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Predictors of Pulse Rate and Time to First Recovery among Diabetes Mellitus Patients under Treatment; Application of Joint Model

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Abstract

Background: The main objective of this study was to investigate joint predictors of pulse rate and time to first recovery among diabetes mellitus patients under treatment.

Method: A retrospective cohort study design was conducted in this study. Linear mixed model and cox-proportional hazard model for separate analysis and joint model for the two responses were used.

Results: Among the participants, 66.7% of patients were female, and 19% of the patients had a family disease history. The time needed to reach the first recovery among male patients was significantly longer compared to female patients. The time needed to reach the first recovery among patients with no other related disease was significantly shorter as compared with patients with other related diseases (HR=0.0893).The estimated association parameter (α) in the joint model was -1.5108, with a p-value<0.001. The result indicates that the higher the pulse rate was associated with the lower time to the first recovery.

Conclusion: The variable age, residence area, other related diseases, and hypertension significantly and jointly affected both of the two responses. Due attention should be given to aged patients, patients with family disease history, patients with other related diseases, and rural patients.

Keywords: Linear mixed model • Insulin • Time to first recovery • Cox-proportional hazard model • Joint model

Abbreviations: SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; PR: Pulse Rate; AIC: Akakie Information Criterion; BIC: Bayesian Information Criterion; CI: Confidence Interval; DM: Diabetes Mellitus

Introduction

Diabetes Mellitus (DM) is a metabolic disorder that has been resulting from a defect in insulin secretion, insulin action, or both. Insulin shortage in turn leads to chronic hyperglycemia with instabilities of carbohydrate, fat, and protein metabolism [1]. It is one of the chronic non-communicable diseases which have emerged as a leading worldwide health problem. It is also a known risk factor for blindness, vascular brain diseases, renal failure, and limb amputations [2]. Diabetes mellitus is a disease in which the body does not produce or respond properly to insulin (a hormone necessary for controlling the levels of glucose) [3]. Some of the signs and symptoms of diabetes are increased thirst, frequent urination, extreme hunger, unexplained weight loss, presence of ketones in the urine, fatigue, and frequent infections, such as gums or skin infections. The rate of diabetes patients with complications is increasing on a daily basis, admission is made either due to diabetes or diabetes complications such as stroke, hypertension, amputation, nephropathy, neuropathy, retinopathy, cardiovascular, impotence, skin lesions. A survey of trends in the leading causes of death in the USA between 1970 and 2002 found that the largest percentage reductions in age-adjusted death rates were stroke (63%) and heart disease (52%) [4]. Urbanization has driven dramatic changes in lifestyle and in particular in developing countries. With these quick or speedy transitions come accompanying increases in risk factors for non-communicable disease like type 2 diabetes. Estimates of the current and future burden of diabetes are important to appropriately allocate or assign

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allocate or assign resources, drive health promoting policies, and encourage action to prevent diabetes in future generations [5].

Diabetes is one of the thoughtful health problems in the world and contributes directly or indirectly for thousands of deaths annually worldwide [6]. Diabetes is an important public health challenge, it is a global non-communicable chronic disease and it is highly asymptomatic, a person experiences very few signs and symptoms until damage occurs to a target organ [7]. Diabetes is increasing at speedy rate throughout the world and about 80% of diabetic patients found in low and middle income countries. The occurrence of diabetes, especially type II, is rapidly growing in the world. In 1985, an estimated 30 million people suffered with this chronic disease and by the end of 2006, had increased to 230 million [8].

In Africa, the disease is very common and serious problem in which many people are suffering by the disease [9]. The prevalence of hypertension was highest in Africa at 30% for all adults combined in 2014 [10]. Hypertension has shown a rapid increase in prevalence affecting significant numbers of individuals in Sub-Saharan Africa [11]. The prevalence in Sub-Saharan Africa was in the range of 25.4%-41.1% in men and 27.2%-38.7% in women [12].

The prevalence of diabetes mellitus in Ethiopia, According to the 2011 report of the International Diabetes Federation (IDF), about 3.5% of adults are living with diabetes [13]. A study done by IDF Atlas in 2017, the projected national diabetes (20-79 years of age) prevalence in Ethiopia was estimated to be 5.2% [14]. Ethiopia as one of the developing countries has been showing changes that shifts the lifestyle of the people towards urbanization, particularly in recent decades. These rapid changes have led to the emergence of non-communicable chronic diseases such as diabetes mellitus. It is important to bear in mind that, currently up to 50% of patients with type 2 diabetes already have some evidence of complications at the time of diagnosis. Moreover, due to limited materials and human resources, the major focus in the country is on combating infectious diseases.

Even if the prevalence of Diabetes Mellitus (DM) is substantially increasing in Ethiopia, particularly in the study area, little researches has been conducted for diabetes and related cardiovascular diseases in separate analysis [15]. As far as the authors' knowledge is concerned, there is scarcity of studies on the regard of the determinant factors affecting jointly for progression change of pulse rate and time to first recovery for diabetes mellitus patients using joint modeling.

Therefore, the main objective of this study was to identify factors affecting jointly on pulse rate and time to first recovery among diabetes mellitus patients under treatment at Felege-Hiwot teaching and specialized hospital, Ethiopia whose follow-ups were from 1st April 2017 to 31 March 2020.

Methods and Materials

Study area and study design

This study was conducted using retrospective cohort study designs based on the data obtained from Felege-Hiwot teaching and specialized hospital, Bahir-Dar, North-Western Amhara, Ethiopia. The hospital provides clinical care for patients infected with DM patients and it has been producing a number of health professionals. The study area selected with regard to large catchments' of population and accessibility regardless of budget and time constraints. Furthermore, the area endowed with availability of diabetes mellitus patient services, since the present study targets on of diabetes mellitus.

Source of data and period

In current investigation, secondary data extracted in charts of each patient in the outpatient department of the hospital was used. In the hospital, the longitudinal variable of interest (pulse rate) was recorded at each follow up visits. The time for first recovery of the patients was also properly recorded by the health staff.

The chart of each patient contained epidemiological, laboratory and clinical information of all DM patients with time to first recovery including socio-demographic variables. The outcome variables and related covariates were measured at every 3 months irrespective of patient visits to OPD section of chronic disease at Felege Hiwot referral hospital.

Study variables

Response variable: The response variables for current investigation were the pulse rate which is measured in beats per minute and time to first recovery of diabetic patients.

Predictor variables: The explanatory variables in current investigation were age in years, gender (female=0, male=1), marital status (without partner=0, with partner=1), place of residence (rural=0, urban=1), presence of related diseases (no=0, yes=1), family disease history (no=0, yes=1), systolic and diastolic blood pressures, albumin and follow up visits.

Inclusion and exclusion criteria

Diabetic patients whose age of 18 years and above and started their treatment at Felege Hiwot teaching and specialized hospital in the study period with a minimum two follow ups were included under investigation. On the other hand, diabetic patients less than 18 years, who had less than two follow ups and whose registration was out of the study periods were excluded in this study.

Method of data analysis

In this study, a linear mixed effects model for longitudinal pulse rate data, cox-proportional hazards model for survival data and joint model for joint predictor of pulse rate and time to first recovery for DM patients were employed.

The separate model of longitudinal analysis was used to identify factors affecting the longitudinal change of pulse rate, similarly, the separate analysis of the survival model was employed to identify factors affecting the time to event data. Finally, the joint model of the two response variables was conducted to investigate the joint predictors of both longitudinal outcome and time to event responses. The data was analyzed using statistical software packages R version 4.00, SAS version 9.2.

Descriptive statistics and data exploration

Exploratory data analysis was conducted in order to investigate various associations, structures and patterns exhibited in the data. This consists of individual profile plots, mean structure, correlation structure and variance structure plots were obtained in order to gain some insights of the data [16,17]. Since the data in current investigation was unbalanced and had not equal observation time, smoothing techniques that highlight the typical response was used as a function of an explanatory variable without reliance on specific parametric model.

Longitudinal data analysis

There are two common cases that can overcome longitudinal responses, the first is when multiple observations are made on the same subject over time and the second is when the measurements are taken on related subjects. In both cases, the responses are likely to be correlated. Usually conceptualize longitudinal data involves at least two repeated measurements made over a relatively long period of time [18]. There are two source of variations considered in the longitudinal data sets. Those are the within-subject and between subject variations; the former arises during the measurements within each subject and help us to study changes overtime; and the latter arises during the measurement between different subjects and help us to understand differences between subjects.

Measurements made on the same variable for the same subject are likely to be correlated. Models fitted to longitudinal or repeated measures data involve the estimation of covariance parameters to capture this correlation.

Linear Mixed Model (LMM)

A standard modeling framework for the analysis of longitudinal data is the mixed effects model a mixed model is one that contains both fixed and random effects. The fixed effects represent the mean response, while the random effects represent the individual level responses. Linear Mixed Models (LMM) may be expressed in different but equivalent forms. For the continuous case, the LMM provide a general and flexible modeling framework where subject specific random effects, assumed to follow a normal distribution, are included to account for the correlation [19].

Variance-covariance structure

For an analysis to be valid, the covariance among repeated measures must be modeled properly.

Hence, the covariance structure was compared using certain criterion like AIC, BIC.

Parameter estimation for current investigation was conducted using maximum likelihood estimation includes both regression coefficient and the variance component, that is, both fixed-effects and random effects terms in the likelihood function and it treats β as fixed but unknown quantities.

Survival data analysis: It involves the modeling and analysis of data that has a major endpoint the time until an event occurs (time-to-event data). In analyzing survival data, two functions that are dependent on time are of particular interest: the survival function and the hazard function. The survival function (t) is defined as the probability of surviving at least to time t. The hazard function is the conditional probability of dying at time t having survived to that time [20].

Missing data treatment: Missing values were handled using is multiple imputations, which is one way to address this problem by imputing multiple values for a single unobserved one. Consequently, the uncertainty of the imputation was taken into account, by including the discrepancy between the imputed values in the final estimation. The multiple imputations replace each missing item with two or more acceptable value representing a distribution of possibilities.

Joint modeling of longitudinal and survival data: The joint model of the longitudinal and survival data was conducted by imposing the survival model, which is of primary interest, with a suitable model for the repeated measurements.

Results

The baseline socio-demographic and clinical characteristics of patients included in the analysis where presented in Table 1.

Variable	Category	Total (%)	Recovered (%)	Censored (%)
Sex	Male	126 (33.3)	42 (11.1)	84 (22.2)
	Female	252 (66.7)	84 (22.2)	168 (44.5)
Residence area	Rural	157 (41.5)	48 (12.7)	109 (28.8)
	Urban	221 (58.5)	78 (20.6)	143 (37.9)
Marital Status	With Partner	306 (81)	90 (23.8)	216 (57.2)
	Without partner	72 (19)	36 (9.5)	36 (9.5)
Family history	Yes	72 (19)	30 (7.9)	42 (11.1)
	No	306 (81)	96 (25.4)	210 (55.6)
Type of DM	Type 1	108 (28.6)	36 (9.5)	72 (19.1)
	Type 2	206 (57.1)	72 (20)	144 (37.1)

	Type 3	54 (14.3)	18 (4.8)	36 (9.5)
Related disease	Yes	198 (52.4)	54 (14.3)	144 (38.1)
	No	180 (47.6)	72 (19.0)	108 (28.6)
Total		378 (100)	126 (33.3)	252 (66.7)

Table 1. Summary statistics for categorical independent variables included in the study.

The average number of baseline pulse rate was 90.1 beats per minute with standard deviation 15.12. Thus, based on the current data, out of 378 patients, 126 (33.3%) patients were recovered from DM while the other 252 (66.7%) of patients were censored patients.

According to Table 1 results of the patient's characteristics of categorical predictor variables of DM patient out of a sample of 378 patients 126 (33.3%) were males and the remaining 252 (66.7%) were female. Majority 221 (58.5%) diabetes mellitus patients were residence in urban area and the rest 157 (41.5%) patients were residence in rural area. When we see the marital status of patient 72 (19%) were living without partner during the study and majority of the patient 306 (81%) live with a partner during a study period. Nearly one-fourth (19%) of the patients had family history of disease. According to the Type of diabetes mellitus, 108 (28.6%) of them were had by type 1, 206 (57.1%) were had by Type 2 and the remaining 54 (14.3%) patients were had by type 3. Among the participants, 198 (52.4%) of them had related disease and the remaining 180 (47.6%) of patients had no related disease.

Based on the result of Table 1, out of the total of 378 diabetes mellitus follower patients about 22.2% of female patients were first recovered from the disease and the remaining 44.5% were censored. When viewed from the residence area of the patients, 20.6% of urban area residence and 12.7% of rural patients were first recovered from the disease in a follow up period. Based on the type of diabetes mellitus, out of 108 type 1, 206 type 2 and 54 type 336 (9.5%), 72 (20%) and 18 (4.8%) of patients showed first recovery from the disease respectively. And the remaining variables are interpreting the same way. Similar to the categorical variables, covariates were also described and the result indicates that the mean base line age of patients was 35.6 years with standard deviation of 12.45 years. The mean base line of SBP and DBP were 155.1 with standard deviation of 25.37 and 100.9 with a standard deviation of 24.02 respectively. The mean of base line pulse rate was 90.1 with a standard deviation of 15.12. The mean of base line of albumin was 1.5 with the standard deviation of 1.74.

Separate analysis of longitudinal data: To conduct the separate analysis of longitudinal data, the assumptions of linear mixed effect model was conducted using Q-Q plots and box plots. The normality assumption of the pulse rate was also tested with histogram and the result revealed that the right and the left tails seem to be equal.

Selection of covariance structure in linear mixed model: To identify the appropriate covariance structure, the four covariance structures namely, Compound Symmetry (CS), first order Autoregressive (AR (1)), Toeplitz (TOEP) and Unstructured (UN) were compared using AIC and BIC assuming that the model with smaller AIC and BIC as best model to fit the data. Based on the result in Table 2, autoregressive (1) covariance structure was selected due to the smallest value of AIC and BIC compared to with the remaining covariance structures.

Covariance structure	Information criteria	
	AIC	BIC
AR(1)	16523.32	16631.69
TOEP	16874.97	17251.4
UN	16594.88	16791.35
CS	16647.74	16892.36

Table 2. Covariance structure comparisons for LMM.

Selection of random effect for LMM was also done using AIC and BIC as indicated in Table 3. The result in Table 3 indicates that, random intercept and random slope model was selected to investigate the random component of linear mixed effect model.

Model	Random effect	Information criteria	
		AIC	BIC
1	Random intercept only	16969.12	16952.39
2	Random slope only	17205.1	17145.82
3	Random intercept and random slope	16725.64	16822.48

Table 3. Selection of random effect to be included in LMM.

Univariate analysis for linear mixed model: A univariate analysis was performed in order to see the effect of each covariate on pulse rate by using purposeful variable selection in linear mixed effect model analysis and to select variables to be included in the multivariable analysis. Based on univariate analysis the variable follows up time of patient, family history, residence, age, systolic blood pressure, diastolic blood pressure, related disease and sex of patients were some candidate variables for multivariable analysis of linear mixed model at 5% level of significance.

Multivariate analysis for linear mixed model

Multivariable analysis of linear mixed model was done by using all significant covariates at univariate analysis. The result, in Table 4, indicates that the predictor variables age, place of residence, related disease, family history of diabetes mellitus, SBP, DBP were significantly associated with the change of pulse rate at 5% of level of significance. Under the random effect result, the estimated subject-specific variability was statistically significant at 5% significant.

Variables	Estimate	Sd. Error	95% CI		p-value
			LCI	UCI	
Intercept	93.2141	0.2009	92.8203	93.6079	<0.0001
Age	2.1021	0.0512	2.0017	2.2024	0.0210*
Sex (ref=male)					
Female	0.1728	0.0929	-0.0093	0.3548	0.0675
Residence (rural)					
Urbane	1.6598	0.0415	1.5785	1.7411	0.0136*
Related disease (ref=no)					
Yes	1.2047	0.0462	1.1141	1.2953	0.0047*
FHDM (ref=no)					
Yes	0.0634	0.0211	0.0204	0.1047	0.0431*
SBP	0.1124	0.0378	0.0383	0.1865	<0.001*
DBP	0.8793	0.0512	0.7789	0.9796	<0.001*
Random effect		Std. deviation	95% CI		
Intercept (b_{0i})		11.2478	10.1141	12.3819	
Follow up times (b_{1i})		0.2456	0.2208	0.2704	
Corr (b_{0i}, b_{1i})		-0.4895	-0.4401	-0.5388	
Residual (ε_i)		9.8108	8.8218	10.7998	

*Indicates statistically significant at 5% level of confidence

Table 4. Result of the final linear mixed model for DM patients.

Separate analysis of survival data

The Kaplan-Meier estimator was used to estimate the survival curve for categorical predictors in this study. The Kaplan-Meier survival curve indicates that whether there is a difference in time to first recovery between different categories of the variables. To check the significance of differences among categories of factors we applied the log-rank tests to all categorical variables. The null hypothesis is there is no significance difference between the survival experiences of different groups of categorical variables. The result in Table 5 indicates that there is a significant difference in the time of first recovery between rural and urban patients, patients with family disease history and those without disease history between males and females at 5% level of significant.

Predictor	*Chi-square* test	Df	p-value
Residence	1.51	1	0.0024
FHDM	19.8	1	0.0002
Related disease	0.43	1	0.04
Sex	0.77	1	0.0321

Marital status	3.36	1	0.507
Type of DM	2.4	2	0.3

Table 5. Log Rank test of categorical independent variables.

Model selection for survival analysis: Different survival models were compared for survival data analysis. Since, the Cox PH assumption was not satisfied, cox proportional hazards model was selected for current survival data analysis.

The results of separate survival model are presented in Table 6. From this separate analysis of cox regression model, patients who had family history of DM, related disease, who residence in urban area and female patients were positively associated with time of first recovery. However, age of patients, SBP and DBP of patient were negatively associated with time of first recovery from treatment of DM patients at 5% significance level.

Parameter	Estimate	Std. error	HR	95% CI of HR	P-value
Base line age	-0.06587	0.00776	0.9363	(0.9221, 0.9506)	0.00453**
FHDM (ref.=no)					
Yes	1.05912	0.303206	2.8838	(1.5918, 5.2247)	0.008701**
base line SBP	-0.0589	0.004957	0.9428	(0.9337, 0.9521)	0.02035**
Related disease (ref=no)					
Yes	0.82569	0.06359	2.2835	(2.0159, 2.5866)	<0.0001**
Sex (Male=ref)					
Female	0.45872	0.22289	1.5821	(1.0221, 2.4488)	0.005624**
Residence (rural=ref)					
Urban	0.45724	0.00249	1.5797	(1.5721, 1.5874)	<0.0001**
Base line DBP	-0.35261	0.124793	0.7029	(0.5503, 0.8976)	0.00452
**Indicates statistical significance variable at 5% level of confidence					

Table 6. Final cox proportional hazard model for parameter estimation.

Joint model analysis for longitudinal and survival data

The result of joint model was obtained by combining the selected random-intercept and slope effect from linear mixed model and cox-proportional hazard model. The result in Table 7 indicates that the predictors age, residence area, related disease and SBP significantly and statistically affected both response variables namely PR and time of first recovery. The result in the joint model indicates that there was negatively strong association between the two responses (α=-1.5108, P-value=<0.0001). The negative association indicates that patients with high pulse rate measurement had low rate of first recovery.

Longitudinal sub-model				Survival sub-model			
Covariate	Estimate	Std. error	P-value	Estimate	Std. error	HR	P-value
Intercept	88.254	0.236	<0.001*				
Age	0.0325	0.021	0.0078*	-0.0241	0.007	0.9764	0.0343*
Sex (ref=male)							
Female	0.258	3.254	0.0823	0.6823	0.1546	1.9784	0.0421*
Residence (ref=rural)							
Urban	-0.365	0.0562	0.0221*	-1.5147	0.1422	0.2199	<0.001*
Related disease (ref=no)							
Yes	0.5113	0.0442	0.0440*	-2.4157	0.2478	0.0893	<0.001*
FHDM (ref=no)							

Yes	0.0903	0.02831	0.0082*	-0.3168	0.7584	0.7285	0.1732
SBP	-0.0826	0.0291	0.0017*	0.5489	0.1544	1.7313	0.0108*
DBP	0.1986	0.0143	<0.001*	0.0041	0.6547	1.0041	0.0892
Follow time	-0.0425	0.0031	<0.001*				
Association				-1.5108	0.1724	0.2207	<0.001*
Random effects	Std. dev						
Intercept (b_{0i})	10.2589						
Follow up time (b_{1i})	0.2147						
Corr (b_{0i}, b_{1i})	-0.4556						
Residual (ε_i)	7.2548						

*Indicates statistically significant at 5% level of confidence

Table 7. Result of parameter estimation for the joint model of PR and time to 1st recovery.

Table 7 indicates that for a unit increased in age, the average PR of patients was significantly increased by 0.0325 beats per minutes (p-value=0.0078) keeping all other variables constant. For a unit increase in SBP, the average PR of patients was significantly decreased by 0.0826 beats per minutes (p-value=0.0017) keeping all other variables constant. For a unit increased in DBP, the average PR of patients was significantly increased by 0.1986 beats per minutes (p-value<0.0001) keeping all other variables constant.

The average PR of the patients who had other related disease were significantly higher by 0.5113 beats per minutes (p-value=0.0440) compared to the patients who hadn't related disease keeping other variables remains constant. The average PR of the patients with family history of diabetes were significantly higher by 0.0903 beats per minutes (p-value=0.0082) compared to the patients with no family history of diabetes keeping other variables remains constant. The average Pulse Rate of urban residence patients were significantly lower by 0.365 beats per minutes (p-value=0.0221) compared to the rural patients keeping other variables remains constant. For a unit increase in follow time the average PR of DM patients was significantly decreased by 0.0425 beats per minutes (p-value<0.0001) keeping other variables constant.

According to the survival sub model, the rate of achieving first recovery for female patients was 1.9784 times higher than male patients (HR=1.9784, p-value<0.04211). That means, the time needed to reach first recovery among male patients was significantly longer compared to female patients. The rate of achieving first recovery among patients who has related disease was 0.0893 times lower than patients with no other related disease (HR=0.0893, p-value<0.0001). This means, the time needed to reach first recovery among patients with no other related disease was significantly shorter compared with patients with other related disease.

Similarly, the rate of achieving first recovery among patients in urban area was 78.01% lower than rural patients (HR=0.2199, p-value<0.0001). That means, the time needed to reach first recovery among patients residence in rural area was significantly longer compared to patients residence in urban area.

For a unit increase in SBP, the rate of achieving first recovery for patients was increased by 73% (HR=1.7313, p-value<0.0108). For a unit increase in age of patient, the rate of achieving first recovery for patients was decreased by 2.38% (HR=0.9762, p-value<0.0343).

Comparison of separate and joint model

The estimates of the parameters of the separate and joint models were approximately similar to each other but not the same. The result in the separate and joint models revealed that the joint model had smaller standard error as compared to separate models for all significant variables. The performance of the two models was also compared based on model parsimony and goodness of fit and the joint model was performed better based on its lower AIC, BIC and based on a significant likelihood ratio test as well. The statistical significance of the association parameter is also evidence that the joint model was better than the separate models in this study.

Discussion

In this study three different models were applied; linear mixed effect model for longitudinal measure of pulse rate, Cox-Proportional hazard ratio for survival time-event outcomes and joint model for the two responses together. In the separate analysis different assumptions were checked for longitudinal pulse rate and for the survival outcomes.

The result in current investigation revealed that the mean profile plot of PR linearly decrease over a time this finding lined with the study.

Age of patient was an important clinical variable of PR and time to first recovery implies that the average PR increase as age increase and time to first recovery decrease as age increase. This result was consistent with another study.

The average pulse rate was higher for patients who had other related disease compared to patients who had no other related disease. Patients who had other related disease require longer time to first recovery than patients who had no related disease this result was consistent with another study.

Female patients attained first recovery time within a short time as compared to male patients. This result was consistent with another study. But the result was contradicted to another study. The result shows that males tend to take a longer time for first recovery than females. Average PR was higher for rural patient as compared to urban patients. The time required for first recovery time to rural patients was longer than urban patients which is similar with another previously conducted study.

Baseline SBP was also an important clinical variable for both pulse rate and time to first recovery which implies that the average PR decrease as SBP increase. This result was consistent with another study. On the other hand, patients with high SBP has long time to achieve first recovery time which is the same result as obtained in the previous study.

Family disease history was an important variable for longitudinal change of pulse rate such that average pulse rate was higher for patients with family disease history as compared to patients without family disease history. This result is supported by another study. The average pulse rate was increases as an increase of DBP. This result was consistent with another study.

Conclusion

As a conclusion, in current investigation the joint model was the better fit as compared to the separate models. In this study, the association parameter was statistically significant in the joint model, indicates that the two responses were negatively correlated and shows that the joint model was better fit to the data than the separate models. The finding was consistent with another study. The separate linear mixed model showed that other related disease, family history of diabetes mellitus, residence, baseline age, SBP, DBP and follow time of the patient were significant predictors for the longitudinal progression of pulse rate. Among the significant variables, existence of related disease, family disease history, baseline age of patient and DBP had positive association with PR, whereas, the variables residence area, SBP and follow time had negative association with PR.

From the survival sub model, age of patient, other related disease, sex of patients, residence area, SBP and unobserved true pulse rate were significant predictors for time to first recovery. Out of these, SBP had positive association with time to first recovery, whereas, the variables other related disease, age, residence area and unobserved true pulse rate had negative association with time to first recovery.

Due attention should be given for patients with other related disease, for those patients with family disease history, for rural patients and aged patients. Health related education should be given to all patients to change their life style.

Ethical Approval and Consent to Participate

Ethical clearance certificate had been obtained from Bahir Dar university ethical committee, Ethiopia with Ref RCS/1412/2013. We can attach the ethical clearances certificate up on request. Consent from participants was not taken because of the data secondary and there was no communication between authors and participants.

Availability of Data and Materials

The data used for current investigation is available with hands of corresponding author.

Competing Interests

No conflict of interest between an author and institutions.

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