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Survival Analysis of Time to Cardiovascular Disease Complication of Hypertensive Patients at Felege Hiwot Referal Hospital in Bahir-Dar, Ethiopia: A Retrospective Cohort Study

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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ABSTRACT

Background: Cardiovascular disease complication is the current issue throughout the world.
Objective of the Study: The aim of this study was to analyze the major risk factors which lead to cardiovascular disease complication in hypertensive patients.
Method: A retrospective cohort study with one hundred fifty three hypertensive patients have been taken from a hospital record at the Felege Hiwot Referral Hospital, Bahir Dar, Ethiopia, during 2012 to 2016. Kaplan-Meier comparison and Cox proportional hazard model were applied.
Results: From the long rank test result, Patients who had baseline cardiovascular disease significantly differ from patients who hadn't complication for a shorter cardiovascular disease complication time. From the Cox regression result, the risk of developing cardiovascular complication rises 3.7%, when a single year increment of age (p value=0.0486). The possibility of a patient to develop cardiovascular disease who lives in rural area was 0.377 times lower than a patient who lives in urban area (P value=0.0275). The risk of developing cardiovascular complications in a short period was 8% and 6%, depending on 10 MmHg increment of systolic and

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diastolic blood pressure respectively. Patients who had baseline complication were found to be associated with shorter survival time within their pain, that hazard ratio was 4.684 times than that of patients who had not baseline complication (P value=0.0004).
Conclusion: From the Cox proportional hazard model, there were five major factors that affect the cardiovascular disease complication time of hypertension patients. Those are: residence, baseline cardiovascular complication status, baseline diastolic blood pressure, baseline systolic blood pressure and baseline age at 5% significance level.

Keywords: Hypertension; cardiovascular disease.

ABBREVIATIONS

CVD= Cardiovascular disease
HTN= Hypertension
HR= Hazard ratio
KM= Kaplan Meier

1. INTRODUCTION

1.1 Background of the Study

Disorders related to the cardiovascular system are termed as cardiovascular diseases and which are the main cause of death in the world [1] statistically 17.3 million deaths in 2013 [2]. Hypertension is one type of non-communicable chronic diseases which is called the silent killer [3]. It is the most well known risk factor for cardiovascular disease complication [4].

Cardiovascular disease is a unique double burden challenge for the whole of Africa [5,6]. The estimated number of hypertensive patients in Sub-Saharan Africa in 2025 will be 150 million [7]. Additionally, there is an evidence which shows complications of hypertension such as stroke and heart failure are increasing at an alarming rate in this region [8] even though the control of this condition in Africa is low [9].

In Ethiopia, due to economic development and urbanization, non communicable diseases and their related risk factors are growing and becoming a double burden [10]. Some hospital based studies in the country showed that the prevalence of death due to cardiovascular disease was high. As a result, the impact of cardiovascular disease and associated risk factors is the current issue [11–13].

A study, which was conducted in Bahir-Dar, Ethiopia showed that hypertension and its impact on economic development and human health is particularly critical since urbanization is expanding, lifestyles are changing, the literacy rate is low, and people are still living in poverty in the country [14]. High blood pressure has been a major health problem, concern in Felege Hiwot Referral Hospital patients in Bahir-Dar, Ethiopia. The overall view and the rate of increment of hypertensive patient's year by year lead to frustration. Since hypertension is the leading cause of cardiovascular disease complication, the current situation calls for intervention in view of cardiovascular disease complication. In Ethiopia, there are insignificant researches conducted on cardiovascular disease complication specifically for hypertensive patients. Therefore, to fill this gap, the researcher investigated to conduct this research. The main aims of this study were to identify the major risk factors which lead to cardiovascular disease complication on hypertensive patients.

2. MATERIALS AND METHODS

2.1 Source of Data

The study was conducted at the Felege Hiwot Referral Hospital, which is found in Bahir-Dar city. The hospital is located in the Northwest of Amhara Region at a distance of 565 kilometers from Addis Ababa, the capital city of Ethiopia. Bahir-Dar is the leading tourist destinations in Ethiopia, which has a variety of attraction sites in the nearby Lake Tana and the source of the Blue Nile. Secondary data were used for the study.

2.2 Target Population

The target population of this study is patients under the follow-up of anti-hypertension treatment at Felege-Hiwot Referral Hospital from September 2012 to February 2016.

2.3 Data Collection

All patients who visited Felege-Hiwot Referral Hospital between 2012-2016, were included in the sampling frame. Here each patient has a

chart/record with a distinctive identification number. One medical doctor and two experienced statisticians were involved in the data collection under the supervision of the investigator.

2.4 Inclusion and Exclusion Criteria

All patients who fulfilled all variables of interest and visited this hospital more than once as a hypertensive patient were included in the study. But pregnant women were excluded.

2.5 Sampling Design

The availability of data in the hospital was not sufficient. Only 196 hypertensive patients' data were available. As a result, by using inclusion and exclusion criteria 153 patients were included in the study. Since the number of study population was small, all patients were considered.

2.6 Study Design

The study was a retrospective cohort type because it investigates time to cardiovascular disease complication since 2012-2016.

2.7 Methods

2.7.1 Survival data analysis

Survival analysis consists of a set of specialized statistical techniques used to study response time data. In analyzing such data, the main objective is to determine the length of time interval spent in a state and the transition probabilities from the current state to the previous state. The interest of this statistical tool is mainly focused on two distinguishing features of time to event data. Primarily, duration times are positive values usually exhibiting highly skewed distribution and therefore the assumption of normality may be violated. Secondly, censoring may occur or the true duration is not always observed or known, that is, some subjects potentially being unobserved for the fulltime to cardiovascular disease complication. The main characteristic of these data is the issue of censoring which occurs when the periods of time to event occurrence for some individuals cannot be completely explained. The process of censoring and truncation make these data unsuitable to analyze with usually regression method and hence, the appropriate techniques and analyses, usually called survival analysis. Kaplan-Meier estimators were applied to estimate survival curves and log rank test was used for the comparison between the variable categories and Cox model was applied. And with this understanding, we start our method by giving the definition of censoring, Kaplan-Meier and Cox proportional model.

2.7.1.1 Censoring

The time period confinement for survival data gives rise to considerations specific to survival analysis, censoring and truncation. A censored observation is one whose value is incomplete due to random factors for each individual. The most common form of censoring for incomplete data is right censoring where a subject's follow-up time terminates before the outcome of interest is observed. The second one is left censoring, an observation is said to be left censored if all that is known is that the individual developed the event of interest prior to the beginning of the study. And an observation is categorized into interval censored if it is only known that the event of interest occurs within an interval of time without the knowledge of when exactly happened. Here the study used only the right censored ones.

2.7.1.2 Kaplan-Meier estimation

The Kaplan-Meier method is a non parametric method used to estimate the probability of survival past given time points. Furthermore, the survival distributions of two or more groups of a between-subjects factor can be compared for equality. The KM estimator consists of the product of a number of conditional probabilities resulting in an estimated survival function in the form of a step function. It is a non parametric estimator of the survivor function S (t).

$$\hat{S}(t) = \prod_{t_j < t} (1 - \frac{d_j}{n_j})$$

Where d_j , is the number of individuals who experience the event at time t_j , and, n_j is the number of individuals who have not yet experienced the event at that time.

2.7.1.3 Cox proportional hazards model

Now a day, the Cox proportional hazards model is the most commonly used multivariate approach for analyzing survival time data in medical research. It is a survival analysis,

regression model, which describes the relation between the event incidence, as expressed by the hazard function and a set of covariates. The Cox model is given as:

$$h(t) = h_o(t_i)\exp(b_1x_1 + b_2x_2 + \ldots\ldots\ldots + b_px_p).$$

Hazard function h (t) is dependent on a set of p covariates (x_1, x_2,.. , x_p), whose impact is measured by the size of the respective coefficients (b_1, b_2,. .., b_p). The term h_0 is called the baseline hazard, and is the value of the hazard if all the x_i are equal to zero (the quantity exp (0) equals 1).

2.8 Analysis

SAS version 9.2 and STATA version 12.0 were used for analysis. A long rank test used for survival ability comparison by categorical independent variables. Cox proportional hazard model was applied to fit the associations of predictive factors with time to cardiovascular disease complication.

3. RESULTS AND DISCUSSION

3.1 Results

3.1.1 Descriptive statistics for categorical variables

From the total of 153 of Hypertensive patients considered, 22% of them developed CVD complication while the rest 78% were censored. The mean time of patients to develop cardiovascular complication was 18.7 months. The incidence rate was 1.2 percent per each month.

The graphical assessment in below (Fig. 1) shows that the chance of developing other cardiovascular disease for a patient who lives in CVD was greater than that of a patient free from. Comparing the survivor functions between a patient live in baseline complication and free from baseline complication, a patient who lives in baseline complication had shorter cardiovascular complication time as compared with a patient who hadn't (log-rank test P<0.0001 explained in Table 1).

From multiple covariates analysis, the CVD complication risk in terms of hazard ratio showed that a patient live in residence rural is 0.377 times lower than those patients who live in urban (HR=0.377). When the age of the patient increases by a single year, the risk of developed CVD is increased by 3.7% (HR=1.037). The hazard of cardiovascular disease complication for HTN patients with a 10MmHg increases of diastolic blood pressure was 1.060times greater (HR= 1.060). When the systolic blood pressure value of a patient increased by 10 MmHg units, the probability of CVD complication was 1.080times greater (HR= 1.080). In other words, when the value of the systolic blood pressure increased by 10MmHg, the risk to develop cardiovascular disease rise by 8%. Looking at the baseline complication status, patients who had baseline complication were found to be associated with shorter survival time within their pain, that hazard ratio was 4.684 times that of a patient who had not the baseline complication (HR=4.684) (more in Table 2).

3.2 Discussion

This study tried to estimate and compare the survival time to cardiovascular disease complication with a given time of hypertension patients and to determine major predictive factors on the cardiovascular disease complication time of hypertension patients. From Kaplan-Meier estimate, the long rank test explained that the survival ability between baseline complication categories were significant. The Cox's proportional hazard model fitted using complete case analysis found five variables that can serve as predictive factors on the complication cardiovascular disease of hypertension patients. These are age, baseline complication, residence, systolic blood pressure and diastolic blood pressure. Age of a patient is an important predictor for the cardiovascular disease complication for hypertension patients. This study shows that the hazard ratio of being at risk of cardiovascular disease increased as the age of hypertension patient increase. This result is in accordance with the study [6,15]. Gender is not a significant predictor variable in this finding but some hospital based cross- sectional studies in Kenya showed that females were more at risk than male, this difference may arise due to study type [16]. In the previous study in Japan, proteinuria had a significant association with the risk of cardiovascular disease. This result contrast with this finding may be due to nature of population, geographical difference, study type and this investigation was concerned only hypertensive patients [17].

Table 1. Kaplan-Meier survival comparison between categorical variables

Variable	Mean complication time (in months)	Test of equality over group		
		Log Rank test		
		Chi-square	Df.	Sig.
Gender				
Male	26.098	1.0292	1	0.3103
Female	39.270			
Residence				
Rural	35.2866	1.2692	1	0.2599
Urban	39.270			
Diabetes mellitus				
Positive	35.2866	1.4188	1	0.2336
Negative	34.8697			
Proteinuria				
Negative	36.0544	1.5195	1	0.2177
Positive	8			
Medication type				
One medication	32.8835	0.5418	2	0.7627
Two medication	32.1452			
Above two	36.8571			
Baseline complication				
Yes	27.9311	61.9091	1	<.0001*
No	41.6540			

*Note that Sig. = significance value and Df.= degree of freedom as well as * means there is a significant association.*

Table 2. Cox result

Variable	Parameter	Se.	Wald	Df	Sig.	Hr.
Gender						
Male	0.35390	0.41080	0.7422	1	0.3890	1.425
Female(Ref)						
Residence						
Rural	-0.97654	0.44288	4.8619	1	0.0275	0.377
Urban(Ref)						
age	0.03659	0.01855	3.8902	1	0.0486	1.037
Diabetes status						
Positive	-0.08416	0.43215	0.0379	1	0.8456	0.919
Negative (Ref)						
Proteinuria status						
Negative	1.51492	1.03730	2.1329	1	0.1442	4.549
Positive (Ref)						
Systolic BP	0.0789	0.0297	7.05	1	0.0034	1.08
Diastolic BP	0.05853	0.01907	9.4220	1	0.0021	1.060
Number of medication type						
One medication	0.74073	0.77177	0.9212	1	0.3372	2.097
Two medication	0.65232	0.77607	0.7065	1	0.4006	1.920
Above two (Ref)						
Baseline complication						
Yes	1.54424	0.43669	12.5052	1	0.0004	4.684
No(Ref)						

Note that, SE: Standard Error; Df: Degree of freedom; HR: Hazard Ratio; Ref: Reference category

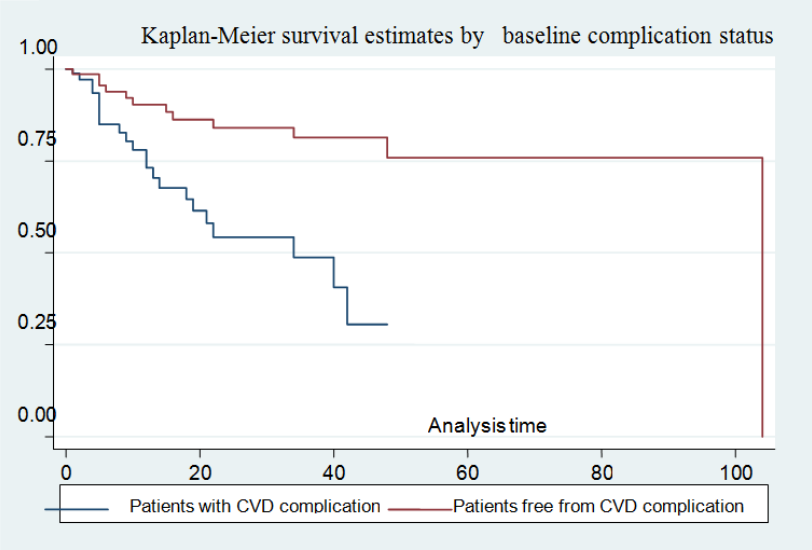

Fig. 1. KM graph comparison between baseline cardiovascular status categories

Another factor that causes cardiovascular disease complication on the hypertension patient is patient's baseline cardiovascular disease complication. The hazard of a patient who had baseline cardiovascular complication has been higher as compared to a patient who hadn't baseline cardiovascular disease which is compatible with a study [18,19]. The residence of a patient is also one of the risk factors for cardiovascular disease complication of hypertension patients. This study shows that the hazard ratio of a patient who lives in urban is higher than who lives in rural but a cross-sectional study conducted in Kenya, Tanzania, Nigeria and Namibia explained that hypertension was the most frequently observed risk factor for CVD in both urban and rural communities in sub-saharan Africa region [20].

Diastolic blood pressure and systolic blood pressure are prognostic factors that significantly predict the cardiovascular disease complication time of hypertension patients. The hazard ratio of a hypertension patient to become a cardiovascular disease patient with higher diastolic blood and systolic blood pressure is linear. The result is consistent with a study [21–23]. Unlike American heart association, Diabetes Millets hadn't a statistically significant impact in this study [24].

4. STUDY LIMITATIONS

This study had some limitations: the first one is the study used data from a single hospital. The second limitation is the total number of patients may not be enough because of lack of sufficient data availability in the hospital. Finally, all variables under the study were taken only on baseline.

5. CONCLUSION

The aim of this study was to identify factors that affect time to the cardiovascular complication of hypertension patients. From the survival data analysis log rank test, Patients, who had baseline complication much contributed to smaller time to cardiovascular complication at 5% of a significant level. From the Cox proportional hazard result, residence, age, baseline systolic blood pressure, baseline diastolic blood pressure and baseline complication were the major factors that affect time to the cardiovascular complication of hypertension patients. The cardiovascular complication time of hypertensive patients who had baseline complication is lower than those patients who hadn't. The cardiovascular complication times of hypertensive patients who live in urban had a smaller time of complication than that of a patient who lives in rural. Finally, special attention for hypertension patients with higher blood pressure, older age, live with cardiovascular disease and those who live in urban areas are necessary.

ETHICS APPROVAL

Ethics approval was given by the research committee.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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APPENDIX

SAS version 9.2 Syntax for Cox proportional hazard model

```
data y;
input gender residence age diabetes status protienuria status number of
medication type systolic blood pressure diastolic blood pressure CVD complication
status baseline complication time;
cards;

Insert data here
;
run;
proc print data=y;
run;
proc phreg data=y;
class gender residence diabetes status protienuria status number of medication type
baseline complication;
model time(CVD complication status 1) = gender residence age diabetes status
protienuria status number of medication type baseline complication systolic blood
pressure diastolic blood pressure ;
run;
```


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