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TIME-TO-OPTIMAL CONTROL OF HYPERTENSION USING KAPLAN-MEIER ESTIMATOR, COX PROPORTIONAL HAZARD AND WEIBULL MODEL

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ABSTRACT

Hypertension is a worldwide public health challenge. The study investigated the time it takes to attain an optimal control of hypertension and the major factors that influence the control in Specialist Hospital, Sokoto. A retrospective cohort study was conducted involving 300 patient records. The population consisted all hypertensive patients on follow-ups at Specialist Hospital Sokoto from1st February, 2015 to 1st February, 2021.Statistical Package for the Social Sciences version 20 and R software were used for descriptive, Kaplan-Meier estimator, Cox Proportional Regression (CPH) Model and Weibull Regression Model analyses.
Hypertensive patients attain an optimal control after a median survival time of 40.43 (at 95% CI: 33.67- 47.19) months (3.37 years) and mean survival time of 44.18 (CI: 37.24-51.12) months (3.68 years). The CPH analysis revealed that the factors that influenced an optimal control of hypertension were body mass index (BMI) (P <0.001), number of anti-hypertensive drugs (P <0.001), place of residence (P = 0.030). similarly, the Weibull model revealed that the factors that affected an optimal control of hypertension were BMI (P <0.01), number of anti-hypertensive drugs (P <0.001), place of residence (P = 0.042) and educational status (P = 0.036).
In conclusion, BMI, number of anti-hypertensive drugs, Place of residence, Educational status. should be watched out during management of hypertensive patients. This also call for an extension of this study through a prospective design to be able to measure the effect of other factors in the achievement of optimal control of hypertension.

Keywords: Hypertension, Time-to-Event, Optimal control, Cox proportional hazard, Weibull model

INTRODUCTION

Hypertension is a worldwide public-health challenge and a leading modifiable risk factor for cardiovascular disease and death. According to the World Health Organization (WHO) Global Health Observed Report, globally, the overall prevalence of Hypertension in adults aged 25 and over was around 40% in 2008 and was is estimated to cause 7.5 million deaths, about 12.8% of the total of all deaths worldwide. Blood pressure is summarized by two measurements, systolic and diastolic, which depend on whether the heart muscle is contracting or relaxed between beats. Normal blood pressure at rest is within the range of 100-140 mmHg systolic (top reading) and 60-90 mmHg diastolic (bottom) (WHO 2013). Elevated blood pressure means that your heart needs to work harder than normal, putting both your heart and arteries under great strain. On average, people with uncontrolled hypertension are seven times more likely to have a stroke and six times more likely to develop congestive heart failure (Giles *et al.*, 2005).

In sub-Saharan Africa, emerging epidemiological data suggest that hypertension has become a major public health challenge (Addo & Leon, 2007). Wide variation in prevalence, awareness and treatment of hypertension are reported within and between countries of the region (Kayima *et al*., 2013, Akinlua *et al.*,2015). Various factors ranging from non-standardization of survey methods, use of varying thresholds for diagnosis of hypertension and non-report of age standardized prevalence rates make pooling of the data generated from various studies practically impossible. The overall result is dearth of evidence to inform robust health policies targeted at control of hypertension epidemic in the region (Odili *et al*., 2017).

In Nigeria, 38% of adult aged 18 years and above were hypertensive. Out of the hypertensive subjects, 60% were aware of their status, one-third were receiving treatment and 12% had their blood pressure under control (Odili *et al*., 2020).

Therefore, the aim of this research is to carry out a retrospective cohort study to investigate the time it takes to have an optimal control of hypertension and the factors that influence the control using Kaplan-Meier (K-M) estimator, Cox PH model and Weibull model.

METHODOLOGY

A retrospective cohort study was conducted with a total number of 300 participants. The population consisted all hypertensive patients who had been under follow-up at Specialist Hospital Sokoto from February, 2015 to 31stFebruary, 2021.

Secondary data from the hospital registry was used to obtain the data. The calculated sample size for this study was 300 hypertensive patients of source population who received treatment from Specialist Hospital Sokoto form February, 2015 to 31stFebruary, 2021. A data collection form was used for the data collection. Information was collected from patient's hospital file. Patient sociodemographic data and blood pressure information were examined and carefully collected.

The response (dependent) variable of the study is the survival time of the hypertensive patients, that is, the length of time from the start date of taking antihypertensive drugs unit the date of optimal control of hypertension (or censor), to be measured in months. The independent variable of age, gender, occupation, educational status, place of residence of residence, systolic blood pressure (SBP), diastolic blood pressure (DBP), Anti-hypertensive drugs, Body mass index.

The completeness and consistency of the data were checked, coded, and double entered Statistical Package for the Social

Sciences(SPSS) version 20 (IBM Corporation, Armonk, NY, USA) and R version 3.0.2 statistical software were used for analysis.

Kaplan-Meier (K-M) Estimator

The Kaplan-Meier estimator, also known as the product limit estimator, is a non-parametric statistic used to estimate the survival function from lifetime data (Kaplan-Meier, 1959). Suppose that k patients have events in the period of follow-up at distinct times $t_1 < t_2 < t_3 < t_4 < t_5 < \ldots < t_k$. As events are assumed to occur independently of one another, the probabilities of surviving from one interval to the next may be multiplied together to give the cumulative survival probability (Clark *et al*., 2003). The estimator of the survival function $\widehat{S}(t)$ is given by:

$$\widehat{S}(t) = \prod_{t:t_i \le t} \left(1 - \frac{d_i}{n_i}\right) \quad (1)$$

Where t_i is a time when at least one even (optimal control) happened, while d_i is the number of events that happened at time t_i and n_i is the number of participants that have not yet had an event or censored.

Cox Proportional Hazard Model

The Proportional Hazards Model, proposed by Cox (1972), has been used primarily in medical testing analysis model the effect of secondary variables on survival. Its strength lies in its ability to model and test many inferences about survival without making any specific assumptions about the form of the life distribution model (Hangal, 2011). Let $X_i = (X_i, \ldots X_{ip})$ be the realized values of the covariates for subject *i*. The hazard function for the Cox proportional hazard model has the following form:

$$\lambda(t / X_i) = \lambda_0(t)\exp(\beta_1 X_{i1} + \ldots + \beta_p X_{ip}) = \lambda_0(t)\exp(X_i.\beta) \quad (2)$$

The above expression gives the hazard function at *t* for subject *i* with covariate vector (explanatory variables) X_i (Cox, 1972).

Weibull Proportional Hazard Model

The parametric proportional hazards model is the parametric kind of the Cox Proportional Hazards Model. It is given with the similar form to the Cox PH models. The hazard function at time t for the particular patient with a set of p covariates $(x_{1,} x_2, \ldots, x_p)$ is given as follows:

$$h(t / X) = h_0(t)exp(\beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_p x_p) = h_0(t)exp(\beta' X) \quad (3)$$

Suppose that survival times are assumed to have Weibull distribution with scale parameters λ and shape parameter α, so, that the survival and hazard function of $W(\lambda, \alpha)$ distribution is given by:

$$S(t) = exp(-\lambda t^{\alpha}) \quad (4)$$

$$h(t) = \lambda\alpha(t)^{\alpha-1} \quad (5)$$

The hazard rate increases when $\alpha > 1$, decreases when $\alpha < 1$ and it becomes constant when $\alpha = 1$, which is a special exponential case.

RESULT

Descriptive Statistics

Table 1: Summary table for some covariates

S/n	Covariates	Mean	Median	Standard deviation	Minimum	Minimum
1	Time (Months)	21.50	19.08	15.96	1.00	95.00
2	Age (years)	52.52	53.00	12.36	21.00	87.00
3	SBP (mmHg)	154.64	150.00	23.04	130.00	260.00
4	DBP (mmHg)	93.73	90.00	13.16	80.00	140.00
5	Weight (kg)	68.00	67.90	5.19	55.00	85.70
6	Height (m)	1.64	1.63	0.44	1.51	1.80
7	BMI	25.10	25.00	1.61	21.10	30.20
8	No. of anti-hypertensive drugs	2.85	3.00	0.90	1.00	6.00

The mean and median follow-up time of the patients were 21.50 months and 19.10 months respectively, with a standard deviation of 16.00 months and minimum and maximum of 1.00 months and 95.00 months, respectively. While the mean and median age of the patients were 52.57 and 53.00 years, respectively with a standard deviation of 12.36 years, and minimum and maximum of 21.00 years and 87.00 years, respectively. The mean value of Systolic Blood Pressure (SBP) is 155.64mmHg and the median is 150.00mmHg with a standard deviation of 23.04mmHg and minimum and maximum of 130.00mmHg and 260.00mmHg, respectively. The mean value of Diastolic Blood Pressure (DBP) is 93.73mmHg and the median is 150.00mmHg with a standard deviation of 13.16mmHg and minimum and maximum of 80.00mmHg and 140.00mmHg, respectively. The mean and median weight of the patients were 68.00kg and 67.90kg respectively with a standard deviation of 5.19kg and minimum and maximum of 55.00kg and 85.70kg. The mean and median height of the patients were 1.72m and 1.63m respectively with a standard deviation of 0.44m and minimum and maximum of 1.51m and 1.80m. The mean and median body mass index (BMI) were 25.40 and 25.30 respectively, with a standard deviation of 1.61 and minimum and maximum of 21.10 and 30.20. The mean and median number of anti-hypertensive drugs administered were 2.86 and 3.00 respectively, with a standard deviation of 0.90 and minimum and maximum 1.00 and 6.00

Nonparametric analysis

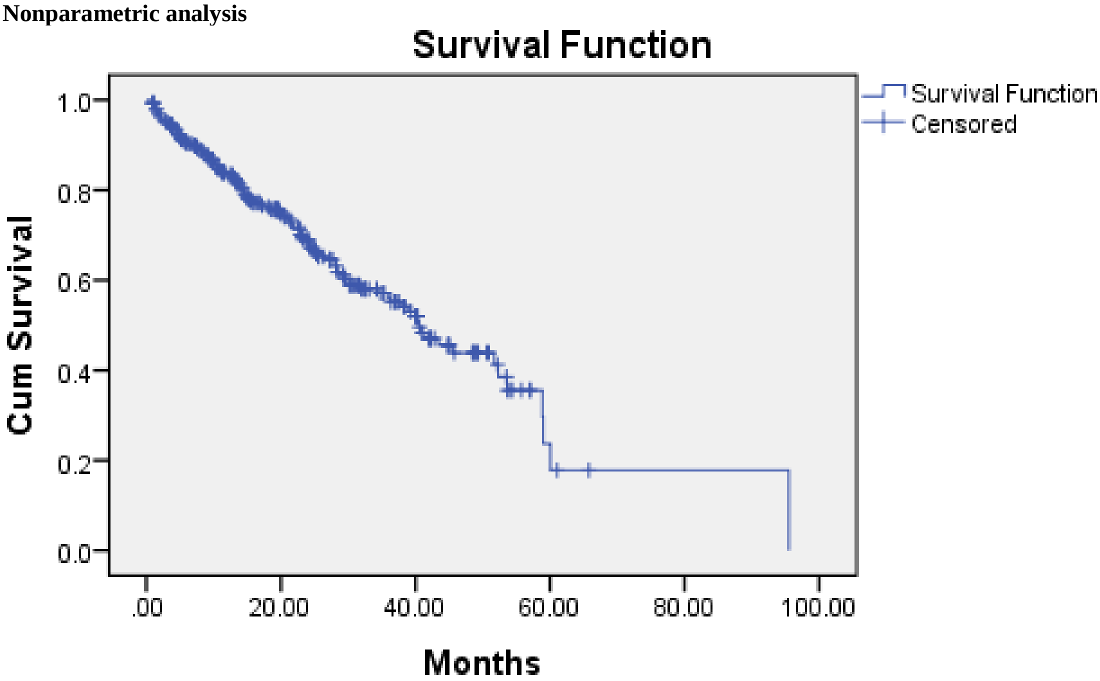

Figure 1: Kaplan-Meier (K-M) curve for the overall survival estimate

At 95% CI, the overall mean and median survival time for patients to attain an optimal control hypertension 44.17 (CI: 37.24-51.12) months (3.68 years) and 40.43 months (CI: 33.67-47.19), (3.37 years) respectively, this implies that 50% of the hypertensive patients attain an optimal control in 40.43 months (CI: 33.67-47.19), (3.37 years) and the other 50% attain an optimal control longer than 40.43 (CI: 33.67-47.19), months (3.37 years) after they are diagnosed with hypertension (Figure 3.1).

Cox Proportion Hazard Model

Table 3: The possibility of attaining an optimal control was higher among patients that have normal body weight (HR: 0.71; 95% CI: 0.63, 0.82, P<0.001). While patients living in Urban areas tend to attained a control faster compared to those living in rural areas (HR: 1.66; 95% CI: 1.05, 2.63, P=0.03). similarly, hypertensive patients that were administered with small number (≤3) of anti-hypertensive drugs during follow-up attained an optimal control than those that were administered high number (>3) of anti-hypertensive during follow-up (HR: 0.65; 95% CI: 0.52, 0.81, P<0.001). While the rest of the covariates did not have an influence on the optimal control considering their Hazard ratio, confidence interval of the hazard ratio and the probability value.

Table 3: Multivariate analysis of cox proportional hazard (95% CI)

S/n	Covariates	B	Standard error (β)	Wald	P-value	HR	95% CI for HR	
							Upper	Lower
1	Age	-0.01	0.01	1.67	0.20	0.99	0.97	1.01
2	Gender	0.52	0.36	2.16	0.14	1.69	0.84	3.40
3	BMI	-0.34	0.067	25.03	<0.001	0.71	0.63	0.82
4	SBP	-0.01	0.01	0.84	0.36	1.00	0.99	1.01
5	Occupation	0.15	0.11	1.90	0.17	1.16	0.94	1.43
6	Educational Status	0.25	0.13	3.578	0.06	1.28	0.99	1.65
7	Place of residence	0.51	0.23	4.70	0.03	1.66	1.05	2.62
8	Number of anti-hypertensive drugs	-0.44	0.12	14.54	<0.001	0.65	0.52	0.81

Weibull Model

Table 5: shows that body mass index (BMI) with a p-value of <0.001, educational status with a p-value of 0.04, place of residence with a p-value of 0.04 and number of antihypertensive drugs with a p-value of <0.001 are the covariates that influence the optimal control of hypertension.

While the remaining covariate: age with a p=value of 0.21, gender with a p-value of 0.13, systolic blood pressure with a p-value of 0.39, occupation with a p-value of 0.15 do not affect the optimal control of hypertension.

Table 5: Multivariate analysis of Weibull model

S/n	Covariate	Mean	Coef	Exp(Coef)	se(Coef)	Wald p
1	Age	53.15	-0.01	0.99	0.01	0.21
2	Sex	1.57	0.53	1.70	0.35	0.13
3	BMI	25.62	-0.35	0.71	0.07	<0.001
4	SBP	155.31	-0.01	1.00	0.01	0.39
5	Occupation	2.73	0.15	1.165	0.11	0.15
6	Educational Status	1.59	0.27	1.31	0.13	0.04
7	Place of residence	1.27	0.47	1.60	0.23	0.04
8	Number of antihypertensive drugs	2.93	-0.46	0.63	0.12	<0.001

DISCUSSION

The median survival time of hypertensive patients to attain an optimal control was 33.67 months. This rate is lower than the median survival of country like Ethiopia (Sendex and Hebo 2017). The covariates: body mass index (BMI), number of antihypertensive drugs, place of residence and educational status were the factors that influenced the optimal control of hypertension. BMI is similar with finding in Vietnam and India. (Nhon *et al.*, 2018; Eslavath & John 2020). While place of residence also correlates with findings of Cappuccio *et al*., 2004; Ayalew *et al*., 2019. Number of anti-hypertensive drugs is the same with a study in Nevada (Quant *et al*.,2010). But, covariates: age, gender and systolic blood pressure (SBP), do not influence the optimal control of hypertension. Gender is found to be statistically insignificant, it corresponds with the study of (Khan *et al*., 2013, Bcheraoui C. E. *et al*., 2014, Ayalew *et al*., 2019, Eslavath &John 2020). while age is also found to be insignificant, this is consistent with the study of Wamala *et al*., (2009), Bcheraoui *et al*., (2014), but contradicts Seifu *et al*., (2016),; Kishore *et al*., (2016); Ayalew *et al*., (2019); systolic blood pressure (SBP) is found to be statistically insignificant, the finding contradicts the study of Ayalew *et al*., (2019); the covariate, occupation is found to be insignificant, it agree with a research carried out by Eslavath &John (2020).

CONCLUSION

This research revealed that form the start date of taking anti-hypertensive drugs, the follow-up time for hypertensive patients on average was 21.50 months (1.79 years) with median survival follow-up time estimated to be 19.10 months (1.56 years). Hypertensive patients attained an optimal control of hypertension an average of 44.18 months (3.68 years) with a median survival time of 40.43 months (3.37 years).

Hypertensive patients that have normal body weight attained an optimal control of hypertension faster than those that are overweight. The hypertensive patients that were administered three anti-hypertensive drugs during the follow-up, attained an optimal control faster than those that were administered less than three or more than three anti-hypertensive drugs.

The Cox Proportional Hazard analysis showed that the major factors that affects an optimal control of hypertension were body mass index (BMI) and number of anti-hypertensive drugs, educational status, and place of residence.

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