investigation discovered that people with diabetes had higher average SBP and DBP than those without. The average SBP and DBP of individuals with diabetes were significantly higher than those of non-diabetic patients, which is consistent with earlier research.[5,37,38] This suggests that the coexistence of diabetes mellitus and hypertension is associated with an increase in blood pressure.

Our results are consistent with those of previous studies,[39–41] the average SBP and DBP were higher for patients who had a family history of HTN than for those who had no family history of HTN. A possible reason could be the increased renal proximal sodium reabsorption. The average SBP and DBP with time to cardiovascular disease complications in patients with hypertension were significantly associated with diabetes. A study conducted in the United States revealed a similar finding of an association between increased SBP and DBP and the development of cardiovascular events, which was more pronounced in hypertensive patients with diabetes than in those without diabetes.[42]

Consistent with previous studies,[43,44] the survival sub-models in the current study revealed a higher risk of cardiovascular complications in patients with diabetes than in those without diabetes or diabetes. It was argued that the risk of cardiovascular complications in patients who had developed diabetes had a higher probability of developing cardiac complications than in those who did not develop diabetes. The risk in patients with a family history of cardiovascular disease was higher than that in patients with no family history of cardiovascular disease. Similarly, patients with a family history of cardiovascular disease had a shorter survival time than those without a family history of cardiovascular disease. Studies conducted in Ethiopia and the Philippines revealed similar findings, where the risk of cardiovascular disease complications in patients with a history of cardiovascular disease with their family was higher than that in patients who had no history of cardiac disease with their family.[24,29] This is because the parents' genetic code is then copied into every cell of the child's body during development, and genes control every aspect of the cardiovascular system, from the strength of the blood vessels to the way cells in the heart communicate. Genetic variations (mutations) in a single gene can affect the likelihood of heart disease development.[35,36]

Limitations

This study used secondary data from a single hospital. In addition, the authors did not observe an interaction effect of the predictors; hence, the results may vary when considering more hospitals all over Ethiopia and including interaction

effects. Therefore, researchers should consider hospitals across Ethiopia and include the interaction effects of the predictors in the model.

Conclusion

The estimate of the association between SBP and DBP was positively significant with time to develop cardiovascular disease in patients with HTN. Hence, in this study, bivariate mixed effects and a Cox proportional hazards survival sub-model were preferred based on the minimum AIC value criterion. The joint bivariate mixed-effects model analysis showed that outpatients with HTN with a family history of HTN and clinical stage II HTN developed cardiovascular disease complications and had higher average SBP and DBP than their counterparts. Similarly, HTN outpatients with diabetes had higher SBP and DBP than their counterparts, and in general, SBP and DBP stabilized over the follow-up period of treatment. In this study, age, residence, and family history of cardiovascular disease for SBP, age for DBP, and residence and adherence to developed cardiovascular disease complications were not statistically significant. In light of the results of this study, the authors suggested that health professionals and concerned bodies should focus on patients with diabetes, family history of HTN, clinical stage II HTN, family history of cardiovascular disease, aged and poor adherence patients to control HTN, and cardiovascular disease complications using technology, such as text messaging,[45] and mobile application[46] to promote cardiovascular health at early stage. It is important to provide early interventions for these groups of people, especially for those with family history.

Abbreviations

AIC, Akaike information criteria; BDU, Bahir Dar University; BIC, Bayesian information criteria; CI, confidence Interval, DTHS: DebreTabor specialized hospital; FHCVD: Family history of cardiovascular disease; FHHTN: Family history of hypertension; HR: Hazard ratio; HTN, Hypertension; KM, Kaplan Meier; NCD, Non-communicable disease; SBP: Systolic blood pressure; SHTN: Stage of hypertension; WHO, World Health Organization.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the first author upon reasonable request.

Ethical Approval and Consent to Participate

The data used in the current investigation were collected by the health staff for outpatient treatment. To use the previously collected data, ethical clearance was obtained from the Ethical Review Board of Bahir Dar University (ref. no. RCS/0102/12). Informed consent was waived due to the anonymized data. This study was conducted in accordance with the Declaration of Helsinki, which states that in medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage, and/or reuse.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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