

Bayesian Joint Modeling of Longitudinal and Survival Time Measurement of Hypertension Patients

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Background: High blood pressure is a health risk for all populations, worldwide. Globally the number of people with uncontrolled hypertension rose by 70% between 1980 and 2008.

Objective: This paper aims to investigate the association of survival time and fasting blood sugar levels of hypertension patients and identify the risk factors that affect the survival time of the patient.

Methods: We considered a total of 430 random samples of hypertension patients who were followed-up at Yekatit-12 Hospital in Ethiopia from January 2013 to January 2019. A linear mixed effects model was used for the longitudinal outcomes (fasting blood sugar) with normality assumption, although four parametric accelerated failure time distributions: exponential, Weibull, lognormal and loglogistic are studied for the time-to-event data. The Bayesian joint models were defined through latent variables and association parameters and with specified noninformative prior distributions for the model parameters. Simulations are conducted using Gibbs sampler algorithm implemented in the WinBUGS software. The model selection criteria DIC is employed to identify the model with best fit to the data.

Results: The findings from Bayesian joint models are consistent. The association parameter in each Bayesian joint model is significant. This implies that there is dependence between the two processes: longitudinal fasting blood sugar level and the time-to-death event under joint models. With investigation of the model comparison criteria, the Bayesian–Weibull model was preferred to analyze the current data sets. Based on joint analysis the baseline age, place of residence, family history of hypertension, khat intake, blood cholesterol level of the patient, hypertension disease stage, adherence to the treatment and related disease were associated factors that affect the survival time of hypertension patients.

Conclusion: The analysis suggests that there is strong association between longitudinal process (fasting blood sugar) and time-to-event data. The researcher recommends that all stakeholders should be aware of the consequences of these factors which can influence the survival time of hypertension patients in the study area.

Keywords: Bayesian, joint model, hypertension, survival analysis, parametric models

Background

Hypertension is a major long-term health condition and the leading cause of premature death among adults throughout the world, including developed, developing, and lesser developed countries. Sometimes called arterial hypertension, which is a chronic medical condition in which the blood pressure in the arteries is elevated, this requires the heart to work harder than normal to circulate blood through the blood vessels.¹

Hypertension is a worldwide public health challenge and a leading flexible risk factor for cardiovascular disease and death. Globally the number of people with uncontrolled hypertension rose by 70% between 1980 and 2008. The rising epidemic

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of hypertension is thought to be due to mechanization, population growth, and ageing.^{2,3}

Hypertension doubles the risk of cardiovascular diseases such as coronary heart disease, congestive heart failure, stroke, renal failure, and peripheral arterial disease.⁴ The global burden of cardiovascular disease over a fairly short period is attributable mainly due to changes in lifestyle such as diet and physical activity.⁵

Hypertension in Africa has now changed from a relative rarity to a major public health problem.⁶ Current disease estimates for Sub-Saharan Africa are based on sparse data, but projections indicate increases in noncommunicable diseases caused by demographic and epidemiologic transitions; however, hypertension control assumes a relatively low priority and little experience exists in implementing sustainable and successful programs.

Ethiopia is a country currently prioritizing prevention of communicable and nutritional deficiency diseases. However, it is experiencing double mortality burden as evidenced among the adult population in Addis Ababa.⁷ A study conducted in Ethiopia in the last decade showed that the prevalence of cardiovascular diseases increase the risk factor rapidly.⁸ Recently comprehensive assessment of the evidence concerning hypertension in Ethiopia does not exist. However, recent evidence indicates that hypertension and raised blood pressure are increasing partly because of the increase in risk factors. The goal of this study was to investigate the association of survival time and fasting blood sugar levels of hypertension patients and identifying the risk factors that affect the survival time of the patient

Methodology

Data Description

The data for this study was obtained from hypertension patients from Yekatit-12 Hospital under follow-up from January 2013 to January 2019. The data was extracted from the patient's chart which contains epidemiological, laboratory, and clinical information of all hypertension patients under follow-up. A total of 430 patients were selected using a simple random sampling technique among a total of 2126 hypertension patients under follow-up. The description of the covariates are presented in Table 1.

Statistical Estimation

The joint models are defined in Henderson et al^{9, 10} and Guo and Carlin. The longitudinal and survival process is linked

Table 1 Explanatory Variables with Codes

	Variables	Description and Codes
1	Gender	Female (0), Male (1)
2	Age	>50 Years (0), ≤50 Years (1)
3	Place of residence	Rural (0), Urban (1)
4	Family history of hypertension	Positive (0), Negative (1)
5	Tobacco use	0= No (0), Yes (1)
6	Alcohol use	No (0), Yes (1)
7	Khat intake	No (0), Yes (1)
8	Related disease	None (0), Stroke (1), Heart case (2)
9	Cholesterol level	Normal (0), Raised (1)
10	Diabetes mellitus	No (0), Yes (1)
11	Fasting blood sugar	Continuous
12	Stages of hypertension	Stage 1(0), Stage 2(1), Stage 3(2), Stage 4(3)
13	Adherence	Low (0), High (1)
14	Visit time	Continuous

through stochastic dependence. Consider that we have a set of n patients followed over a time interval $(0, T)$. The i^{th} patient provides a set of longitudinal measurements Y_{ij} which is fasting blood sugar at a follow-up time t_{ij} of visit $j = 1, 2, \dots, n_i$ with n_i number of follow-up of patient $i = 1, 2, \dots, n$.

Survival time of the patients measured by years, months, weeks, or days from the beginning of follow-up until an event occurs. For the survival data, let $T_i = \min(t_i, c_i)$ be the observed time for the i^{th} patients, where t_i is time to death and c_i is the censoring time which is assumed independent of t_i and $\delta_i = 1$ if the event is observed, $\delta_i = 0$ otherwise. Let the covariates of the longitudinal and survival processes be respectively denoted by X_{1i} and X_{2i} . Some of these covariates may be time dependent.

Linear Mixed Effects Model

The linear mixed effect model is often used in the literature for modeling a longitudinal data and provides a general and flexible modeling framework based on a random effects approach.^{11,12}

For the given k vector of predictors X_{1i} , the linear mixed effects model is given as:

$$Y_{ij} = \mu_i(t_{ij}) + W_{1i}(t_{ij}) + \epsilon_{ij} \quad (1)$$

Where $\mu_i(t_{ij})$ is mean response which is a linear function of X_{1i} , $W_{1i}(t_{ij})$ is subject specific random effects having Gaussian distribution, and $\epsilon_{ij} \sim N(0, 1/\sigma_e^2)$ is a sequence of mutually independent measurement errors.

Survival Models

The survival time is a random variable defined on non-negative real numbers. The observed time is taken as the minimum $T_i = \min(t_i, c_i)$ of the time-to-event t_i and time to censoring c_i . The time variable was modeled with four AFT distributions (exponential, Weibull, lognormal or loglogistic) as considered.^{10,13,14} The log-linear form of the AFT model for survival time T_i is given as:

$$\log(T_i|W_{2i}) = X'_{2i}\alpha + W_{2i}(t_i) + \varepsilon_i \quad (2)$$

Where, α is a vector of unknown and fixed coefficient of the covariates, $W_{2i}(t)$ refers to subject specific random effects of the survival time having Gaussian distribution, ε_i is a sequence of mutually independent measurement errors. The random error terms follow a distribution such that the time-to-event, in this case, exponential, Weibull, lognormal and loglogistic distributions. If the error follows normal distribution, the time is lognormal, and the error follows logistic distribution, the time is loglogistic. The Weibull distribution arises as a general linear form of the smallest extreme value distribution.¹⁴

The four AFT models considered in this study are exponential, Weibull, lognormal and loglogistic distributions. Table 2 lists their probability densities, hazard rate functions, and survival functions.

Bayesian Joint Model

Likelihood Model

The association between the longitudinal and survival processes is assumed to come through stochastic dependences denoted by $W_{1i}(t)$ and $W_{2i}(t)$. There are many ways of making the linkages.⁹ Here we consider the links used in Guo and Carlin.¹⁰ The linear mixed effects model for the longitudinal process in Equation (1) and the AFT model for the time-to-event in Equation (2) are linked through random effects W_{1i} and W_{2i} as follows:

$$W_{1i}(t) = U_{1i} + U_{2i}t \quad (3)$$

$$W_{2i}(t) = r_1 U_{1i} + r_2 U_{2i} \quad (4)$$

The parameters r_1, r_2 measure the association between the two sub-models (1) and (2) that are expected to be induced by the longitudinal process to the time-to-event process. They represent random intercept and random slope terms in model (1). The variables U_{1i} and U_{2i} are assumed independent latent variables representing subject-specific random effects having normal distributions with mean zeros and precisions τ_{u1} and τ_{u2}

The respective likelihood function of interest is:

$$L(y, t, \delta | \theta_1, \theta_2) = \prod_{i=1}^n \int (y_i | (\theta_1, w_{1i}) f(t_i, \delta_i | (y_i, \theta_2, w_{2i}))^{\delta_i} (1 - F(t_i, \delta_i | y_i, \theta_2, w_{2i}))^{1-\delta_i} f(w_{2i} | w_{1i}) f(w_{1i}) dw_{2i} dw_{1i} \quad (5)$$

where $\theta_1 = \{\beta, \sigma_{FBS}^2, \sigma_u^2\}$ are population parameters in the linear mixed effects model, $\theta_2 = \{\alpha, \sigma_t^2, r\}$ are the population parameters in the survival model, β are regression parameters in the mixed effects model, σ_{FBS}^2 is the variance of the Fasting blood sugar, σ_u^2 are the variance of subject specific random effects, α are regression coefficients in the AFT model, σ_t^2 is the variance of the transformed event time, r represent the association parameters r_1 and r_2 , $f(x)$ and $F(x)$ are probability density and distribution functions, respectively

Prior Distribution

Noninformative joint prior distribution of the parameters are considered: β 's and α 's are normally distributed with mean zero and large variance 1000, association parameters r_1, r_2 are each assumed to have normal distribution with mean zero and variance 1000; the shape parameter ρ in Weibull and loglogistic distributions follows Gamma (2,0.5); all precisions parameters follow Gamma(2, 0.5).

Posterior Distribution

The joint posterior distribution $\pi(\theta, w | y, t, \delta)$ of model parameters θ and random effects W is given by:

Table 2 List of Accelerated Failure Time Distributions

Models	Parameter	$f(t)$	$h(t)$	$S(t)$
Exponential	λ	$\lambda \exp(-\lambda t)$	λ	$\exp(-\lambda t)$
Weibull	$\rho, \lambda = \eta^{-\rho}$	$\lambda \rho t^{\rho-1} \exp(-\lambda t^\rho)$	$\lambda \rho t^{\rho-1}$	$\exp(-\lambda t^\rho)$
Lognormal	μ, τ	$\frac{\sqrt{\tau}}{\sqrt{2\pi} t} \exp\left(-\frac{\tau}{2} \{\ln(t) - \ln(\mu)\}^2\right)$	$\frac{f(t)}{S(t)}$	$1 - \Phi\left(\frac{\ln(t) - \mu}{1/\sqrt{\tau}}\right)$
Loglogistic	$\rho, \lambda = \mu^{-\rho}$	$\frac{\lambda \rho t^{\rho-1}}{(1 + \lambda t^\rho)^2}$	$\frac{\lambda \rho t^{\rho-1}}{1 + \lambda t^\rho}$	$\frac{1}{1 + \lambda t^\rho}$

$$\pi(\theta, w|y, t, \delta) = \frac{f(y, t|\theta, w)\pi(\theta, w)}{\int f(y, t|\theta, w)\pi(\theta, w)d\theta dw} \quad (6)$$

Where, $f(y, t|\theta, w)$ is the likelihood function, $\pi(\theta, w)$ is the joint prior probability distribution, and $\int f(y, t|\theta, w)\pi(\theta, w)d\theta dw$ is the normalizing constant. It is a high dimensional problem that requires modern computations. Thus inference is based on the Gibbs sampler algorithm using full conditional distributions of the parameters. The Gibbs sampler algorithm is

implemented in the WinBUGS software version 14.3.¹⁵ Inferences are made based on simulation of 40,000 iterations with burn-in of 20,000 and thinning of 10. Time series plots, autocorrelations and Gelman–Rubin statistics are assessed and they all confirm convergences.

Model Comparisons

In this study, we compare the four Bayesian joint models with the AFT exponential, Weibull, lognormal,

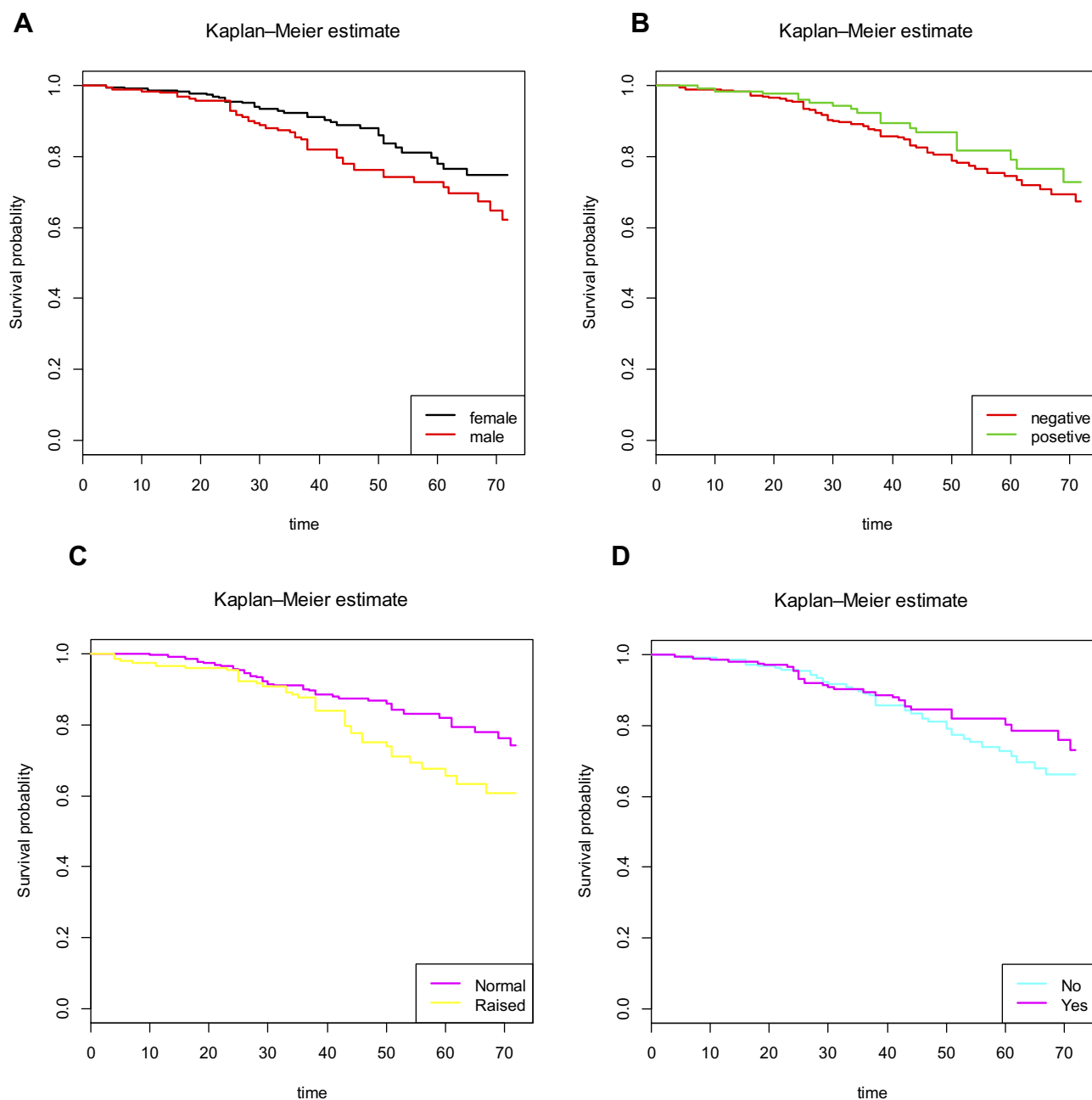


Figure 1 Kaplan–Meier survival function curves of hypertension patients. (A) Gender of patient. (B) Family history of hypertension. (C) Cholesterol level. (D) Diabetes mellitus.

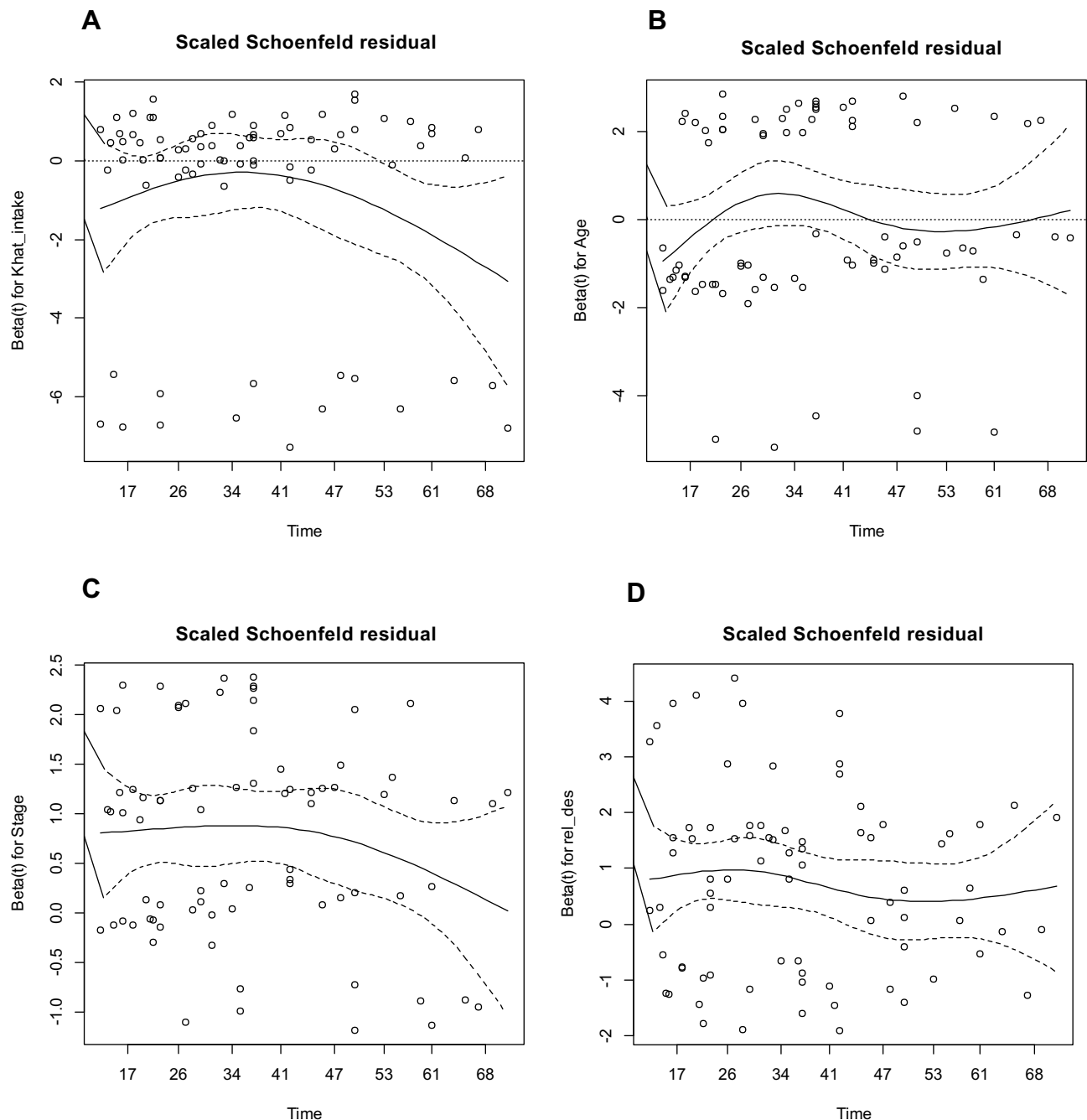


Figure 2 Plot of scaled-Schoenfeld residuals vs follow-up time. **(A)** Khat intake. **(B)** Age. **(C)** Stages of hypertension. **(D)** Related disease.

loglogistic probability distributions using the deviance information criterion (DIC), Akaike's information criterion (AIC) and Bayes information criterion (BIC). It measures how best the selected model can predict future observations given that it best fits the data at hand.¹⁶

DIC involves posterior mean that takes into account prior information and penalized likelihood. It is computed as:

$$\text{DIC} = E[D(\theta)|\text{data}] + pD \quad (7)$$

Where, $D(\theta) = -2\log(\text{Likelihood}(\theta|\text{data}))$ is deviance and $E[D(\theta)|\text{data}]$ is the posterior mean of the deviance and pD is effective number of parameters. The AIC and BIC are computed as follows:

$$\text{AIC} = E[D(\theta)|\text{data}] + 2p \quad (8)$$

$$\text{BIC} = E[D(\theta)|\text{data}] + p\log(n) \quad (9)$$

Table 3 Model Comparison Among the Bayesian Joint Models

Model	Dbar	Dhat	pD	DIC	AIC	BIC
Exponential	15,232	14,737.50	494.80	15,726.80	15,272	15,337.34
Weibull	15,087.40	14,592	495	15,582.40	15,127.40	15,192.74
Lognormal	15,171.20	14,684.40	486.80	15,658	15,211.20	15,277.54
Loglogistic	15,142.80	14,507.40	635.37	15,778.10	15,182.80	15,248.14

Where, p is the number of parameters in the model and n is the sample size. The models used in this study involve random effects and so the DIC is more relevant for the model selection.

Results and Discussion

The objective of this study was to investigate the association of survival time and fasting blood sugar levels of hypertension patients and identifying the risk factors that affect the survival time of the patients. The linear mixed effect model was assumed for the longitudinal process, while exponential, Weibull, lognormal, and loglogistic distributions were assumed for the survival time. A random sample of 430 hypertension patients was selected from 2126 hypertension patients under follow-up and the data analyzed using Bayesian joint models. The findings from the models are all interpreted as they are important in many ways. The statistical packages SPSS version 20 (IBM Corporation, Armonk, NY, USA) and WinBUGS software version 14.3 have been used to analyze the data.

Descriptive Survival Analysis

In the data set considered 430 hypertension patients among which 55.3% are females and 44.7% are males. In the survival data, 17.9% are dead and 82.1% are censored. The death proportion of male patients was 23.4% and of a female patient was 13.4%. Among 430 patients 88% of them live in a rural area and only 12% of them reside in an urban area.

To observe the event experiencing time between two or more groups plotting the survival function for the group is recommendable. To obtain a closer look at estimate of the survival time we used the Kaplan–Meier estimation technique. The pattern of survivorship function lying above another means the group defined by the upper curve had a better survival than the group defined by the lower curve. The log rank test also used for comparing two or more independent survival curves, the analysis show that the log rank test for covariate

gender ($\chi^2=5$ with 1 df, $p=0.03$), khat intake ($\chi^2=9.7$ with 1 df, $p=0.002$), blood cholesterol ($\chi^2=5.9$ with 1 df, $p=0.02$), stage of hypertension ($\chi^2=59.7$ with 3 df, $p=0.00$), adherence ($\chi^2=12$ with 1 df, $p=0.00$) and related disease ($\chi^2=29.6$ with 2 df, $p=0.00$), at 5% level of significance, there is evidence to reject the null hypothesis. Therefore, they are statistical significant in survival experience of the patients in different categories of gender, khat intake, blood cholesterol, stage of hypertension, adherence and related disease. Also, the log rank test for the covariate place of residence ($\chi^2=0.4$ with 1 df, $p=0.5$), family history of hypertension ($\chi^2=1.4$ with 1 df, $p=0.2$), tobacco use ($\chi^2=0.1$ with 2 df, $p=0.8$), alcohol use ($\chi^2=1.4$ with 2 df, $p=0.2$) and diabetes mellitus status ($\chi^2=1$ with 2 df, $p=0.3$) are not statistically significant at 5% level of significance, therefore they are not statistically significant in survival experience of the patients in different categories of place of residence, family history of hypertension, tobacco use, alcohol use, and diabetes mellitus. Figure 1 shows that there were statistical differences among survival curves of sex group, family history of hypertension, cholesterol level, diabetes mellitus.

To check the PH assumption, the scaled Schoenfeld residuals were plotted over time and the corresponding p -values, as well as the p -value associated with a global test of non-proportionality are tested. The global test suggested strong evidence of non-proportionality ($p < 0.025$). Figure 2: shows plots of Schoenfeld residuals against transformed time for each covariate. There is a systematic departure from a horizontal line that indicates violation of the proportional hazard assumption.

Inferential Analysis

The Bayesian joint AFT analysis involves the random effects $W_{1i} = U_{1i} + U_{2i} * t$ in the longitudinal and $W_{2i} = r_1 * U_{1i} + r_2 * U_{2i}$ in the time-to-event models. Prior distributions used are $\beta_j \sim \text{Normal}(0, 0.001)$, $\alpha_k \sim \text{Normal}(0, 0.001)$, $\rho \sim \text{Gamma}(2, 0.5)$, $\tau_{LN} \sim \text{Gamma}(2, 0.5)$, $r_1 \sim \text{Normal}$

Table 4 Parameter Estimations of the Bayesian Joint Weibull Models

Parameter	Mean	SD	MC Error	95%CI
β_o	0.316	0.030	0.001	(0.259, 0.377)*
β_{Vtime}	-0.154	0.0011	0.000	(-0.05, -2.001)*
$\beta_{tobuse}(ref. = No)$ β_{yes}	2.173	0.025	0.001	(0.125, 3.280)*
$\beta_{alcohol use}(ref. = No)$ β_{yes}	1.046	0.024	0.001	(0.099, 1.19)*
$\beta_{place of residence}(ref. = Urban)$ β_{Rural}	0.036	0.001	0.000	(0.013, 0.18)*
τ_{u1}	0.072	0.01	0.002	(0.049, 0.165)*
τ_{u2}	1.415	0.127	0.014	(0.924, 2.522)*
σ_{ϵ}	8.027	0.006	0.000	(7.68, 10.25)*
$\alpha_{Gender}(ref. = Female)$ α_{Male}	0.091	0.001	0.000	(0.049, 0.113)*
$\alpha_{age}(ref. = \geq 50)$ 26 – 50 ≤ 25	1.063 0.016	0.021 0.023	0.000 0.001	(0.821, 1.96)* (0.01, 1.14)*
$\alpha_{FamilyHist}(ref. = Postive)$ $\alpha_{Negative}$	0.046	0.004	0.000	(0.020, 0.089)*
$\alpha_{tobuse}(ref. = No)$ α_{No}	0.17	0.005	0.001	(0.125, 0.222)*
$\alpha_{alcohol use}(ref. = No)$ α_{yes}	0.146	0.024	0.001	(0.099, 0.197)*
$\alpha_{khat intake}(ref. = No)$ α_{yes}	3.016	0.017	0.000	(1.01, 4.081)*
$\alpha_{Cholesterollevel}(ref. = Normal)$ α_{raised}	0.044	0.021	0.002	(-0.000, 0.084)
$\alpha_{Diabetes}(ref. = Yes)$ α_{No}	0.021	0.016	0.000	(-0.010, 0.054)
$\alpha_{Hypertension stage}(ref. = Stage4)$ α_{Hyst3} α_{Hyst2} β_{Hyst1}	0.090 0.077 0.095	0.0199 0.022 0.020	0.000 0.000 0.000	(0.052, 0.130)* (0.032, 0.121)* (0.055, 0.135)*
$\alpha_{Adherence}(ref. = low)(ref. = low)$ α_{high}	0.087	0.018	0.000	(0.050, 0.123)*
$\alpha_{Related disease}(ref. = None)$ α_{stroke} $\alpha_{Heartcase}$	0.021 -0.017	0.018 0.022	0.0002 0.000	(-0.014, 0.057) (-0.062, 0.026)
r_1	-0.21	0.012	0.000	(-0.01, 0.002)
r_2	-0.41	0.011	0.001	(-1.01, -0.007)*

Note: *Significant.**Abbreviations:** MC error, Monte Carlo error; CI, credible interval.

$(0, 0.001)$, $r_2 \sim \text{Normal}(0, 0.001)$, $\tau_{u1} \sim \text{Gamma}(2, 0.5)$, $\tau_{u2} \sim \text{Gamma}(2, 0.5)$, $\tau_{CD4} \sim \text{Gamma}(2, 0.5)$.

The posterior means of the parameters, standard deviations, Monte Carlo errors, and 95% credible intervals are estimated. The simulation of the posterior distribution was made using the Gibbs sampler algorithm and produced three realizations of 40,000 iterations with different initial states. A burn-in of 20,000 iterations was considered and convergence diagnoses are assessed. Inferences are then made based on independent samples taken.

Model Comparison

Analysis of data for model comparison is given in Table 3. Estimates of total DIC for the four models are 15,726.8 for BJ-exponential, 15,582.4, for BJ-Weibull, 15,658 for BJ-lognormal, and 15,778.1 for BJ-loglogistic models. The Bayesian–Weibull joint model has the smallest total DIC, AIC and BIC. Based on model comparison, inferential analysis was done using the Bayesian–Weibull joint model.

Bayesian Weibull Analysis

The posterior estimates of subject-specific random effects U_1 and U_2 are found to be significant as $\hat{\tau}_{u1} = 0.072$, 95%CI(0.049, 0.165) and $\hat{\tau}_{u2} = 1.415$, 95%CI(0.924, 2.522). It supports the assumption of heterogeneous variance for the repeated fasting blood sugar measurements.

The association parameter r_2 is significant ($\hat{r}_2 = -0.41$, $(-1.01, -0.007)$) but not the intercept ($\hat{r}_1 = -0.021$, $(-0.01, 0.002)$). The significance of the association parameter suggests that there is strong dependence between fasting blood sugar levels and survival time of hypertension patients. The Bayesian–Weibull joint model analysis in Table 4 below show that the longitudinal sub-model and fasting blood sugar were significantly associated with visit time, tobacco and alcohol use and place of residence. In survival sub-model, the survival time of hypertension patients was significantly related with baseline age, gender, family history of hypertension, khat intake, tobacco use, alcohol use, stage of hypertension, and adherence. The posterior means of the parameters, standard deviations, Monte Carlo errors, and 95% credible intervals are estimated and displayed in Table 4.

The effects of covariates identified in this study are fairly consistent with the previous findings. For example, a researcher^{17–21} found that family history of patients, alcohol use, baseline age, and stage of hypertension were risk factors associated with survival time of the patients.

The four Bayesian models based on the AFT exponential, Weibull, lognormal, loglogistic distributions were studied.

Conclusion

The aim of this study was to investigate the association of survival time and fasting blood sugar levels of hypertension patients and identify the risk factors that affect the survival time of the patients. Bayesian joint models were used with the assumption of linear mixed effect model for the longitudinal fasting blood sugar observations and of four AFT distributions for the survival time of hypertension patients.

Covariates with significant effects are identified from analysis of the Bayesian–Weibull joint model. The findings reveal that the health of hypertension patients under follow-up can be improved over time and female hypertension patients had better survival probability than male hypertension patients. Survival time of a hypertension patient was affected by baseline age, gender, family history of hypertension, khat intake, tobacco use, alcohol use, stage of hypertension, and adherence.

In conclusion, a significant number of patients were found to lack knowledge about behavioral risk factors of hypertension and so they need great attention. Therefore, teaching patients about the effect of behavioral risk factor of hypertension like alcohol use, tobacco use, and khat intake and improvement of the surveillance systems implementation of community based screening programs for early detection of hypertension are highly recommended.

Ethical Consideration

The ethical clearance was checked and approved by ethical clearance committee of Arba Minch University Department of Statistics and the Addis Ababa Administration Health Bureau Yekatit 12 Hospital Medical College medical director's office granted permission to use the patients' data for this study. For the purpose of confidentiality, there were no links with individual patients and all data had no personal identifier and were kept confidential and therefore did not require informed consent.

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Disclosure

The author declares no conflicts of interest regarding the publication of this paper.

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