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Time to Cardiovascular Complications and Associated Factors among Hypertensive Patients under treatment at Government Hospitals in Amhara Region

Awoke Seyoum Tegegne*

Department of Statistics, Bahir Dar University, Bahir Dar, Ethiopia

***Corresponding Author**
Awoke Seyoum Tegegne, Department of Statistics, Bahir Dar University, Bahir Dar, Ethiopia.

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Abstract

Background

Cardiovascular disease complication is a current public issue throughout the world. This study aimed to investigate the time to cardiovascular complication and associated factors among hypertensive patients under treatment at government Hospitals in Amhara region, North-West Ethiopia.

Methods

A retrospective cohort study design was conducted on 1014 hypertensive patients. The data were secondary and had been taken from a chart of each patient, recorded at government hospitals in Amhara region, Ethiopia, whose follow ups were from 2018 to 2023.

Result

Among the predictors, baseline complication significantly affected the variable of interest in the current study. Hence, the risk of developing cardiovascular disease complications for patients, who had baseline complications, was 4.684 times that of patients without baseline complications (P-value= 0.0004). The hazard of hypertensive patients who had related disease was 2.437 times that of patients without the related disease (p-value ≤ 0.001). Smoking status also significantly affected the event in this study which indicates that the Expected hazard of developing cardiovascular disease complications for a smoker patient was 3.463 times that of a non-smoker patient (p-value ≤ 0.001). The hazard of developing cardiovascular disease complication for stage 2 hypertensive patients was 3.406 times that of stage 1 patients (P-value= 0.012).

Conclusions

The result of the Cox proportional hazard model indicates that baseline complications, the existence of the related disease, smoking status, and stage of hypertension significantly affected cardiovascular disease complications of hypertensive patients at a 5% significance level. Due attention should be given to smoker hypertensive patients, hypertensive patients with baseline complications, hypertensive patients with related disease and hypertensive patients of stage 2.

Keywords: Cox-Proportional Hazard Model, Governmental Hospitals, Hypertension, Cardiovascular Disease Complications, Time to Complication

List of Abbreviations: CVD= Cardio vascular disease, HIN= Hypertension, APHI= Amhara public health institution, HR= hazard ratio, CI= confidence Interval.

1. Introduction

Cardiovascular disease (CVD) is the advancement of pathology that happens in the vascular framework [1]. Cardiovascular disease is related to at least one quality of a person that improves the probability of building up an illness [2]. Hypertension is the most common risk causes for CVD, such as heart disease or stroke and chronic kidney diseases, and the leading cause of premature death worldwide [3].

As a result, 116 million people have one or more forms of heart disease or stroke, and almost 25 million people are expected to die from heart disease or stroke by 2030, WHO and the United States

Centers for Disease Control (CDC) and prevention launched the Global Hearts Initiative (GHI) in 2016 [4]. Around the world, the essential hazard factors are expanding because of urbanization [5]. Globally, hypertension is a public health problem in both economically developed and developing nations [6]. Hypertension was the leading global contributor to premature death in 2015, accounting for almost 10 million deaths and over 200 million disability-adjusted life years [7].

The African Union has recognized CVDs as one of the landmasses' greatest well-being challenges after Human Immunodeficiency Virus (HIV) and Acquired Immunodeficiency Syndrome (AIDS) [8]. In Africa, CVDs are the largest contributor to the total of non-communicable disease, accounting for 38.3% [9]. Africa disproportionately bears the brunt of CVD burden and has one of the highest risks of dying from non-communicable diseases (NCDs) worldwide [10]. There is currently an epidemiological transition on the continent, where NCDs is projected to outpace communicable diseases within the current decade [9].

Ethiopia, a country in Sub Saharan Africa, have many hypertensive patients suffering from Cardiovascular disease complications [11. In Ethiopia, due to low economic development and urbanization, CVD complications are growing fast and becoming a basic public health issue due to different factors [12]. A systematic review and meta-analysis of subjects aged 15 years and above showed that the prevalence of hypertension among the Ethiopian population was estimated to be 19.6 % and that the prevalence was higher in the urban population (23.7 %) than in rural and urban (14.7%) [13]. Despite significant effort of the Ministry of Health to reduce such complications, there are still obvious difficulties in tackling the burden of Cardiovascular disease complications and considered as a top priority for public health in Ethiopia [14]. Previous studies conducted in the country indicate that Cardiovascular disease complications ranges from 1% to 20% [15]. Ethiopia recently adopted the WHO 2020 cardiovascular risk score charts to be used for the primary prevention of Cardiovascular disease since the score is more applicable for resource poor countries like Ethiopia [16]. In the country, the laboratory tests for serum cholesterol and blood glucose are not widely available, and a non-laboratory WHO cardiovascular risk prediction chart can be used in areas where these tests are not available or un affordable [17].

Amhara region, one of the 11 well known regions in Ethiopia, where many hypertensive people are also living with cardiovascular disease [18]. One of the zonal level and cross sectional studies conducted previously on hypertension in the region indicates that its over all prevalence across the region was 11.4% [19]. One of the previous studies also indicate that early detection and treatment of modifiable risk factors can lower an individual's risk of developing cardiovascular disease complication and helps to identify an easy interventions [20]. With out doing such interventions, cardiovascular disease complications lead for severe, uncontrolled high blood pressure and this further leads for significantly increase of the risk of heart failure, stroke and coronary artery disease [21].

A single institutional based studies with limited variables on cardiovascular complications among hypertensive patients have been conducted previously [22]. Zonal based and district level studies have been also conducted on CVD complications [23]. However such studies do not used to generalize for regional policy implications as a whole. Such studies also recommend for conducting region wide studies on CVD complication among hypertensive patients and this helps in developing region wide policy implications [23]. As far as author's knowledge is concerned, there is scarcity of region wide research conducted on the complication of cardiovascular disease among hypertensive patients. A region wide research helps for regional government policy implication and for correct directives for its implementations [24]. Therefore, the main aim of this study was to investigate the time to cardiovascular disease complications and associated factors among hypertensive patients under treatment at government hospitals in Amhara region, whose follow ups were from September, 2018 to April, 2023. This study also aimed to assess whether factors affecting the variable of interest in the developed country also worked in the study area.

2. Operational Definitions

2.1 Adherent Versus non-Adherent: A patients was considered as medication adherent if he/she adhered at least 95% of the prescribed medication , otherwise, the patient was classified as non-adherent to the prescribed medication.

2.2 Existence of related diseases: These refers to the presence of two or more chronic diseases in an individual.

3. Methods and Participants

3.1 Study Area and Population: The study was conducted in Amhara region, which is one of the eleven regions in Ethiopia. In the region, there are referral, zonal and district public hospitals in which many HIV patients are served for treatments. In the current study about 18 governmental hospitals namely Felege-Hiwot Comprehensive and specialized, Gondar referral, Debre Tabor, Woldia, Dessie, Ataye , Enat, Debre Birhan, Debre Markos, Fenote Selam, Injebara, Tefera Hailue, Metma Hospital, Debark, Mehal Meda, Mota and Kemissie Hospitals were selected based on the number of HIV patients served in the hospital. An institutional-based retrospective cohort study design from 2018-2023 was conducted for the current study. The participants under this study were hypertensive patients who enrolled in the first ten months of 2018 and followed up to 2023. Hence, the study period was five years of follow ups.

3.2 Source of Data and Collection Procedures

The data used for the current study was obtained as secondary source obtained from Amhara Public Health institution (APHI). The name of participants were removed from the list and only their codes or chart number was given for the current study. Data for the current study were collected using a standardized data

extraction checklist by reviewing Hypertension follow-ups from ART registration books, and SMART care electronic database. For the current study, two sources of data were considered. The first source was patients' charts which was main source of data for the current study and the second source was the SMART care electronic database.

Data from the first sources were collected by a trained health professionals with short term training (orientation about the variables needed for the current study). Data from the second source (SMART care electronic database) were collected by information technology professionals. SMART care had only a few key data elements like existence of related disease, stage of HIN and level of adherence.

3.3 Sample Size and Sampling Technique

A sample of 1014 hypertensive patients whose follow-ups were between September 2018 and April 2023 in 18 government hospitals in the region was included in the study. The hospitals were selected based on the number of hypertensive patients served in the hospitals. Hence, a purposive sampling technique was applied for sample selection. After selecting the hospitals based on number of hypertensive patients, patients at the selected hospital were randomly selected to be representative for the patients at the selected hospitals.

3.4 Data Collection Procedures

A data extraction check-list was designed and used to extract the required secondary data. The quality of data was monitored by data controllers from a pediatric section of the hospital.

3.5 Inclusion Criteria

All hypertensive patients receiving the treatment, who visited all government hospitals in Amhara region whose follow ups, from September 2018 to April 2023, were included in the sampling frame.

4. Variables in the Study

4.1 Response Variables: The response variable for the current study was time to cardiovascular complication measured in months.

4.2 Independent Variables: The predictor variables considered in this study with their categories were gender(male, female) , age (<=49, >=50), smoking status(no, yes), alcohol usage(no, yes), residence area (rural , urban), existence of related disease(no, yes), stage of HIN(stage I, stage II) and level of adherence(adherent, non-adherent).

5. Methods of Data Analysis

5.1 Semi-Parametric Models: The Cox-Proportional Hazard Model was used for estimating time-varying, time-independent, continuous, and discrete covariates [25]. Kaplan-Meier estimate and log-rank test were also used for all categorical variables to know whether there is a significant difference among the categories of each predictor variable [26]. Cox proportional hazard model was also fitted to examine the effects of different predictive factors on the time to CVD complication of hypertensive patients [27]. STATA statistical software, version 14 was used for analysis purposes at a 5% level of significance.

6. Time to Event Sub Model (Survival Analysis and Cox-PH Model)

6.1 Survival Function: The survival function S(t) is defined as the probability that the survival time of a randomly selected subject is greater than or equal to a specified time, t [28, 29]. Thus, it gives the probability that an individual survives beyond a specified time. Moreover, the distribution of survival time is characterized by three functions: (a) the survivor ship function, (b) the probability density function, and (c) the hazard function.

Let T be a random variable associated with the survival times, let t be the specified value of the random variable, and let f (t) be the underlying probability density function of the survival time T. The survival function, S (t) is given as [23].

$$S(t) = p(T > t = 1 - F(t), t \geq 0$$

Where F (t) is the cumulative distribution function, which represents the probability that a subject selected at random would have a survival time less than or equal to some sated value t.

$$F(t) = p(T \leq t) = \int_0^t f(u)du, \quad t \geq 0$$

The relationship between $S(t)$and $f(t)$ is given as

$$f(t) = \frac{d}{dt}F(t) = \frac{d}{dt}(1 - s(t)) = -\frac{d}{dt}S(t), \quad t \geq 0$$

6.2 Hazard Function: The hazard function is widely used to express the risk or hazard of death at some time t and is obtained from the probability that an individual dies at time t, conditional on he or she having survived to that time. The hazard function, typically denoted as h (t), represents the risk or likelihood of an event, such as death, occurring at a specific time t. It quantifies the instantaneous rate of the event per unit of time, assuming that the individual has survived up to time t. The hazard function is derived from the probability that an individual experiences the event within a small interval (t, Δt), given that they have survived up to time t. The hazard function considers the probability that the random variable associated with an individual's survival time, T lies between t and t +Δt, conditional on T being greater than or equal to t, written as $P(t \leq T < t + \Delta t / T \geq t)$. It is the instantaneous probability of having an event at time (per unit time) given that one has survived up to time [30].

6.3 Kaplan–Meier Estimate: the number of observed events at t (j), j= 1, …,r . The K–M estimator of S (t) is the commonly used non-parametric estimator of the survival function, which is designed to estimate the survival probabilities from observed survival times both censored and uncensored [30]. K–M plots

were used to determine whether there was a difference in survival time between groups of covariates under investigation. However, the Kaplan–Meier (KM) plot cannot be used to determine whether the survival time of hypertensive patients differed according to each covariate instead, the log rank test is used.

6.4 Log-Rank Test: The log-rank test was used for comparing two or more survival curves in the case that the distribution is right-skewed and censored data sets [31]. On the other hand, the Wilcox-on test was used when there is no censoring in the data set [32]. The log-rank test, developed by Mantel and Haenszel (1959), is a non-parametric test for comparing two or more independent survival curves. Since it is a non-parametric test, no assumption about the distributional form of the data is needed. This test is most powerful in detecting higher cured proportions in one group than in other groups [31] . The log rank test statistic for comparing two groups was as follows [25]:

$$\chi^2_{logrank} = \frac{\sum_{j=1}^{r}\left[d_{1j} - n_{1j}\frac{d_j}{n_j}\right]^2}{\sum_{j=1}^{r}\frac{n_{1j}n_{2j}d_j(n_1-d_j)}{n_j^2(n_j-1)}}$$

where r is the total number of rank ordered events. d_{1j} is the number of failures at the j^{th} time of the 1^{st} group, and is the number of failures at the j^{th} time of the 2^{nd} group, d_j is the number of failures at the j^{th} time of the $d_{1j} + d_{2j}$ group, n_{1j} is the number at risk at the j_{th} time of the 1^{st} group. n_{2j} is the number at risk at the j^{th} time of the 2^{nd} group, and n_j is the number at risk at the j_{th} time of the (d_{1j}+ d_{2j}) group.

7. Assumption of PH Model

The Cox model relies on the assumption of proportional hazards (PH) across different covariates. In a regression type setting, this means that the survival curves for two or more strata (determined by the particular choices of values for the study of interest) must have hazard functions that are proportional over time [33]. Specifically, the model assumes that the hazard of each covariate does not change over time [34]. Violation of the PH assumption may lead to misleading and erroneous scientific findings. If the hazard of variable increases or decreases over time, the usual Cox Proportional Hazard model ignores the time-dependent changes [35].

7.1 Checking the PH Assumption

The proportional hazards (PH) assumption was checked using statistical tests and graphical diagnostics considering the Schoenfeld residuals. The result in current study indicates that the Schoenfeld residuals were independent of time and a graphical diagnostics indicates that there were a random pattern against time, which is evidence for occurrence of PH assumption [36].

7.2 The Impact of Dropouts on Data Analysis

Patients who defaulted from treatment will develop drug resistant virus and further results in treatment failure and high risk of clinical events [37]. A logistic regression was conducted to assess whether or not missing values were affected by previous results; and this indicated that dropouts were independent of the previous outcomes (χ^2_1 = 0.2018, p = 0.964). Hence, dropout patients did not have reasons from their previous visits; therefore dropout trend was Missed Completely at Random (MCAR) [38].

8. Results

8.1 Descriptive Statistics

Of the total of 1014 Hypertensive patients considered, 23.9 % of them developed CVD complications while the rest 76.1% were censored. The median survival time of patients to develop cardiovascular complications was 38 months ($\hat{S}$ (t=38) = 0.5). The incidence rate of CVD was 0.88 % per month. The baseline characteristics of participants with the occurrence of proportion and median time-to-developing CVD across the predictor variables are summarized as indicated in Table 1.

Variable	Categories	Status		Median survival time	Total
		Censored	Event		
		Frequency (%)	Frequency (%)	Months	Frequency (%)
Gender	Female	273(26.9)	131(12.9)	36	404(39.8)
	Male	366(36.1)	244(24.1)	40	610(60.2)
Age	≤ 49	277(27.3)	113(11.2)	40	390(38.5)
	≥ 50	462(45.6)	262(25.8)	36	724(71.4)
Smoking status	No	307(30.3)	113(11.1)	40	420(41.4)
	Yes	232(22.9)	362(19.7)	32	594(58.6)
Alcohol usage status	No	366(36.1)	150(14.8)	40	516(50.9)
	Yes	173(17.1)	325(32.1)	37	498(49.1)
Baseline complications	No	379(37.4)	134(13.2)	40	513(50.6)
	Yes	160(15.8)	341(33.6)	36	501(49.4)
Residence	Urban	362(35.7)	312(30.8)	38	674(66.5)
	Rural	177(17.5)	163(16.1)	37	340(33.5)

Related disease	No	401(39.5)	316(31.2)	40	717(70.7)
	Yes	138(13.6)	159(15.7)	36	297(33.3)
Stage of HTN	Stage 1	571(56.3)	105(20.2)	---	676(66.7)
	Stage 2	168(53.5)	170(22.3)	36	338(75.8)
Adherence	Adherent	477(47.1)	120(11.8)	41	597(58.9)
	Non-adherent	162(16.0)	255(25.1)	37	417(41.1)

Table 1: Baseline Characteristics of Hypertensive Patients

Among the total of 1014 hypertension patients, 26.9 % were female, of these about 23.2% were censored. Among the total male hypertensive patients, about 24.1% developed CVD. The median survival time of time-to-developing CVD for female hypertensive patients was 36 months and those of male patients were 40 months. Regarding the age group, patients ≥50 years were observed the highest number of developing CVD cases followed by an age group of ≤49 years while the remaining 25.8% and 11.2 % were censored for the age group >50 years, and ≤49 years respectively.

Among smoker hypertensive patients included in this investigation, about 19.7% developed CVD complications. On the other hand, among the non-smoker hypertensive patients, 11.1% developed CVD and the rest were censored. The median time to develop CVD complications for smoker patients was 36 months and that of non-smoker patients was 40 months.

Out of the participants, 49.1% were alcohol consumers. Among the drunker hypertensive patients, 32.1 % developed CVD complications. The median time to develop CVD complications for drunker hypertensive patients was 37 months and that of non-drunker hypertensive patients was 40 months.

Among the total hypertensive patients in this study, 49.4% had baseline complications and among these, 33.6 % developed CVD complications and 15.8% were censored. The median time to develop CVD complication for patients who developed baseline complication was 36 months and for those of the patients without a baseline, the complication was 40 months (Ref. Table1). Table 1 also indicates that among the total participants under this investigation, 33.3 % had other related diseases and of these, 15.7% developed CVD complications with a median time of 36 months.

Regarding the stage of hypertension, hypertensive patients of stage 2 had greater cases of events as compared to stage 1. Hence, about 22.3% of the hypertensive participants of stage 2 developed CVD complications and 53.5% were censored. Among the participants, about 58.9% were adherent to medication and the rest were non-adherent patients. Among non-adherent patients, 25.1% developed CVD complications with a median time of 37 months.

8.2 The Kaplan- Meier Estimate for Hypertension Patients

Survival times of hypertensive patients were compared for different groups using the K-M plot and to get real differences between groups we used the log-rank test. Non-parametric survival analysis revealed information on the shape of the survival and hazard function as indicated in Figure1 and Figure2 respectively.

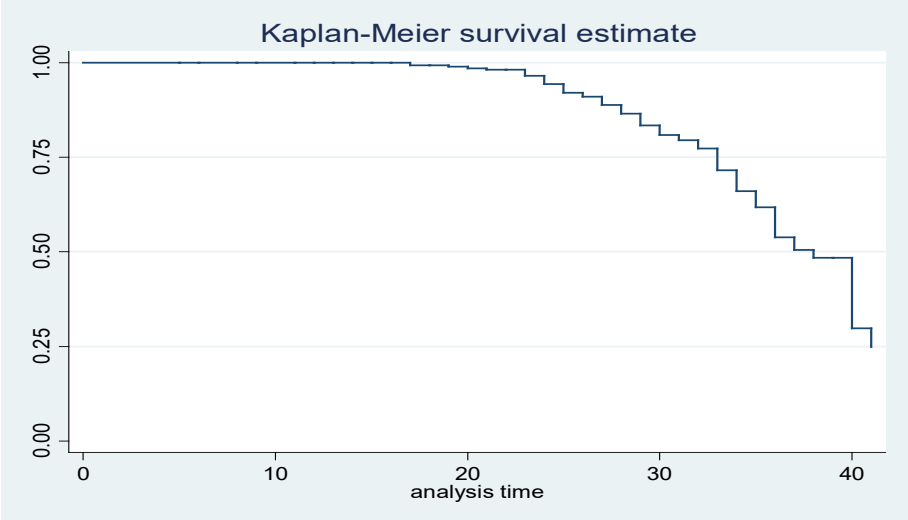

Figure 1: The K-M Plots of Survival Function of Hypertension Patients

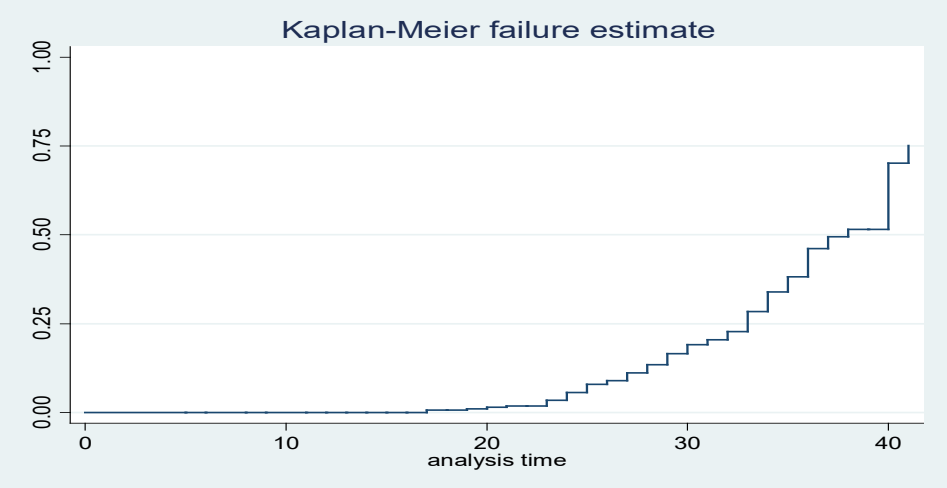

Figure 2: The K-M Plots of Hazard Function of Hypertension Patients

In Figure 1 of the KM curve, the horizontal axis shows the time-to-developing CVD complication, whereas the vertical axis shows the probability of survival. At the initial time, the survival curve shows the estimated value of the survival function is unity from the origin until some point in time, implying that during the time of giving anti-hypertensive treatment there were low numbers of developing CVDS, and the survival probability declines with follow-up times. For the hazard plot of hypertensive patients shown in Figure 2, the horizontal axis shows the time-to-developing CVD of the hypertensive patients, whereas the vertical axis shows the cumulative hazard of developing CVD. The curve indicates that the hazard of developing CVD has increased with the follow-up time.

8.3 Kaplan-Meier Curves of Time to CVD Complications Across Categories of Predictor Variables

KM curves of the survivor function of different predictors were used to compare the survival functions across the categories of predictor variables. Separate graphs for age categories and smoking status are indicated here for visualization.

8.4 Survival Curves of Time to CVD Complication of Hypertension Patients by Age Categories

As it is indicated in Figure 3, the KM curves of time to CVD complications for hypertensive patients with age ≤ 49 had better survival time as compared to patients with age ≥ 50.

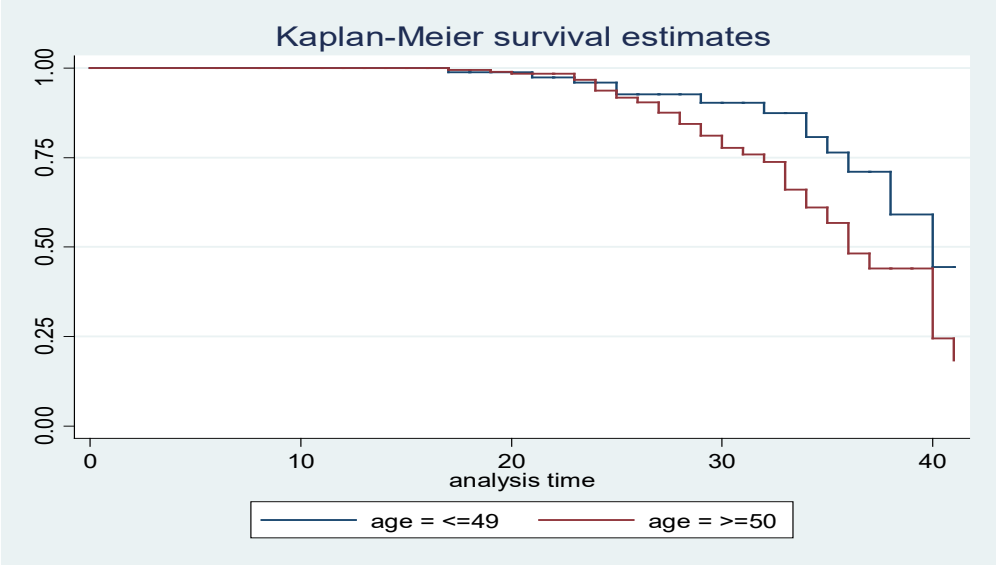

Figure 3: Kaplan-Meier Curves of Time to CVD Complication by Age Category of Patients

8.5 Survival Curves of Time to CVD of Hypertension Patients by Smoking Status

Figure 4 shows the distribution of survival experience of hypertensive patients by smoking status and the result indicates that non-smoker hypertensive patients experienced a good control of CVD complications as compared to smoker hypertensive patients.

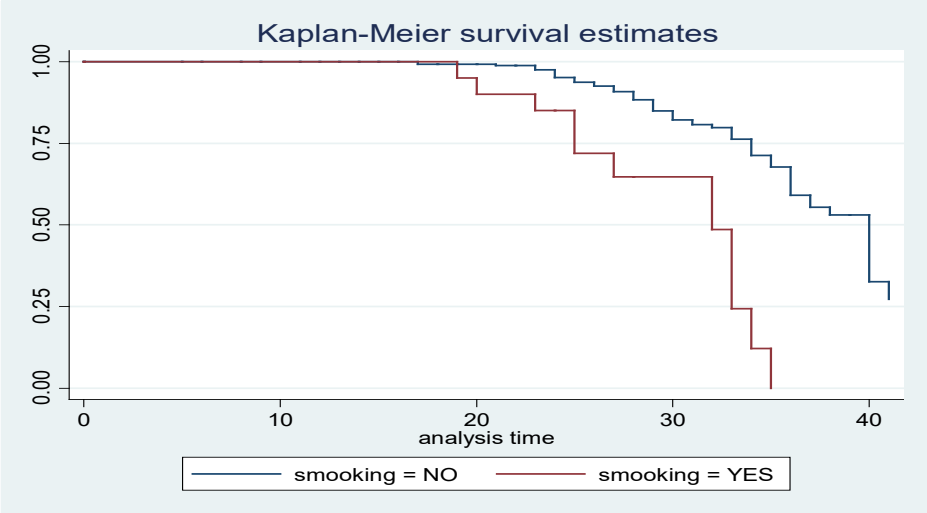

Figure 4: Kaplan-Meier Curves of Time to CVD by Smoking Status

8.6 Survival Curves of Time to CVD Complication by Existence of Related Disease

Similarly, the Kaplan-Meier curves of time to CVD complication for hypertensive patients with related diseases had faster growth as compared to those patients without the related diseases. Hence, hypertensive patients without the related disease had better survival experiences as compared to hypertensive patients with the related disease. The distribution of survival experience of hypertensive patients of stage 1 had better survival time as compared to those patients with stage 2 and the distribution of survival experience of medication-adherent hypertensive patients had better survival time as compared to non-adherent patients.

8.7 Log Rank Test for Hypertensive Patients

The results of the log-rank test have been summarized in Table 2, it evaluates whether the above differences in survival experience are significant or not. Therefore, the log-rank tests indicated in Table2 also investigate whether there is a significant difference between categories of variables (Refer, Table 2).

Variables	Categories	Log rank test		
		Chi-square	DF	Pr.>Chi-square
Gender	Female Male	0.34	1	0.5605
Age	≤ 49 ≥ 50	5.15	1	0.0233*
Smoking status	No Yes	28.57	1	0.001*
Alcohol usage	No Yes	0.25	1	0.6185
Baseline complication	No Yes	10.59	1	0.0011*
Residence	Urban Rural	0.87	1	0.3515
Related disease	No Yes	10.61	1	0.0011*
Stage of HTN	Stage-I Stage-II	13.99	1	≤0.001*
Adherence status	Adherent Non-adherent	1.03	1	0.0106*
*stands for statistical significance				

Table 2: Log Rank Test for Hypertensive Patient

From the result in Table 2, it is evident that there was a statistically significant difference in survival experience across the categories of age, smoking status, baseline complication, related diseases, the stage of hypertension, and adherence status at a 5% level of significance.

8.8 Uni variable Analysis

Single covariate Cox proportional hazard model analysis is an appropriate procedure that is used to screen out potentially important variables before directly including them in the multivariable model. Accordingly, uni variable analysis was performed to examine the effect of each covariate on time to CVD complication of hypertensive patients and to select the variables to be included in the multivariable analysis.

From the result of the uni variable analysis indicated in Table 3, we can observe that the covariate age, smoking status, baseline complications, related disease, stage of hypertension, and medication adherence were significantly associated with the waiting time of hypertensive patients. Whereas: the variables gender, residence, and alcohol usage status were not significant at the 25% level of significance.

Variable	β	Se. (β)	Z	P>z	95% Conf. interval	
Gender	-0.1327	.2057275	-0.56	0.572	0 .553	1.388
Age	0.6606	.5910157	2.16	0.030*	1.064	3.521
Adherence	0.2570	.3380645	0.98	0.226*	0.775	2.158
Smoking Status	1.5211	1.449099	4.80	≤ 0.001*	2.461	8.513
Alcohol usage status	0.1193	.2776301	0.48	0.628	0.695	1.826
Baseline complication	0.7201	.4781289	3.09	≤0.001*	1.302	3.242
Related disease	0.8666	.6715933	3.07	≤0.001*	1.368	1.368
Stage of HTN	1.5407	2.176379	3.30	≤0.001*	1.872	11.64
Residence	0.2891	.4293895	0.90	0.369	0.711	2.508
*stands for statistical significant variables						

Table 3: Univariate Cox Proportional Hazards Model Test Results

8.9 Multivariate Analysis

The Multivariable Cox proportional hazards model was fitted by including all covariates having significant effects in the uni variable analysis at a 25% level of significance. Covariates that became insignificant in the uni variable analysis were then removed from the model by using the stepwise variable selection method.

From the final results presented in Table 4, it is evident that the expected time to cardiovascular complication for hypertensive patients were significantly affected by smoking status, baseline complications, stage of hypertension, related disease status, and medication adherence status.

Hypertensive patients who had related diseases had a risk exposed to CVD complications. Hence, the hazard of hypertensive patients who had related disease was 2.437 times that of patients without the related disease (HR=2.437, 95% CI: (1.399, 4.248) and p-value ≤ 0.001)). In other words, the time to cardiovascular disease complication for hypertensive patients with related disease was shorter than that of hypertensive patients without related diseases.

The smoking status of hypertensive patients significantly affected the time to cardiovascular complications. Hence, the expected hazard of developing cardiovascular disease complications for a smoker patient was 3.463 times that of a non-smoker patient (HR=3.463, 95% CI: (1.845, 6.498) and p-value≤ 0.001)).

The expected hazard of developing cardiovascular disease complications for stage 2 hypertensive patients was 3.406 times that of stage 1 patients (HR=3.406, 95% CI: (1.304, 8.883) and p-value= 0.012)). Hence, the expected time to cardiovascular disease complication for stage 2 hypertensive patients was shorter than that of stage 1 hypertensive patients.

The risk of developing cardiovascular disease complications for hypertensive patients with baseline complications was 1.973 times that of patients without baseline complications (HR=1.973, 95% CI: (1.241, 3.138) and p-value ≤ 0.001)) (Refer to Table4).

Variable	Categories	β	Se. (β)	Z	p>|z|	HR	[95% CI of HR]	
Age	≤49 (Ref.)	-	-	-	-	-		
	≥50	0.354	1.424	1.10	0.273	1.424	1.757	2.679
Smoking status	No (Ref.)	-	-	-	-	-		
	Yes	1.242	1.112	3.87	≤ 0.001*	3.463	1.845	6.498
Baseline complication	No (Ref.)	-	-	-	-	-		
	Yes	0.670	0.467	2.87	≤0.001*	1.973	1.241	3.138
Related disease	No (Ref.)	-	-	-	-	-	-	
	Yes	0.891	0.691	3.14	≤0.001*	2.437	1.399	4.248
Stage of hypertension	Stage-I (Ref.)		-	-	-	-		
	Stage-II	1.225	1.666	2.50	≤0.001*	3.406	1.304	8.883
Medication Adherence	Adherent(Ref.)	-	-	-	-	-		
	Non-Adherent	0.370	0.267	2.67	0.011*	1.873	1.441	3.238
*Stands for statistical significant variables								

Table 4: Multivariable Cox Proportional Hazard Model

The risk of developing cardiovascular disease complications for medication non-adherent hypertensive patients was 1.873 times that of adherent patients (HR=1.873, 95% CI: (1.441, 3.238) and p-value = 0.011)).

9. Assumption Checking for Cox Proportional Hazard Model

9.1Test of Proportional Hazard Assumption by Schoenfeld Residual: The result indicated that the goodness of fit test statistic was insignificant (p-value= 0.1841). From the result, it can be concluded that the proportionality assumption of the Cox PH model was satisfied. Hence, the model fits the current data correctly.

To check the proportionality assumption, the time-dependent covariates were generated by interacting of the predictors with time. However, the result showed that the coefficients for the interaction term obtained were statistically insignificant ($p > 0.05$).

10. Discussion

Baseline complication is the one with a highly significant effect on the time to develop CVD complication. This finding revealed that hypertension patients who had baseline complications were found to be associated with shorter survival time to develop CVD complications, and it has been magnified by the hazard rate of 1.973 times greater than that of a patient who had not the baseline complication. This finding is in line with [39]. The result of the previous study states that, as baseline complications increased, the hazard to develop CVD complications in hypertensive patients also increased [17].

The other important predictor for the time to cardiovascular disease complication is smocking status. The hazard rates of smoker hypertensive patients are more likely to be exposed to developing CVD than that of non-smokers which implies that the time to cardiovascular complication for smoker hypertensive patients was shorter than that of non-smoker hypertensive patients [18]. This result is supported by another study [19] which stated as smoking cigarettes is one of the risk factors for hypertensive patients to develop cardiovascular disease complications.

The existence of related disease is also another significant predictor variable related to the risk of developing CVD in hypertensive patients. Patients who had related diseases had a higher hazard rate than those without the related disease. This result is similar to another study [20]. Patients with stage-II hypertension have a shorter survival time to develop CVD than patients with stage-I hypertension [20].

Medication adherence plays a significant contribution to the development of CVD complications. Hypertensive patients, who do not properly adhere to the prescribed medication, expose to the hazard of CVD complications [20, 21].

11. Conclusion

From the result, it can be clearly shown that hypertensive patients who smoke cigarettes, patients with baseline complications, patients with advanced stage, having related diseases and those of medication non-adherent hypertensive patients were exposed to the risk of developing CVD complications as compared to their counterparts. Identifying significant predictors for the time to cardiovascular complication helps for regional policy implication and for the health staff to conducted health related education while, patients will come for hospital for treatment. The descriptive result of the study showed that out of the total 1014 hypertension patients about 37% experienced the event of developing CVD complication. Among the predictors, baseline complication, smoking status, the existence of the related disease, medication adherence, and stages of hypertension statistically and significantly affected the time to develop CVD complication.

As a recommendation, health-related education should be given to hypertensive patients to tackle the problems related to CVD complications. This requires a good understanding of the conventional risk factors and the less known and newly emerging risk factors and the ways of controlling those factors. The health

staffs should give special attention to hypertensive patients with baseline complications, smoker patients, non-adherent patients, and patients with stage 2 HTN and related diseases. The Ministry of Health (MOH) should create a database system that can share information on disease history, clinical data, and treatment for chronic diseases since these aspects require continuous updating

11.1 Theoretical and Practical Significance of the Current Study

The contribution of the study was assessed based on the criteria formulated by Whetten (1989). The key criterion for assessing research, whether an academic paper or thesis is to what extent it is considered a contribution to knowledge should include both a contribution to the current theoretical understanding of the studied phenomena, and to the practice in a certain field [40]. The heightening of these forms of contribution naturally depends on the focus and nature of research conducted [41].

This paper briefly and systematically introduced the way how to use Cox proportional hazards model for time to cardiovascular complication for hypertensive people. Hence, this study has also summarized the literature review of application of longitudinal data analysis for health science conducted throughout the world, particularly in the study area. Consequently, this help in building a theoretical framework for finding empirical evidences for further investigation and used as a benchmark for further investigation for field of study. Current investigation had many practical contributions like regional policy implications and for evidence based interventions particularly for the health staff conducting for health related educations and counseling.

Declarations

Ethical Approval and Consent to Participate: The data used in the current investigation were secondary and there was no chance of obtaining respondents to obtain consent to participate form from participants, because this fact, informed consent has been waived. To secure the confidentiality and compliance with the Declaration of Helsinki within the manuscript of patient-related data, the name of patients was not given to investigators, rather id number and important variables related to the current investigation were given to researchers. The waiver was done by Bahir Dar University Ethical approval committee, Ethiopia with reference number: RCS/1412/2018. Hence, the Bahir Dar University Ethical Committee approved and waived this study.

Data Availability: The data used for the current investigation is available within the corresponding author and will not be disclosed to keep the privacy of participants.

Consent for Publication: The manuscript submitted to this journal is not published anywhere or didn't consider for publication by any other journal.

Competing Interests: Authors declared that there is no conflict of financial interest between the author and institutions.

Author's Contribution: The corresponding as well first author made substantial contributions to conception and design, acquisition of data, took part in drafting it critically for important intellectual contact, agreed to submit to this journal, gave final approval of the version to be published, and agreed to be accountable for all accepts of the work.

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