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A MODIFIED ADDITIVE HAZARD MODEL FOR SOME RISK FACTORS ASSOCIATED WITH HYPERTENSIVE CONDITION

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ABSTRACT: *In clinical studies, the effect of covariate in their various forms is most often difficult to interpret via the proportional hazard assumption of the cox regression. In this study, proportional hazard assumption test was carried out to access the compliance of some risk factors associated with hypertensive condition (HTC). The global test indicates a violation to proportional hazard assumption. Therefore, a Bayesian survival model was proposed with generalized additive predictors, and modified for the hypertensive dataset for which continuous and linear covariate forms were incorporated in a proportional hazard framework. The findings of the study are: for the Risk Factors (overweight and pregnancy), both categorical variables failed the test with p-values 0.00017 and 0.00030 respectively, less than the significant level 0.05; results suggest that a Regularized Hypertensive Additive Hazard model (RHAHM) performs better with smaller Deviance Information Criterion (DIC) value of 2933.323 and large Log-Peusdo Maximum Likelihood (LPML) value of 1469.415 in comparison to the un-regularized model. Also, age covariate at the seventh knot are more at risk of High-Risk Hypertensive Condition (HRHC) than those of other knots, followed by those who enter the study at the beginning with HRHC. Male patients are about 10% less at risk of HRHC than their female counterparts; those that are married are 59% more at risk of HRHC than subjects that are single. For factors which could be a possible cause of HRHC, patients with chronic illness and those who indulge in excessive alcohol intake have the highest risk of HRHC than those of other risk factors. The study concludes that regular medical check-up on hypertensive status will effectively help in the management of hypertension, especially those with target organ damage.*

KEYWORDS: Hypertension, Risk Factors, Cox Model, Proportional Hazard, Regularized Hypertensive Addictive Hazard model (RHAHM)

INTRODUCTION

Hypertension (HTN) or high blood pressure (HBP) is a chronic medical condition in which the blood pressure in the arteries is elevated. It is classified into four as normal, prehypertension (mild), stage 1 (moderate or primary) and stage-2 (Severe or Secondary or Symptomatic) hypertension (Beth *et al.*, 2009). About 90-95% of the cases are termed “primary hypertension” which refers to high blood pressure for which no medical cure can be found. The remaining 5-10% are secondary hypertension caused by conditions that affect the kidneys, arteries, heart or endocrine system in what we may refer to as High Risk Hypertensive Condition (HRHC) (Reboussin *et al*., 2017).

(Papadakis *et al.*, 2015), states that hypertension is a condition in which there is sustained elevation of the arterial blood pressure; actually, the normal range is 110/70 to 120/80 mm Hg. Abnormal high blood pressure (Hypertension) occurs in shock and after excessive fluid or blood loss from any cause. Hypertension is one of the major public health problems of the developed countries, affecting 15-20% of adults. It may be unknown cause (Essential hypertension), or it may occur in association with some other condition, such as Kidney disease (Secondary or Symptomatic Hypertension). It is usually controlled with low salt diet and drugs. (Mamas Health, 2010) stressed that variation in arterial blood pressure occurs under the influence of factors such as age, exercise, emotions and weight. Others attribute this variation to alcohol in-take, diet, occupation, heredity, while other disease likes: diabetes and drugs like birth control pills could be possible factors (Mulatero and Bertello, 2016). Persistence hypertension is one of the risk factors for stroke, heart attacks, heart failure and arterial aneurysm which is a leading cause of chronic kidney failure, Moderate elevation of arterial blood pressure leads to short life. Both dietary and lifestyles changes as well as medicines can improve blood pressure control and decrease the risk of associated health complications (Shaw *et al.*, 2009).

The benefit of antihypertensive treatment for blood pressure (BP) ≥160/100 mm Hg and BP of 140 to 159/90 to 99 mm Hg with high cardiovascular risk has been established (Mancia *et al*., 2013 and Leung et al, 2017). However, evidence about the clinical benefits of antihypertensive treatment for BP of 140 to 159/90 to 99 with low risk and no organ damage or associated cardiovascular disease is lacking (Leung *et al.*, 2017). Most of the recommendations for pharmacological treatment of uncomplicated hypertension have been based on expert opinions or post hoc data (Mancia *et al.*, 2013, Leung *et al*., 2017 and Reboussin *et al*., 2017). Because of the lack of evidence, the National Institute for Health and Care Excellence guidelines for the diagnosis and management of hypertension state that antihypertensive treatment is recommended for patients aged <80 years with BP of 140 to 159/90 to 99 mm Hg if they have target organ damage, established cardiovascular disease, renal disease, diabetes mellitus, or a 10-year cardiovascular risk of ≥20% (Krause, 2011).

This paper therefore modifies a Bayesian Survival Generalized Additive Model to examine the hazard rates of reported cases of hypertensive patients along with associated risk factors.

MATERIALS AND METHOD

The data used for this paper is a secondary data collected from the record office of the General Hospital, Keffi, Nasarawa State. For the purpose of the study, a sample size of 763 patients were extracted from the register from 2007-2019.

Model Specification

The cox hazard model

$$\lambda_i(t, X) = \lambda_0(t) \exp\left(\sum_{j=1}^{p} \beta_j X_j\right). \tag{1}$$

The baseline hazard rate is unspecified, and assumes that covariates $x = (x_1, \dots, x_p)$ act multiplicatively on the hazard rate through the exponential link function (Abiodun, 2007).

An additive representation of model 1

$$\eta(t; w, z, x, s) = f_0(t) + \sum_{j=1}^{p} f_j\,(w_j) + x'\gamma \tag{2}$$

This is a re-parameterization of the cox model

where $f_0(t) = log\lambda_0(t)$ which implies, $\exp\big(f_0(t)\big)$, other aspects of the models include the functions $f_j(w_1)$... $f_q\big(w_q\big)$ are possibly nonlinear effects of metrical covariates $w_1, \dots, w_q$ andγ is the usual linear part of the predictor for some categorical covariates (Abiodun, 2009) and (Hennerfeind *et al.*, 2006)

Bayesian P-Splines

The Bayesian P-splines method is based on a hierarchical model with non-informative priors for the regression coefficients (β) and a Gaussian Random Walk (RW) prior of order d for the coefficients of the hazard function (B-spline), conditional to a smoothing parameter $\tau^{\,2}$ The general expression of the RW prior as suggested by (Lang, *et al.*, 2004) is the following:

$$\beta_j/\tau_j^2 \propto \exp\left(-\frac{1}{2\tau_j^2}\lambda_j \beta'_{\,j}\, K_j \beta_j\right) \tag{3}$$

The penalty matrix K_j is of the form $K_j = D'D$, where D is a first or second order difference matrix.

For an independent and identical random effect, the penalty matrix is the identity matrix, i.e.K_j= I. The variance parameter τ_j^2 controls the trade off between flexibility and smoothing and an inverse gamma prior (the conjugate prior) is assumed. i.e. $\tau_j^2 \sim IG(a, b)$.

Model with a Regularized Hazard Function

$$\begin{cases} \eta(t; w, x) = \underline{B_0^T f_0(t)} + \underline{B_0^T}\ \underline{f_j(w_j)} + X_0^T \underline{\gamma} \\ \qquad\qquad \underline{\beta\gamma} \sim \pi_{\underline{\gamma}} \\ \left(\underline{f_0(t)}\middle|\tau^2\right) \sim RW(\tau^2, P_d);\ \tau^2 \sim \pi_{\tau^2} \\ \left(\,f_j(w_j)\middle|\tau^2\right) \sim RW(\tau^2, P_d);\ \tau^2 \sim \pi_{\tau^2} \end{cases} \tag{4}$$

where B_0 is the vector form of a B-spline of degree 0 defined for the follow-up period, and π_β and π_{τ^2} are generic prior densities for the regression coefficients and the smoothing parameter (Marano, et al, 2016).

Data Transformation

The records of patients diagnosed with Hypertensive condition (HTC) at the General hospital, Keffi, Nasarawa State. The record of each patient contained information on duration from diagnosis, through treatment (recorded in years). Factors consider were, age, sex, Weight, height, Marital status, Factors responsible for increase blood pressure for each subject in the study, such as; Age, diet, Overweight, chronic illness, family lifestyle, sedentary lifestyle, stress, family history, pregnancy, excessive alcohol (EA) and obesity. Blood Pressure Status, BPS (outcome), indicates a patients managed for BPS in range greater than 140/90 (hypertensive stage 2 or crises) as at the point of data collection, while those whose BPS were less or equal to 140/90 (hypertensive stage 1) were considered as right-censored because such patients had not entered high risk condition as at the time of the data analyses. Survival time is defined in terms of the length of time patients visit the hospital with HTC.

For the sake of analysis, the variable "age", was considered as continuous variable, other categorical covariates were coded as follows; sex was coded "1" for "Male" patients and "0" for "Female" patients. Marital Status, was coded "1" for "patients that are married" and "0" for patients that are "single". Age factor, was coded "1" if age is the factor responsible for patients' hypertensive condition and "0" if otherwise. Diet as a factor responsible for HTC was coded "1" and "0" if some other factors, Overweight as a factor responsible for HTC was coded "1" and "0" if elsewhere", Chronic illness as a factor responsible for HTC was coded "1" and "0" if some other factors", Family lifestyle as a factor responsible for HTC was coded "1" and "0" if otherwise", sedentary lifestyle as a factor responsible for HTC was coded "1" and "0" if otherwise", stress as a factor responsible for HTC was coded "1" and "0" if some other factors", Family history as a factor responsible for HTC was coded "1" and "0" if otherwise", pregnancy as a factor responsible for HTC was coded "1" and "0" if otherwise, excessive alcohol as a factor responsible for HTC was coded "1" and "0" if elsewhere", Obesity as a factor responsible for HTC was coded "1" and "0" if otherwise". Analysis was carried out in R using the coda package for spBayesSurv, version 3.6.2.

Test for Proportionality Assumption

To test the hypothesis that the proportional hazard assumption is valid, the following statement of hypothesis is made.

$\boldsymbol{H_0}: \delta_1 = \delta_2 = \cdots = \delta_p$(Assumption is valid)

$\boldsymbol{H_1}: at\ least\ one\ of\ the\ \delta_i's\ is\ not\ equal\ to\ zero$ (Assumption violated)

Decision Rule: Reject H_0 if $p - value\ \leq\ \alpha$ (level of significance)

Residual measures are used to investigate the departure from the proportional hazard assumption. Schoenfeld residuals are used to test the assumption of proportionality. Schoenfeld residuals are usually calculated at every failure of time under the proportional hazard assumption, and usually not defined for censored observations. The overall significance test is called the global test of the model in equation 2 (sighted in Adeniyi and Akinrefon, 2018)

DATA ANALYSIS

This section presents the results of analysis for hypertensive patients' dataset who reported at the General hospital Keffi.

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Table 1: Test for Proportional Hazard Assumption

Covariates	Chi-square	p-value
Age	2.689	0.10104
Sex	3.959	0.04662
Marital Status	0.837	0.36037
Diet	2.076	0.14965
Overweight	14.144	0.00017
Chronic illness	3.959	0.04661
Stress	0.127	0.72185
Family History	0.584	0.44477
Pregnancy	13.063	0.00030
Sedentary	2.541	0.11090
lifestyle	0.890	0.34556
Excessive	2.889	0.08918
alcohol	0.890	0.34556
Obesity	2.889	0.08918
Global Test	**44.897**	$\mathbf{1.1 \times 10^{-05}}$

Interpretation: It is seen from table 1 that the covariates (Overweight and Pregnancy) are not proportional with p-values 0.00017 and 0.00030, less than the significance level. The global test again indicates a violation of the proportional hazard assumption. This test was performed to enable a straight forward interpretation of the hazard rates, to enhance our model which was fashioned in a proportional hazard framework.

Models Considered

Modification of the Hypertensive Addictive Hazard model

$$\eta_{HTC} = f_0(t) + f(age) + f_{sex} + f_{Marital\ status} + f_{Diet} + f_{Chronic\ illness} + f_{\text{Stress}} + f_{Family\ history} + f_{Sedentary\ lifestyle} + f_{Excessivealcohol} + f_{Obesity} \quad (5)$$

Here, the covariates, Over weight and pregnancy where excluded from the proportional hazard models as their hazard rates have the tendency to exhibit change over the study period.

Regularized Hypertensive Additive Hazard Model

$$\eta_{HTC} = B_0^T f_0(t) + B_0^T f_{Age} + f_{sex} + f_{Marital\ status} + f_{Diet} + f_{Chronic\ illness} + f_{\text{Stress}} + f_{Family\ history} + f_{Sedentary\ lifestyle} + f_{Excessivealcohol} + f_{Obesity} \quad (6)$$

Comparison of Deviance Information Criterion (DIC) and Log-Peusdo Maximum Likelihood (LPML)

The smaller the value of Deviance Information Criterion (DIC), the better, whereas the larger the value of Log-Peusdo Maximum Likelihood (LPML), the better (Zhou *et al*., 2017).

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Table 2: Posterior Means for Regression Coefficients for Un-regularized Hypertensive Additive Hazard Model (URHAHM)

	URHAHM		**DIC**	**LPML**
Covariates	$\hat{\gamma}$	Hazard ratios	2978.82	-1489.608
Age	0.005283	1.00529698		
Sex	- 0.09680	0.907737535		
Marital Status	0.238462	1.269295472		
Diet	-0.053438	0.947964713		
Chronic illness	0.409709	1.506379365		
Stress	-0.109498	0.896283957		
Family history	0.190939	1.210385616		
Sedentary lifestyle	0.350514	1.419797137		
Excessive alcohol	-0.239513	0.787011042		
obesity	-0.735519	0.47925666		

From table 2, it is observed that: for every unit increase in age, there is 0.005% increase in the hazard rate of high “High Risk Hypertensive Condition”; male patients are 0.9077 times at risk of “high risk hypertensive condition than female patients; those that are married are 1.2693 at risk than those that are single; those whose hypertensive condition was caused by “diet” are about 5% less at risk than other factors responsible for HTC; those with chronic illness are about 51% more at risk of “High Risk Hypertensive Condition” in comparison to those of other risk factors; those whose hypertensive condition was caused by “stress” are about 10% less at risk than other factors responsible for high risk HTC; those whose hypertensive condition was caused by “Family history” are about 13% more at risk than other factors responsible for “High Risk Hypertensive Condition”; those whose HTC was caused by sedentary lifestyle are about 42% at hazard of hypertensive stage 2 condition than those of other risk factors; those whose hypertensive condition was caused by “Excessive alcohol intake” are about 27% less at risk of high risk hypertensive condition than other risk factors responsible for HTC; and those that are obese are 0.47926 times at risk of “High Risk Hypertensive Condition” than those caused by other factors.

Table 3: Posterior Means for Regression Coefficients for Regularized Hypertensive Additive Hazard Model (RHAHM)

	RHAHM		**DIC**	**LPML**
Covariates	$\hat{\gamma}$	Hazard ratios	2933.323	-1469.415
Age	661.72014 659.25104 659.57223 658.73681 660.18543 660.58301 679.21959	2.4066E+287 2.0375E+286 2.8092E+286 1.2183E+286 5.1867E+286 7.7189E+286 9.579E+294		

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Sex	-0.10825	0.897403218		
Marital Status	0.46228	1.587689794		
Diet	-0.12109	0.88595422		
Chronic illness	0.33664	1.400234888		
Stress	- 0.07894	0.924095369		
Family history	-0.02854	0.971863419		
Sedentary lifestyle	0.22654	1.254252779		
Excessive alcohol	-0.31070	0.732933723		
obesity	-0.74208	0.47612255		

From table 3, with penalty spline estimation for continuous covariate "Age", RHAHM performs better with smaller DIC value and large Predictive power. Age here was estimated in seven (7) knots, with the highest hazard rate observed at last knot where most of the subjects are expected to experience "High Risk Hypertensive Condition" (hypertensive stage 2 condition), and followed by the hazard rate on the first's knot where some patients entered the study with such condition. Hazard rates were seen to vary between knots over the study period.

Male patients are 0.8974 times at risk of "High Risk Hypertensive Condition" (HRHC) than female patients, those that are married are 1.5876 times at risk than those that are single, those whose hypertensive condition was caused by "diet" are about 11% less at risk than other factors responsible for HTC, those with chronic illness are about 40% more at risk of "High Risk Hypertensive Condition" in comparison to those of other risk factors, those whose hypertensive condition was caused by "stress" are about 8% less at risk than other factors responsible for high risk HTC (HRHC), as those whose hypertensive condition was caused by "Family history" are about 3% less at risk than other factors responsible for ""High Risk Hypertensive Condition", those whose HTC was caused by sedentary lifestyle are about 25% more at hazard of "hypertensive condition 2 than those of other risk factors, those whose hypertensive condition was caused by "Excessive alcohol intake" are about 27% less at risk of "High Risk Hypertensive Condition than other risk factors responsible for HTC, those that are obese are 0.47612 times at risk of "high risk hypertensive condition" than those caused by other factors.

CONCLUSION

High Risk Hypertensive Condition is a critical state that exposes patients to all forms of antennary and other chronic diseases (Mancia *et al.*, 2013), has been tagged as the leading cause of death in the world by the WHO, it has become pertinent that the covariate age should be carefully observed with other associated risk factors at each point of clinical assessment of the subjects for the hazard of HRHC, those associated with other risk factors like; family history, sedentary lifestyle, which were some of the leading risk should engage more in regular exercise, observe the required hours of rest and stay away from excessive alcohol intake. A diet change is highly recommended in our study to improve blood pressure and decrease the risk of HRHC which is consistent with the resolve of (Shaw *et al.*, 2009). Regular check on hypertensive status couple with physician's advice should effectively help in the management of hypertension, especially patients with target organ damage or chronic disease.

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