Open Access Medical Statistics

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Modeling time-to-good control of hypertension using Cox proportional hazard and frailty models at Bahir-Dar Felege Hiwot Referral Hospital

This article was published in the following Dove Press journal:
Open Access Medical Statistics
3 May 2017
Number of times this article has been viewed

Ergoye Melese Sendek[1]
Sultan Hussen Hebo[2]

[1]Department of Biostatistics, [2]Department of Reproductive Health, Arba, Minch University, Arba Minch, SNNPR, Ethiopia

Purpose: The main purpose of this study was to explore possible modeling approaches of time-to-good control of hypertension using Cox proportional hazard (Cox-PH) and frailty models, using data from Bahir-Dar Felege Hiwot Referral Hospital.

Patients and methods: An institution-based retrospective cohort study was conducted in June 2014. The study population consisted of all hypertensive patients who had visited the hospital at least three times between January 1, 2009, to December 31, 2013. Five hundred patients were selected using simple random sampling. The data were collected by trained data collectors using a checklist. Statistical Package for the Social Sciences version 20 and R software were used for data entry and to process the data, respectively. First, a single covariate analysis was done using Cox-PH and univariate frailty models. Then, all variables that were significant were included in the multivariable analysis.

Results: The median survival time of hypertensive patients to attain good control was 48 months, and the mean survival time was 43.6 months. Age and systolic blood pressure (SBP) of patients had a negative relationship with the outcome. However, fasting blood sugar (FBS) had a positive relationship with the outcome. Moreover, the results showed that the progression of outcome depended on the patient's age.

Conclusion: Cox-PH-based analysis revealed that the factors that affected good control of hypertensive patients were age, SBP, FBS, and creatinine. The result of the univariate frailty analysis showed that there was unobserved heterogeneity between individuals in the study setup, which indicated that there were unmeasured covariates.

Keywords: hypertension, time-to-event, Cox proportional hazard, frailty model, Schoenfeld residuals, good control of hypertension

Introduction

According to the 1999 World Health Organization-International Society of Hypertension guidelines for the management of hypertension, hypertension is defined as a systolic blood pressure (SBP) of 140 mmHg or greater and/or a diastolic blood pressure of 90 mmHg or greater in subjects who are not taking antihypertensive medication.[1] 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.[2]

Cardiovascular disease has been recognized as being related to high-blood pressure components. It is a potent risk factor for myocardial infarction, stroke, and heart failure, which are the leading causes of death and disability worldwide.[3]

Correspondence: Ergoye Melese Sendek
Department of Biostatistics, Arba Minch University, PO Box 21, Arba Minch, SNNPR, Ethiopia
Tel +251 91 002 3249
Email muhammedergoye8@gmail.com

http://dx.doi.org/10.2147/OAMS.S128088

Hypertension is an important public health challenge that affects approximately one billion persons worldwide.[4] According to the World Health Organization, hypertension is the leading risk factor for mortality (12.7% of deaths attributable) followed by tobacco use (8.7%) and high blood glucose (5.8%).[5] The overall average prevalence of hypertension in the world was estimated as 35% (37% in males and 31% in females).[6]

According to the health and health-related indicators in Ethiopia, hypertension was the seventh leading cause of death in the country in 2001.[7] A study on the prevalence of hypertension and age-related changes in blood pressure in seminomadic and urban Oromos showed a prevalence of 0.40% in the seminomadic and 3.15% in the urban population.[8]

The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure showed that a decrease of SBP in the population by 5 mmHg would result overall in a 14% reduction in mortality due to stroke, a 9% reduction in mortality because of coronary heart diseases, and a 7% decrease in all-cause mortality.

Hypertension is also controllable with interventions. Health care providers work with hypertensive individuals to control the condition and to prevent the deleterious side effects of uncontrolled hypertension.

Although health professionals try to control blood pressure levels, there are many questions that are still unanswered: what is the change over time or does the change of blood pressure levels have different patterns on different covariates and what are the factors that accelerate blood pressure?

In Ethiopia, to the best of our knowledge, there are virtually no studies that document time-to-event data on hypertension cases; however, there are studies that focus on predictors of hypertension incidence using cross-sectional study design.

The traditional Cox proportional hazard (Cox-PH) model has the potential to deal with aspects such as censoring and to investigate the effect of explanatory variables directly on the survival time. On the other hand, frailty modeling approach accounts for this problem by specifying independence among observed data items conditional on a set of unobserved or latent variables.

In this study, we use both the Cox-PH model and its extension individual frailty model to investigate the time-to-good control hypertensive patients using different covariates.

Patients and methods

The institution-based retrospective cohort study was conducted from June 10, 2014, to June 19, 2014, in Bahir-Dar Felege Hiwot Referral Hospital located in Bahir-Dar town, Amhara region, North Western Ethiopia.

The source population were all hypertensive patients who were receiving treatment from Bahir-Dar Felege Hiwot Referral Hospital. The study population included all hypertensive patients aged ≥18 years and who had visited the hospital at least three times between January 1, 2009, and December 31, 2013, at the Bahir-Dar Felege Hiwot Referral Hospital. The patients with incomplete recording of baseline data were excluded from the study.

In this study, secondary data from the hospital registry was used to obtain the data. The calculated sample size for this study was 422 hypertensive patients, but we used all 500 hypertensive patients of source population who received treatment from Bahir-Dar Felege Hiwot Referral Hospital during January 1, 2009, to December 31, 2013. A data collection checklist was used for the data collection. Information was collected from registration forms, follow-up forms, and patient charts by three trained people and was supervised by the principal investigator. Patient sociodemographic data and blood pressure information were examined and carefully collected.

The response variable of the study was the survival time of the hypertensive patients, that is, the length of time from the start date of taking antihypertensive drugs until the date of good control of hypertension (or censor), measured in months. The independent variables of age, sex, residence, SBP, creatinine, blood urea nitrogen (BUN), and fasting blood sugar (FBS) were used for analyses.

For the purpose of data quality control, there were 2 days training for data collectors, data encoder, and data clerk personnel. Intensive supervision was done by the principal investigator. All the data were cleaned, double entered, and cross-checked for their completeness before analysis. Random samples of registration forms were reviewed by the principal investigator to conform reliability of data before data collection.

The completeness and consistency of the data were checked, coded, and double entered into Epi-Data 3.1. The data were exported to Statistical Package for the Social Sciences (SPSS) version 20 (IBM Corporation, Armonk, NY, USA) and R version 3.0.2 statistical softwares for further analysis.

The analysis and modeling were conducted in several steps. First, simple descriptive statistics such as a frequency distribution and percentages were performed to describe the characteristics of the study patients. Kaplan–Meier curve was used for the purpose of comparing the event-experiencing times of two or more groups.

At the second step, a bivariate Cox-PH model analysis was performed for each independent factor and outcome of interest to identify independent predictors.

Upon the completion of the bivariate analysis, variables with a P-value <0.25 were selected for the multivariable analysis to control for confounding and interaction effect. Context and previous studies were also considered to make a variable candidate for multivariate analysis. Once the variables were identified, multivariable analysis was performed by enter method.

Finally, the importance of each variable included in the multicovariate model was verified by different model assessments both graphically and numerically. To decide whether or not a variable is significant, the P-value associated with each parameter was estimated using the P-value <0.05 as a cut off point. The crude and adjusted hazard ratios (HRs) together with their corresponding 95% confidence intervals were computed and interpreted accordingly. To ensure that the PH assumption is valid, the numerical and graphical methods of goodness-of-fit test method that contain P-value and Schoenfeld plot were used.

The letter of ethical clearance was obtained from the ethical committee of Jimma University College of Natural Sciences. A support letter was obtained from the Bahir-Dar Felege Hiwot Referral Hospital Director to access the information from the patient records. The confidentiality and privacy of the information obtained from the patients' records were actively protected. All information were stored in locked cabinets and all staff trained in methods to protect confidentiality. All information from the patients records were assigned unique identification numbers. A backup copy of all information was kept in a locked file cabinet. As the study was retrospective, the ethical committee of Jimma University College of Natural Sciences and the Bahir-Dar Felege Hiwot Referral Hospital waived the requirement for patient consent based on the above confidentiality clauses.

Results

Descriptive statistics and nonparametric analysis

From a sample of 500 hypertensive patients, 205 (41%) patients had events (good control of hypertension) and 295 (59%) patients were censored observations. Among those sampled patients, 263 (52.6%) were female and 237 (47.4%) were male.

The mean and median follow-up time of the patients were 31.99 and 30 months, respectively, with a standard deviation of 14.195. The mean and the median age of the patients were 54.2 and 55 years, respectively. The average value of SBP was 169.8 mmHg and the median was 170 mmHg. The average FBS level of the patients was 129.57 mg/dL and the median was 114.5 mg/dL. The mean BUN level of the patients was 42.2 mg/dL and the median was 35 mg/dL. The mean creatinine value of the patients was 1.356 mg/dL and the median was 1.1 mg/dL. The minimum survival time was 9 months, and the maximum survival time was 60 months (Table 1).

From the 500 sampled cases, 263 patients had a follow-up time of ≤30 months and 237 patients had a follow-up time of >30 months; among these, 133 (50.6%) patients were male and 130 (49.4%) were female who had a ≤30 months follow-up time, and 130 (54.9%) males and 107 (45.1%) females had a >30 months follow-up time (Table 2). The median survival time of hypertension patients to have good control was 48 months (4 years) ($\hat{S}_{(t=48)}$ =0.5), and the mean survival time was 43.6 months (3.63 years).

Nonparametric analysis

Kaplan–Meier survival curves

The Kaplan–Meier survival curves showed that the female group attained a good control of hypertension faster than the male group <40 months; and >40 months, the male group attained a good control of hypertension faster. In other words, <40 months, the proportion of subjects attaining good control of hypertension is greater for females than males. In the Kaplan–Meier curve of age, the curve of patients whose age >45 years lying above patients whose age ≤45 years indicates that the age group >45 years attained good control of hypertension faster than the age group of >45 years. In the Kaplan–Meier curve of SBP, the curve of patients whose SBP >165 mmHg is lying above the curve of patients whose SBP <165 mmHg, indicating that the patients whose SBP

Table 1 Summary table for time-to-good control of hypertension

Covariates	Minimum	Maximum	Mean	Standard deviation	Median
Time (months)	9	60	31.99	14.195	30
Age (years)	18	95	54.2	17.548	55
Systolic blood pressure (mmHg)	145	240	169.8	17.426	170
Fasting blood sugar (mg/dL)	27	343	129.57	56.775	114.5
Blood urea nitrogen (mg/dL)	80	310	42.2	29.897	35
Creatinine (mg/dL)	0.1	10.6	1.356	0.8809	1.10

Table 2 Cross-tabulation of sex, age, and systolic blood pressure of hypertensive patients with status and time

Covariates	Group	Status		Time (months)		Total (%)
		Event (%)	Censor (%)	≤30 (%)	>30 (%)	
Sex	Female	108 (52.7)	155 (52.5)	133 (50.6)	130 (54.9)	263 (52.6)
	Male	97 (47.3)	140 (47.5)	130 (49.4)	107 (45.1)	237 (47.4)
	Total	205 (100)	295 (100)	263 (100)	237 (100)	500 (100)
Age (years)	≤45	75 (36.6)	84 (28.5)	93 (35.4)	66 (27.8)	159 (31.8)
	>45	130 (63.4)	211 (71.5)	170 (64.6)	171 (72.2)	341 (68.2)
	Total	205 (100)	295 (100)	263 (100)	237 (100)	500 (100)
Systolic blood pressure (mmHg)	≤165	103 (50.2)	121 (41.0)	160 (60.8)	64 (27)	224 (44.8)
	>165	102 (49.8)	174 (59.0)	103 (39.2)	173 (73.0)	276 (55.2)
	Total	205 (100)	295 (100)	263 (100)	237 (100)	500 (100)

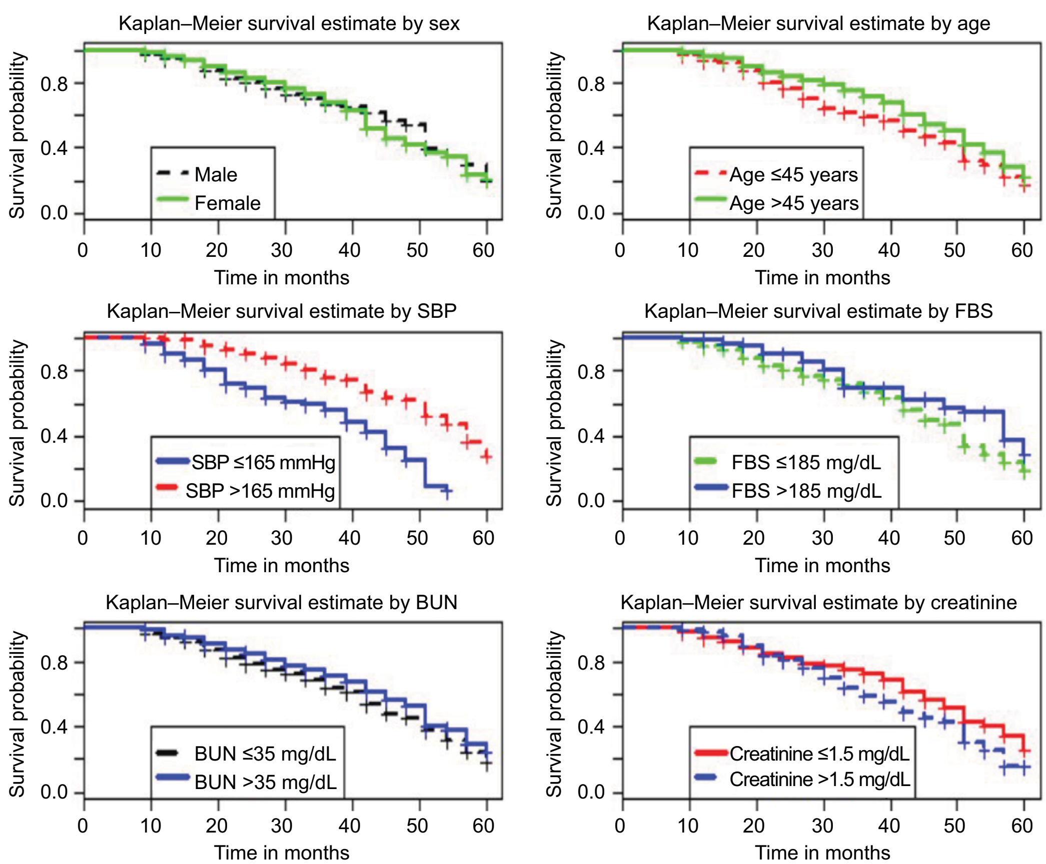

Figure 1 Kaplan–Meier estimates for hypertension data set by sex, age, SBP, FBS, BUN, and creatinine.
Abbreviations: BUN, blood urea nitrogen; FBS, fasting blood sugar; SBP, systolic blood pressure.

>165 mmHg attained good control of hypertension faster than patients whose SBP <165 mmHg (Figure 1).

Comparison of survival curves

Log-rank test for equality of survival functions

The survival curve results indicate that there is a significant difference between the age (≤45 years and >45 years), SBP (≤165 mmHg and>165 mmHg), FBS (≤185 mg/dL and >185 mg/dL), and creatinine (≤1.5 mg/dL and >1.5 mg/dL) groups. On the other hand, there is no significant difference between the survival curves for BUN (≤35 mg/dL and >35 mg/dL) relating to the patients and sex (male and female).

Factors associated with time-to-good control of hypertension

In the univariable analysis, the predictor variables of age, SBP, BUN, and creatinine are statistically significant at a 5% level of significance for good control of hypertension.

Furthermore, using a modest level of significance of 25%, the variable FBS was included in the multivariable model for further investigation. However, the variable sex was not statistically significant at any level, and hence, not included in the multivariable analysis (Table 3).

The predictor variable BUN was statistically significant at a 5% level of significance for good control of hypertension in the univariable analysis, but it was not statistically significant in the multivariable analysis (Table 3).

By removing the variable BUN, a model containing the covariates age, SBP, FBS, and creatinine fitted and all the covariates, except for creatinine, were found to be statistically significant. This is the best model compared with the above and other multivariable models because it has a smaller Akaike Information Criterion (AIC) value (Table 4).

The best Cox-PH multiple covariate model contained age, SBP, FBS, and creatinine. From these, the variables age and FBS were statistically significant at a 5% level, while SBP was statistically significant at all levels of significance (Table 5).

Therefore, the fitted Cox-PH model for hypertension data set can be represented as follows:

$$\lambda(t|X) = \lambda_0(t) * e^{-0.008161\text{Age}-0.036917\text{SBP}+0.002905\text{FBS}+0.124872\text{Creatinine}}$$

HR

The HR for the effect of SBP on patients adjusted for creatinine has the value of 0.964138. This value can be obtained by exponentiation of the coefficient −0.036520 of the SBP variable. The HR value can be interpreted to mean that the larger SBP group (>165 mmHg) has 0.964138 times the hazard as the smaller SBP group (≤165 mmHg) to attain good control of hypertension. With a 95% confidence interval, the hazard ranged from as low as 0.9526 and as high as 0.9759.

The hazard of good control of hypertension for the age group of >45 years is 0.987335 times less likely than the hazard for the age group of ≤45 years. With a 95% confidence interval, the hazard can range from as low as 0.9776 and as high as 0.9972.

Table 3 Univariable and multivariable analyses of Cox proportional hazard

Covariates	Univariable analysis				Multivariable analysis			
	β	*P*-value	HR	95% CI for HR	β	*P*-value	HR	95% CI for HR
Age (years)	−0.0121	0.0017	0.988	0.9805, 0.9955	−0.008050	0.0389	0.9920	0.6339, 1.1390
Systolic blood pressure (mmHg)	−0.0339	$4.3e^{-14}$	0.967	0.9581, 0.9752	−0.03652	$2.59e^{-13}$	0.9641	0.2691, 0.4948
Fasting blood sugar (mg/dL)	−0.00194	0.098	0.998	0.9958, 1	0.002912	0.0282	1.0029	1.0088, 1.7786
Blood urea nitrogen (mg/dL)	−0.00501	0.049	0.995	0.99, 1	−0.00128	0.6213	0.9987	0.6879, 1.2118
Creatinine (mg/dL)	0.15	0.036	1.16	1.01, 1.337	0.124024	0.0683	1.1320	0.5882, 1.3678

Note: β, coefficient for covariates.
Abbreviations: CI, confidence interval; HR, hazard ratio.

Table 4 Model selection for hypertension data set

Models	Covariates in the model	Number of parameters	Akaike Information Criterion	Likelihood ratio	*P*-value
1	Age, SBP, FBS, blood urea nitrogen, creatinine	5	2125.019	76.05	$5.662e^{-15}$
2	Age, SBP, FBS, creatinine	4	2123.271	75.8	$1.332e^{-15}$
3	Age, SBP, FBS	3	2124.25	72.82	$1.11e^{-15}$
4	Age, SBP, FBS, creatinine, age×SBP, age×FBS, age×creatinine	7	2127.517	77.55	$4.341e^{-15}$
5	Age, SBP, creatinine, age×creatinine	4	2126.033	73.03	$5.218e^{-15}$
6	Age, SBP, creatinine, age×SBP	4	2127.607	71.46	$1.11e^{-14}$
7	Age, SBP, creatinine, age×FBS	5	2125.162	75.91	$5.995e^{-15}$
8	Age, SBP, FBS, SBP×FBS	4	2124.215	74.85	$2.109e^{-15}$

Abbreviations: FBS, fasting blood sugar; SBP, systolic blood pressure.

Table 5 Multiple covariate analysis for the best model of Cox proportional hazard

Covariates	β	Standard error (β)	*P*-value	HR (95% CI)
Age (years)	−0.008161	0.003895	0.0361*	0.991873 (0.9843, 0.9995)
Systolic blood pressure (mmHg)	−0.036917	0.004932	$7.13e^{-14}$	0.963756 (0.9545, 0.9731)
Fasting blood sugar (mg/dL)	0.002905	0.001324	0.0282*	1.002910 (1.0003, 1.0055)
Creatinine (mg/dL)	0.124872	0.067934	0.0660	1.133004 (0.9918, 1.2944)

Note: *Statistically significant at $P<0.05$.
Abbreviations: CI, confidence interval; HR, hazard ratio.

Model diagnostic

Cox–Snell residuals

The Cox–Snell residuals plot showed that an estimate of the cumulative hazard lies along a straight line through the origin; this result confirmed that the PH assumption was fulfilled. Therefore, the overall model fits the data reasonably well (Figure 2).

Martingale residuals

The Martingale residual plot showed that this model was the best model to fit the collected hypertension data set due to the approximate straight line produced (Figure 3).

Schoenfeld residuals

The Schoenfeld residual plot showed an approximate straight line for the functional form of each covariate, which indicates that each variable has a linear functional form (Figure 4).

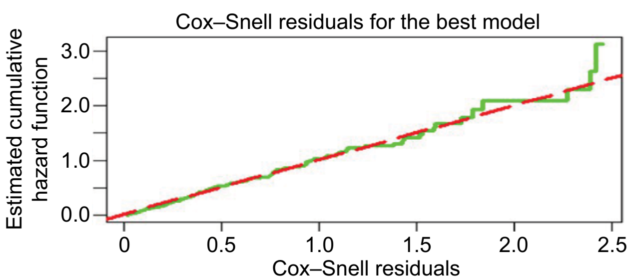

Figure 2 Cox–Snell residual plot of the best-fitted model for hypertension data set.
Note: The red line indicates the linear trend, while the green line indicates the hypertension data set.

Deviance residuals

The deviance residual plot showed a roughly symmetrically distributed around zero with no outlier observation (Figure 5).

Therefore, all four residual plots confirmed that the selected final model for the hypertension data set was a good fit.

PH assumption checking

Tests and graphs based on the Schoenfeld residuals

In this study, the significant cox.zph test for creatinine (P=0.0226) did not fulfill the PH assumption (Table 6).

The Schoenfeld residual plot showed that the variable creatinine did not fulfill the PH assumption because the plot is somewhat quadratic rather than in a straight line. However, the plots of the other three covariates included in the model showed a straight line, which indicates that these variables fulfill the PH assumption (Figure 6).

The plot log [−log S(t)] versus time also showed that the plot of a variable creatinine cross each other; therefore, this variable did not fulfill the PH assumption, but the remaining three covariates fulfill the PH assumption (Figure 7).

Frailty model building

In the univariable frailty analysis, the predictor variables of age, SBP, BUN, and creatinine were statistically significant at 5% for good control of hypertension, such as univariable Cox-PH analysis. Furthermore, using a modest level of significance of 25%, the variable FBS was included in the multivariable model for further investigation. However, the variable sex was not included in the multivariable analysis (Table 7).

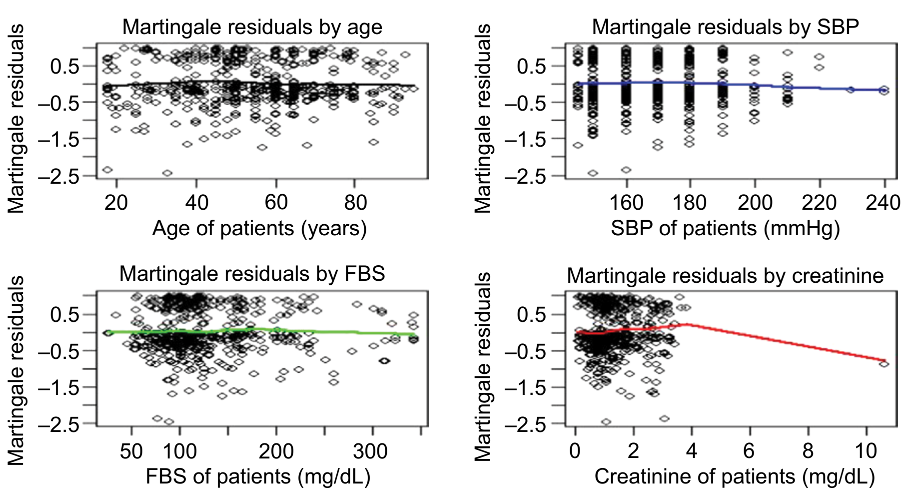

Figure 3 Martingale residuals plot of the best-fitted model for hypertension data set.
Abbreviations: FBS, fasting blood sugar; SBP, systolic blood pressure.

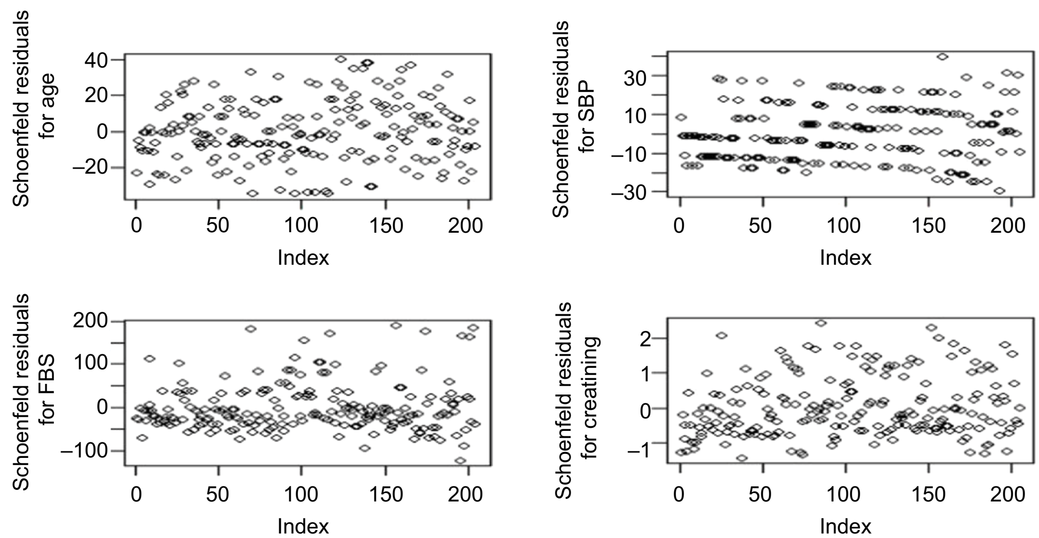

Figure 4 Schoenfeld residuals plot of the best-fitted model for hypertension data set.
Abbreviations: FBS, fasting blood sugar; SBP, systolic blood pressure.

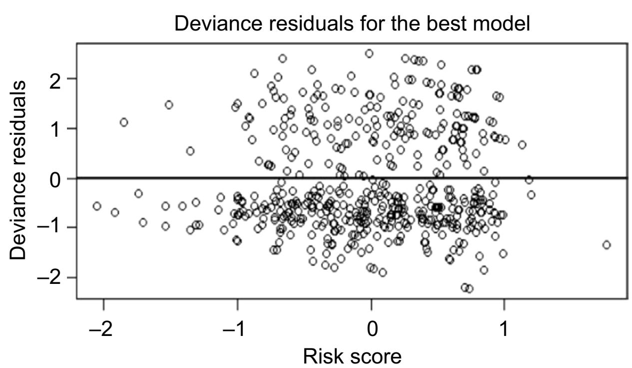

Figure 5 Deviance residuals plot of the best-fitted model for hypertension data set.

Table 6 Statistical test for proportional hazard assumption of the covariates and their interaction with log of time and Schoenfeld residual

Covariates	*P*-value	Rho	χ^2
Age	0.1626	0.10267	1.950281
Systolic blood pressure	0.2154	0.08689	1.534951
Fasting blood sugar	0.9847	0.000369	−0.00129
Creatinine	0.19292	5.202351	0.0226
Global	0.0531	NA	9.341522

Abbreviation: NA, not applicable.

The predictor variable BUN was statistically significant in the univariable analysis based on frailty, but it was not statistically significant in the multivariable analysis. By removing BUN, the model that contained the covariates of age, SBP, FBS, and creatinine fitted and all the covariates were found to be statistically significant. This is the best model compared with the above and other multivariable models because it has a smaller AIC value (Table 8).

The frailty effect was observed for those variables that were statistically significant at 0.10 levels in univariate frailty analysis and indicates high frail, which means that there is unobserved heterogeneity between individuals (other important covariates have not been measured).

Discussion

In this study, the hypertension data set was analyzed using Cox-PH and univariate frailty models. After fitting the Cox-PH model, the goodness of fit was assessed through residual plots.

The median survival time of hypertension patients to attain good control was 48 months, and the mean survival time was 43.6 months. Patients who have a smaller SBP were more effective overall than patients having a larger SBP to attain a good control of hypertension.

The age group >45 years attained a good control of hypertension faster than the group aged ≤45 years and the SBP group >165 mmHg attained a good control of hypertension faster than SBP group ≤165 mmHg. Among the covariates, sex and BUN had no significant effect on the outcome variable, but the remaining five covariates had significant effects on the good control of hypertension. There was a significant difference between survival curves of age, SBP, FBS, BUN, and creatinine groups but no difference between the survival curves between male and female patients.

When checking the PH assumption, except the variable creatinine, all three covariates fulfilled the PH assumption. The model was stratified by creatinine in order to manage nonproportionality.

All three covariates included in the model had a statistically significant effect on the good control of hypertension. The *P*-value of likelihood ratio test with a 54.5 degrees of freedom indicated that rejecting the null hypothesis meant that there was unobserved heterogeneity between individuals

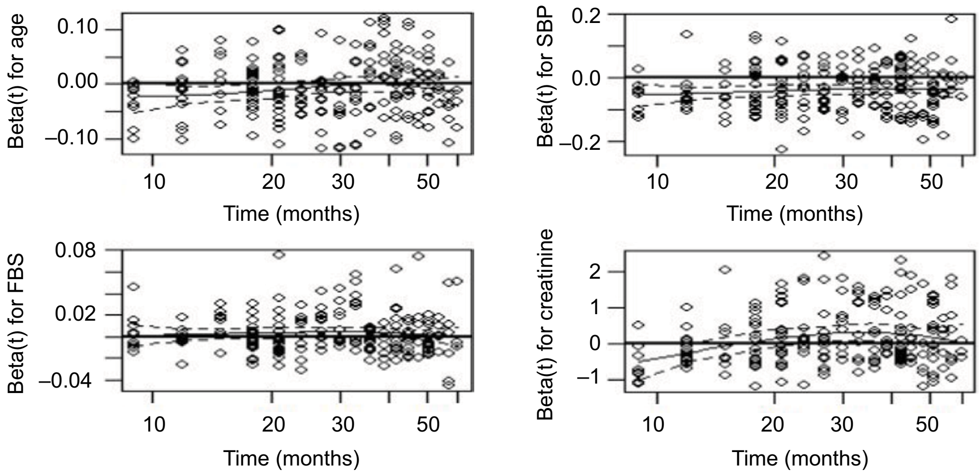

Figure 6 Plots of scaled Schoenfeld residuals for each covariate in a best model.
Abbreviations: FBS, fasting blood sugar; SBP, systolic blood pressure.

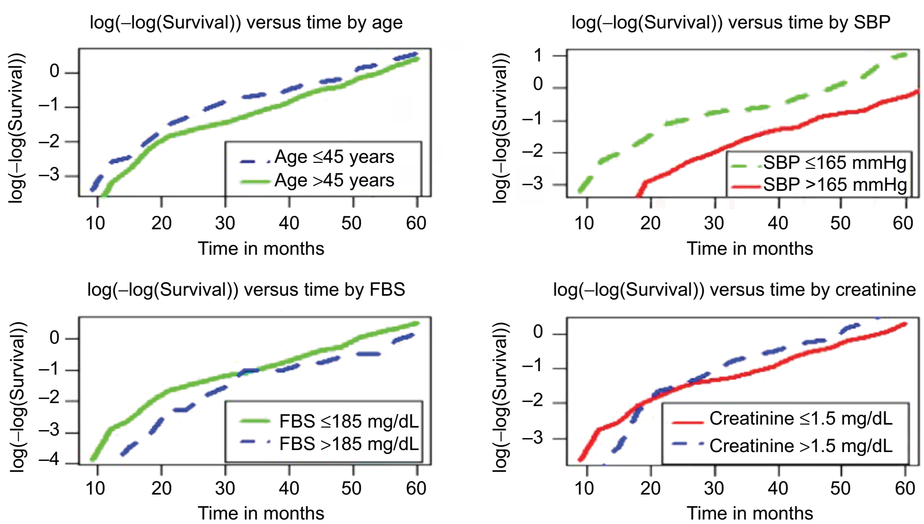

Figure 7 Plots of log [–log S(t)] versus time for each covariate in a best model.
Abbreviations: FBS, fasting blood sugar; SBP, systolic blood pressure.

of hypertensive patients. Modeling a frailty effect was not only a function of unobserved heterogeneity but also of observed covariates.

Finally, the final fitted model showed that as age and SBP of patients increased, it took a short period of time to attain a good control of hypertension and vice versa. However, there was a positive relationship between FBS and the good control of hypertension.

Even though the study attempted to exhaust a wide variety of covariates, the study was observational based on the secondary data, and the results may be subject to confounding factors that were not measured or controlled for. Sociodemographic data might be subject to the inaccuracies and reporting biases inherent in self-reported data. However, it is believed that errors in the exposure measurement were nondifferential and that any bias would be toward the null.

Conclusion

This study revealed that from the start date of taking antihypertensive drugs, the follow-up time for hypertensive patients on average was approximately 32 months (2.67 years) with median survival follow-up time estimated to be 30 months (2.5 years). Hypertensive patients attained a good control of hypertension after an average of 43.6 months (3.63 years), with a median survival time of 48 months (4 years).

The Cox-PH analysis result showed that the major factors that affect the good control of hypertensive patients were age, SBP, and FBS. Among these, age and SBP had an inverse relationship with the outcome variable, but FBS had a direct relationship with the outcome variable (i.e., good control of hypertension).

According to the result of univariate frailty model analysis, there was unobserved heterogeneity between individuals

Table 7 Univariable and multivariable analyses of univariate frailty

Covariates	Univariable analysis					Multivariable analysis				
	β	SE (β)	χ^2	DF	*P*-value	β	SE (β)	χ^2	DF	*P*-value
Age	–0.0121	0.0039	9	1	0.0017	–0.0096	0.0044	4.77	1	$2.9e^{-02}$
Systolic blood pressure	–0.04	0.0052	58.7	1	$1.9e^{-14}$	–0.0405	0.0055	54.14	1	$1.9e^{-13}$
Fasting blood sugar	–0.0019	0.0012	2.74	1	0.098	0.0029	0.0015	4.13	1	$4.2e^{-02}$
Blood urea nitrogen	–0.005	0.0026	3.86	1	0.049	–0.0015	0.0028	0.27	1	$6.0e^{-01}$
Creatinine	0.15	0.072	4.41	1	0.036	0.1339	0.0791	2.86	1	$9.1e^{-02}$
Frailty (id)			0.01	0.01	0.71			59.39	52.9	$2.5e^{-01}$

Abbreviations: SE, standard error; DF, degree of freedom.

Table 8 Parameter estimates (SE) in the univariate gamma frailty model applied to hypertension data set

Covariates	β	SE (β)	χ^2	DF	*P*-value
Age (years)	–0.00962	0.00436	4.87	1	$2.7e^{-02}$
Systolic blood pressure (mmHg)	–0.04082	0.00543	56.61	1	$5.3e^{-14}$
Fasting blood sugar (mg/dL)	0.00296	0.00145	2.91	1	$4.1e^{-02}$
Creatinine (mg/dL)	0.13419	0.07862	57.1	1	$8.8e^{-02}$
Frailty (id, dist=gamma)				57.1	$2.6e^{-01}$

Notes: Likelihood ratio test=179 on 54.5 DF, *P*-value=$3.44e^{-15}$, n=500.
Abbreviation: SE, standard error.

(i.e., there was another unmeasured covariate that affected the good control of hypertension but this was not included in our study).

Therefore, modeling the survival time of this disease helps to identify the factors that affect the success of the therapy, which helps to discover new treatment modality by considering the identified factors. Thus, further studies should be done in the area using these newly developed and flexible methodologies by including additional covariates (social, economic, behavioral, nutritional, environmental, and the like) that may affect good control of hypertension.

Acknowledgments
We would like to say thank you very much for all staff members of Bahir-Dar Felege Hiwot Referral Hospital for their great support and commitment. Our warmest gratitude goes to the Ethiopian Ministry of Education for financial support. The authors are grateful to all health professionals and hypertensive patients who participated in the study.

Author contributions
SHH and EMS conceived and designed the study, developed data collection instruments, and supervised data collection. EMS participated in the testing and finalization of the data collection instruments and coordinated study progress. SHH and EMS performed the statistical analysis, and SHH wrote all versions of the manuscript. Both authors critically revised and approved the final manuscript.

Disclosure
The authors report no conflicts of interest in this work.

References
1. World Health Organization, 1999. International Society of Hypertension Guidelines for the Management of Hypertension. Guidelines Subcommittee. *J Hypertens*. 1999;17(2):151–183.
2. Giles TD, Berk BC, Black HR, et al; On behalf of the Hypertension Writing Group. Expanding the definition and classification of hypertension. *J Clin Hypertens (Greenwich)*. 2005;89:505–512.
3. Benetos A, Thomas M, Safar K, Bean L. Systolic blood pressure, diastolic blood pressure, and pulse pressure: an evaluation of their joint effect on mortality. *J Am Coll Cardiol*. 2001;37(1):163–168.
4. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289(19): 2560–2572.
5. World Health Organization. *Global Health Risks Summary Tables*. Geneva, Switzerland: Health Statistics and Informatics Department, World Health Organization; 2009. Available from: http://www.who.int/evidence/bod. Accessed June 10, 2014.
6. Pereira M, Lunet N, Azevedo A, Barros H. Differences in prevalence, awareness, treatment and control of hypertension between developing and developed countries. *J Hypertens*. 2009;27(5):963–975.
7. World Health Organization, 2004. Ethiopia Strategy Paper. In: *World Health Organization Health Action in Crises*. Available from: www.who.int/entity/hac/crises/eth/Ethiopia_strategy_document. Accessed June 10, 2014.
8. Pauletto P, Caroli M, Pessina AC, Dal Palù C. Hypertension prevalence and age-related changes of blood pressure in semi-nomadic and urban Oromos of Ethiopia. *Eur J Epidemiol*. 1994;10(2):159–164.