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Multivariate Model on Longitudinal Data Analysis for Hypertension and Heart Failure of Diabetes Patients:A Case of Jimma University Specialized Hospital, Jimma, Ethiopia

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Abstract: Hypertension and heart failure is a chronic disease which is rapidly growing public health problem worldwide, especially in low and middle income country including Ethiopia. A hospital-based retrospective cohort study conducted on 100 regular follow-up of diabetes patients whose age 18 and above years since September 11, 2018 to October 11, 2021. Multivariate multilevel model were used to identify the risk factors of hypertension and heart failure. In this study out of 861 diabetes patients', 52.7% lived in rural areas and 57.6% of diabetes patient were male. A 45.8% variation of pulse rate, systolic and diastolic pressure was between patient level and the remaining 54.2% of variation existing within patients. The pulse rate, diastolic and systolic blood pressures were correlated and the data follow multivariate normal distribution with p-value equal to 0.708. Multilevel model of time variant and invariant with random intercept were better fit to the data. In conclusion gender, residence, level of glucose, hypertension status, weight, fasting blood sugar, complication status, and type of complication happening were significantly associated with multivariate responses of pulse rate, systolic and diastolic blood pressures at 5% level of significance. A particular emphasis should be placed on prevention by introducing lifestyle medications and creating awareness

Keywords: Hypertension; Heart failure; diabetes disease; systolic blood pressure; Multilevel

1 Introduction

Heart failure (HF), also known as chronic heart failure, is a condition in which one or both ventricles cannot pump sufficient blood to meet the metabolic needs of the body and a chronic condition that develops over time[1]. It is a chronic disease which is rapidly growing public health issue with an estimated prevalence of greater than 37.7 million worldwide.

Heart failure has great burden in economy that costs total for patients with heart rate case in USA are expected to rise from US 20.9 billion in 2012 to 53.1 billion by 2030 and shared chronic phase of cardiac functional loss secondary to many etiologist[2]. There is a big financial burden on the United Kingdom due to heart failure which caught over 1 million individuals and have prevalence rate expected to extend over subsequent decade[3]. An estimated 12.8% of all causes of deaths per year were as a result of high blood pressure and the prevalence is lower among high income countries[4,5].

According to world health organization guidelines hypertension is one of the most common non-communicable diseases and clinically elevated of systolic blood pressure when individual's has greater than 140mmHg whereas diastolic blood pressure is more than 90mmHg in adults aged 18 years and above. Being hypertensive is cause of cardiovascular disease like congestive heart failure, myocardial infarction and complications of chronic kidney. The patients often have no clinical symptom until organ damage begins and its exact causes are not known well which in turn cause for morbidity and mortality among other non-communicable diseases[6,7,8]. Systolic and diastolic blood pressures are the two markers in assessing the progression of blood pressure by measuring frequently over time after

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treatment to ensure that no signs hypertensive problems. Socioeconomic status of patient affect the two markers of blood pressure in monitoring and correct evaluation since they are correlated [9].

In Africa, Heart Failure is the main public health issue that cause high morbidity and mortality with high rates of repeated hospitalization that leads to loss economic productivity and poor quality of life which affects mostly young and economically active adults. From all medical submissions to the hospital who had cardiac diseases of 7–10% the patients that had heart failure is 3–7% and has highest proportion as compared to developed world which has higher effect on the health and health economics[10,11]. In developing countries two-thirds of people have hypertension approximately from one billion. Hypertension and cardiovascular diseases is a crucial public ill health which have vast economic impact due to high proportion of the productive population becomes persistently ill or die, leaving their families in poverty. An increased heart rate measure is associated with a high risk of heart failure hospitalization and low-level pulse rate measure at the base line which is positively shared with minor risk of mortality and re-hospitalization[12]. World health organization reported that among all deaths in Urban Ethiopia 9% of them were caused by chronic heart failure and predominant causes of mortality in 6.5-24%, morbidity of 4 to 24%, and 8-9% preeminent reasons of medical intensive care unit admission. In addition, 11% of all hospital deaths and averagely 25 % of all household deaths were due to chronic heart disease in Addis Ababa[13]. A study done in Amhara region of Ethiopia suggested that heart failure is a progressive public health problem having high mortality and morbidity[14].

Several studies conducted in Ethiopia reported that the prevalence of hypertension were 28.3 % in north-west and 31.5% for males and 28.9% for females in Addis Ababa. In addition, hypertensive patients following treatment changes over time had significant association with determinants such as age, gender, marital status, residence, educational status, family history, alcohol status, salt usage and body mass index (BMI) that were in-lined to strongly correlated with the progression of bio-markers [15,16,17].

Several studies have been conducted separately on assessment of demographic and risk factors that determining the effect of heart rate and blood pressure in the diabetic patients. Binary logistic regression, multiple and descriptive summary measure were the most commonly used modelling aspect analysing cross-sectional data on diabetic and hypertension patients'. Even linear mixed model was used cohort study design separately rather than jointly deal with the multivariate responses of systolic blood pressure, diastolic blood pressure and pulse rate of diabetic patients. However, the current study takes in to account the variation between and within patients' over change of time considering the longitudinal data of repeated measurements. Joint effect of pulse rate, systolic and diastolic blood pressure responses were concerned using multivariate multilevel regression model and screen out the risk factors associated to those responses at a time and over a time.

2 Methods and Materials

Study Area, Population and Design
A retrospective cohort study design were employed to review the diabetes patients card registered at Jimma University specialized Hospital. The patients with hypertensive disorder and heart failure who registered were study participants and all diabetes patients aged 18 years or older, who were coming to Jimma University specialized hospital for their regular follow up during periods september11, 2018 up to October 11, 2021 and patients who has a minimum of 2 visits and a maximum of 13 visits, were included in the study.

Data analysis strategy and Quality
This study analysed data using SAS version 9.4 software. The quality of the data was controlled by data controllers from ART section of the hospital. The controllers were taken intensive training by the Ministry of Health for different services. The data extraction tools and the variables included in the study were tested for consistency of understanding and the completeness of the data items on samples of patients.

Data Source and Sampling Procedure
From the total diabetes positive adults who started treatment in the hospital from september11, 2018 up to October 11, 2021. Patients with a minimum of 2 visits and a maximum of 13 visits were included in the study. The study exclusively used secondary data and a data extraction check-list was designed to adopt the routinely collected data.

Study Variables
The longitudinal response variables for current study were pulse rate, systolic and diastolic pressure of diabetes patient. The three response variables are correlated in nature and measure the hypertension,heart failure and diabetes level of patients.

Operational Definition
Heart rate is a measurement of the heart rate, or the number of times the heart beats per minute. As the heart pushes blood through the arteries, the arteries expand and contract with the flow of the blood.

Pulse rate is the measure palpable blood pressure increases throughout the body that occurs with each heartbeat. Pulse rate is basically the physical sensation of a heart beat felt through the arterial vascular system. Pulse can be measured

from the earlobe with a pulse meter known as a Photo Reflectance or Infrared Sensor Monitor.
Diastolic blood pressure is measures the pressure on the walls of your arteries between heartbeats. A normal diastolic blood pressure is less than 80 mmHg.
Systolic blood pressure is measures the pressure on the walls of your arteries when your heart beats. A normal systolic blood pressure is less than 120 mmHg.
High blood pressure (hypertension) is a common condition in which the long-term force of the blood against your artery walls is high enough that it may eventually cause health problems, such as heart disease.
Intra- class correlation analysis is used to measure the reliability of ratings in studies where there are two or more patients. The value of an ICC can range from 0 to 1, with 0 indicating no reliability among patients and one indicates perfect reliability among patients. In simple terms, an ICC is used to determine if items (or subjects) can be rated reliably by different patients.
Repeated measures design is a research design that involves multiple measures of the same variable taken on the same or matched 861 patients either under over 100 time periods collectively. Patients with a minimum of 2 visits and a maximum of 13 visits were included in the study. For instance, repeated measurements are collected in a longitudinal study in which change over time is assessed in this study.
The relationship between diabetes and hypertension
Over time, diabetes damages the small blood vessels in your body, causing the walls of the blood vessels to stiffen. This increases pressure, which leads to high blood pressure. The combination of high blood pressure and type 2 diabetes can greatly increase your risk of having a heart attack or stroke. The fixed socio-demographic and clinical factors that expected to associate with pulse rate, systolic and diastolic pressure of diabetic patients were indicated in Table 1.

Table 1: Covariates that included in this study

Variables	Categories
Gender	0=Female,1=Male
Age Group	0=$\leq$20,1=20-44,2=45-64,3=$\geq$65
Fasting Blood Sugar	Continuous
Level of Glucose	Continuous
Level of Triglceride	Continuous
Level of High-Density Lipoprotein	Continuous
Cholesterol Level	Continuous
Level of Low-density Lipoprotein	Continuous
Level of Urea	Continuous
Level of Creatinine Blood Test	Continuous
Residence	0=rural , 1=urban
Hypertension Status	0=no ,1=yes
Complication Status	0=no ,1=yes
Types of Complication Happened	0=no,1= short term ,2= long term

Missing Data Treatment
The main problems in longitudinal studies are missing of data. But, multilevel analysis is very flexible in handling missing data[18].
Inclusion and Exclusion Criteria Inclusion criteria:- Patients whose age was above 18 years old that are attending a minimum of two visit of treatment in ART clinic for refilling their prescription and who were initiated on ART from September11, 2018- October 11, 2021 at Jimma University hospital would be included in the study. On the other side, Patients whose age was below 18 years old that are attending treatment in ART clinic for refilling their prescription, patients who are not registered in the ART clinic and who are not initiated on ART were not included in this study. In addition patients out of this study period are not included.

3 Statistical Data Analysis

Multi-level longitudinal data analysis represents the repeated measurements and observes subjects over time. The basic statistical assumption underlying the Multi-level linear modeling is that the observed values of each dependent variable can be written as the sum of two parts:- a fixed component Xβ which is a linear function of the independent coefficients, and a random noise, or error component Σ.

$$Y = X\beta + \Sigma \tag{1}$$

$$X = \begin{vmatrix} Gender_{11} & Age_{12} & \ldots & FBS_{1p} \\ Gender_{21} & Age_{22} & \ldots & FBS_{2p} \\ Gender_{31} & Age_{32} & \ldots & FBS_{3p} \\ Gender_{41} & Age_{42} & \ldots & FBS_{4p} \\ \vdots & \vdots & \vdots & \vdots \\ Gender_{n1} & Age_{n2} & \ldots & FBS_{np} \end{vmatrix} \quad (2)$$

$$Y = \begin{vmatrix} PulseRate \\ SystolicBloodpressure \\ DiastolicBloodpressure \end{vmatrix} \quad (3)$$

$$\beta = \begin{vmatrix} \beta_1 \\ \beta_2 \\ \vdots \\ \beta_p \end{vmatrix} \quad (4)$$

$$\Sigma = \begin{vmatrix} \varepsilon_{11} \\ \varepsilon_{21} \\ \vdots \\ \varepsilon_{n1} \end{vmatrix} \quad (5)$$

The independent coefficients X are components of design matrices or covariates from the model effects.
Further, the errors for different observations are assumed to be uncorrelated with identical variances i.e E(y_{ij}) = μ and Var(y)= σ^2I.
Where Y is the vector of dependent variable values.
X is the matrix of independent coefficients.
I show the identity matrix, and σ^2 is the common variance for the errors.
For multiple dependent variables, the model is similar except that the errors for different dependent variables within the same observation are not assumed to be uncorrelated. This yields a multivariate linear model of the form

$$E(Y) = X\beta \quad (6)$$

$$Var(Y) = \Sigma I \quad (7)$$

Where Y and β are now matrices, with one column for each dependent variable, vector Y strings Y out by rows, and indicates the Kronecker matrix product.

Multivariate Linear Mixed Model of Joint Models

The joint distribution of three responses is not straight forward; we can use to two approaches for the formulation of multivariate model. The first approach is based on a conditioning argument that allows joint distribution to factor out in marginal and conditional component, where the conditioning can be done either on discrete or continuous outcome which means ignore direct specification of multivariate modeling with introduction of probit approach. The second is direct formulation of multivariate modelling for three response variables with the introduction of Placket–Dale approach which assumption for modeling multivariate outcomes[19]. Instead of using a latent variable approach, one can directly specify the multivariate distribution for three outcomes through mixed model with specification of the marginal distribution, conditional on the correlated random effect. Therefore this study was used the second approach rather than the first approach. In-lined to this, Multilevel model could be employed to incorporate the effect of subject-specific variation in the multivariate repeated measures which measured repeatedly over time or may be observed within a hierarchical trend.

The multivariate multilevel model assumes that each outcome and the univariate models are combined through specification of multivariate distribution for all random effects, in addition to specification of marginal distribution, which is conditional on correlated random effect. This study was explored the common factors between pulse rate; systolic and diastolic pressure of diabetic's patients for the data obtained at Jimma University Hospital, and fit multivariate multilevel which is a powerful analysis tool using several response variables may lead to more powerful than univariate models as consistent with study done by[19]. A general form of the model equation for multivariate multilevel models is:-

$$Y = X\beta + ZU + \Sigma \quad (8)$$

Where, Y is an nx3 vector.
β is px1 vector of unknown constants, the fixed effects of the model.
X is an n xp known design matrix of fixed numbers associated with β.
Z is an nxq known design matrix of random effects.
U a qx1 vector of unknown random effects from N(0,G).
Σ is an nx1 vector of error terms from N (0, R).
The multivariate multilevel model contains fixed effects parameters β, and random effects parameters U.To finding the value of the parameter which maximizes the likelihood function for a given data set using maximum likelihood estimation. In screening potential factors backward elimination method was used that evaluated at 25% level of significance. Once the variable selection have been done, appropriate model which fit the data well could be identified using likelihood ratio test for testing fixed multi parameter and testing about the random part of the model in applications of a hierarchical linear model. It is common selection criteria for choosing between nested models.

4 Results and Discussions

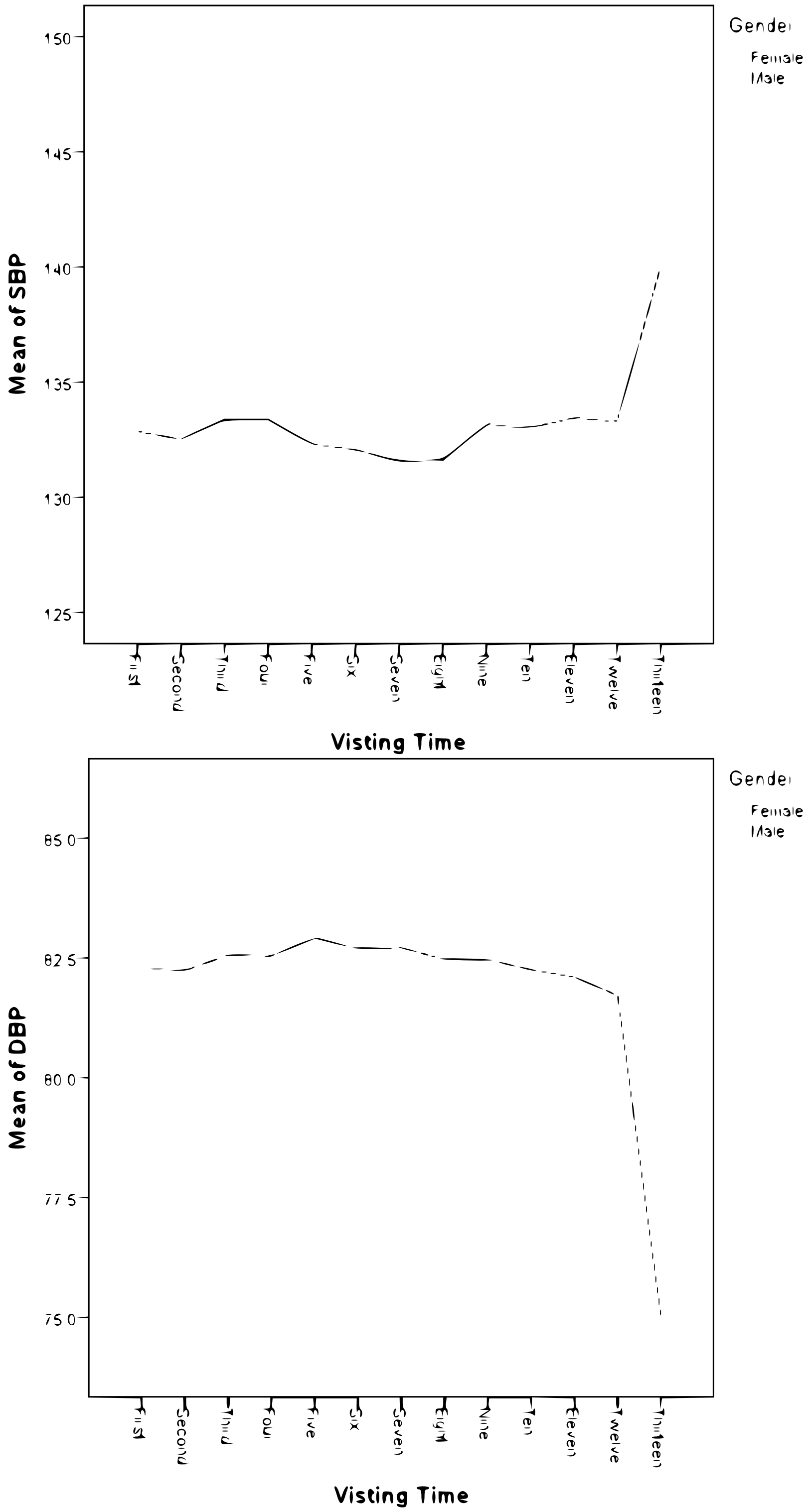
The summary measure of the descriptive statistics in Table 2 showed that diabetic female patients had average of pulse rate 86.09 with standard deviation 9.31, mean of systolic blood pressure 133(SD=20) and diastolic blood pressure 82(SD=9). The average of pulse rate, systolic blood pressure and diastolic blood pressure for male patients' were 85.45, 129 and 79 respectively. Diabetic Patients' who have history of hypertension had average of pulse rate 86.37, Systolic blood pressure 135 and diastolic blood pressure 82 which seems like more as compared to patients without history of hypertension. Another variable that expected to associate with pulse rate and blood pressure were residence of patients.

An average of pulse rate, systolic and diastolic blood pressure of diabetic patients for rural resident were 86.19(SD=10.40),125(SD=19) and 79(SD=10) respectively, whereas Urban resident had 85.20(SD=9.98), 136(SD=17) and 83(SD=9) respectively. The types of complication of diabetes short term had average Pulse rate of 88.43(SD=6.80), Systolic blood pressure 127(SD=18) and diastolic blood pressure 80(SD=8) respectively. The long term complication has also average of Pulse rate, SBP and DBP were 86.78, 136 and 82 with their corresponding standard deviation of 8.27, 20 and 10 respectively as showed in Table 2. Of the total patients 365 (42.4%) were females and the remains 496 (57.6%) were males. More patients who visited for hypertension and heart failure lived in rural areas 454 (52.7%) and experienced hypertension disease 475 (55.2%) respectively. In addition, the details are found in (Table 2) for categorical variables of patients such as complications, age group, and type of complications.

Table 2: Descriptive summary of the categorical explanatory variables

Variables	levels	PR Mean± SD	SBP Mean±SD	DBP Mean±SD	count(%)
Gender	Female	86.09±9.31	133±20	82±9	365(42.4)
	Male	85.45±10.82	129±18	79± 10	496(57.6)
Status of Hypertension	No	84.92± 11.75	125±15	79±10	386(44.8)
	Yes	86.37± 8.72	135± 21	82±10	475(55.2)
Residence	Rural	86.19± 10.40	125± 19	79± 10	454(52.7)
	Urban	85.20± 9.98	136± 17	83± 9	407(47.3)
Complication Status	No	84.68± 11.56	129± 18	81± 10	512(59.5)
	Yes	87.25± 7.58	133± 21	81± 9	349(40.5)
Types of Complication	No	84.51± 11.41	130± 19	81± 10	529(61.4)
	short term	88.43± 6.80	127± 18	80± 8	174(20.2)
	long term	86.78± 8.27	136± 20	82± 10	158(18.4)
Age Group	$\leq$ 20	102.00± .00	110± 0	80± 0	6(0.7)
	20-44	87.30± 10.38	126 ±26	79± 10	198(23)
	45-64	84.03± 10.19	132± 15	81± 10	439(51)
	$\geq$65	87.24± 9.37	131± 18	81± 9	218(25.3)

The graphical exploratory of multivariate response with time invariant covariate gender over visiting time were plotted which showed that the mean of male patients' was increasing from first visit to the last visit (13th visiting time) in systolic, diastolic and pulse rate whereas decreasing for female patients' as showed in figure 1. This implies being gender of male or female patients' of diabetic mellitus have no correlate systolic blood pressure, diastolic blood pressure and pulse rate over visiting time.



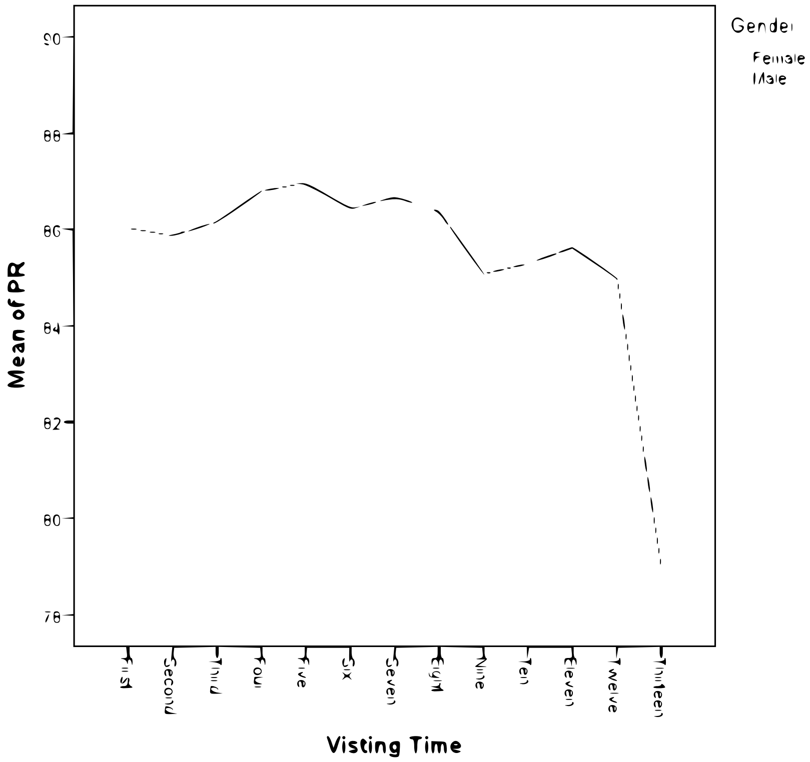


Fig. 1: Graphical exploratory of multivariate responses with time invariant with gender of patients' over visiting time

Multivariate Model Selection and Intra-Class Correlation

This study was used intra-class correlation to check whether the observations variation within and between patients. It can be theoretically meaningful to understand how much of the overall variation in three responses is explained simply by patients. From Table 3 results show that intra−class correlation gives strong evidence that variability was occurring between the patients. The intercept only model estimates the intercept of pulse rate, systolic and diastolic blood pressures were 84.99, 129.66 and 79.96 respectively. The variance of individual observation (lower level) residual errors, symbolized by σ^2e, is estimated as 103.35. The variance of the patient (higher-level) residual errors, symbolized by σ^2u0, is estimated as 87.17 which are significant with P- value less than 0.0001.

$$\rho = \frac{\sigma_{u0}^2}{\sigma_{u0}^2 + \sigma^2 e} = \frac{87.17}{87.17 + 103.35} = \frac{87.17}{190.52} = 0.458 \tag{9}$$

Therefore, 45.8% variation of pulse rate, systolic and diastolic pressure is between patient level and the remaining 54.2% of variation existing within patients that has likelihood ratio test equal to 1231.89.The final model selection have been done by employing log-likelihood method and Random intercept both time varying and invariant covariate model was selected as final model to fit well since the model had smallest -2log−likelihhod value 18798.3 as indicated in Table 4. In fitting the final model to predict the responses, univariate analysis was done to choose the candidate variables. In-lined to this using backward selection method and random intercept both time varying and invariant covariate multivariate multilevel model was screened out at 0.25 significance levels. Based on this gender, fasting blood sugar, level of glucose, level of triglyceride, level of high-density lipoprotein, level of creatinine blood test, cholesterol level, level of low-density lipoprotein, hypertension status, complication status, types of complication happened, residence and level of urea were candidate covariates that associated with pulse rate, systolic and diastolic blood pressure at 25% level of significance.The study used E-statistic test of multivariate normality and the result show pulse rate, systolic and diastolic blood pressure is multivariate normality with p-value equal to 0.708. The pulse rate and diastolic blood pressure, pulse rate and systolic blood pressure, systolic blood pressure and diastolic blood pressure correlation were 0.654, -0.418 and 0.577 respectively.

Table 3: Intercept-only Model Estimates

Model	Effects	Estimates	Sd.Err	P.value	Lower	Upper
Solution for Fixed Effects	Intercept(PR)	84.993	1.00	0.0001	83.03	86.96
	Intercept(SBP)	129.66	1.00	0.0001	127.70	131.63
	Intercept(DBP)	79.96	1.00	0.0001	77.99	81.92
Covariance Parameter Estimates	Intercept(id)	87.17		0.0001		
	Residual	103.35		0.0001		
-2 Log Likelihood= 19608.9 AIC = 19612.9 BIC=19618.1 LRT=1231.89 p-value 0.0001						

Table 4: Final Multivariate Multilevel Model Selection

Models	-2 Log Likelihood
Intercept-only Model	19608.9
Random intercept time varying covariate model	18829.9
Random intercept time invariant covariate model	19588.1
Random intercept both time varying and invariant covariate model	18798.3
Random coefficient both time varying and invariant covariate model	19988.1

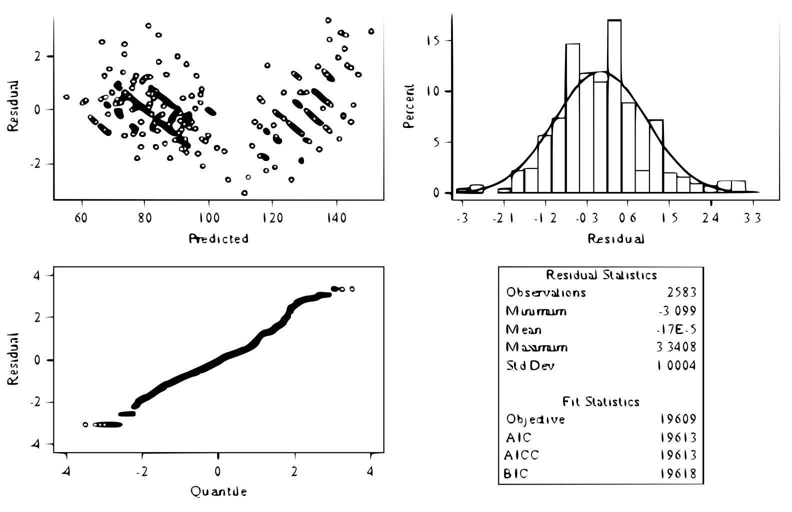


Fig. 2: Scatter plot of conditional Residuals versus predicted for the blood pressure of diabetic patients'

Final Multivariate Multilevel model and interpretation of the parameter

The univariate multilevel model was fitted to select the candidate covariates through incorporating both fixed and random effect to estimate individual parameters in which gender, fasting blood sugar, level of glucose, level of high-density lipoprotein, level of creatinine blood test, cholesterol level, level of low-density lipoprotein, hypertension status, complication status, types of complication happened and residence were significantly associated with multivariate responses of pulse rate, systolic and diastolic blood pressure at 0.25 level of significance. As the result, multivariate multilevel analysis were performed using candidate covariates that revealed gender, glucose level, residence, weight, baseline fasting blood sugar, hypertension status, complication status, and type of complication status significantly associated to pulse rate, systolic and diastolic blood pressure of diabetic patients. According to result of multivariate analysis, gender (male), glucose level, and complication type (long term) were negatively associated with the mean of systolic blood pressure of diabetes patients. But, the mean of systolic blood pressure of diabetes patients were positively associated with residence (urban), hypertensive diabetes patients, and complication treatment for patients. Moreover, the mean of diastolic blood pressures were positively associated with gender (male), and weight of diabetes patients. Likewise, fast blood sugar levels of diabetes patients were positively associated with pulse rate. The sub options of the residual panel request produce two panels. The panel of conditional residuals is constructed from $y-x'\widehat{\beta}-z'\widehat{\gamma}$ (Figure 2). The panel of marginal residuals is constructed from $y-x'\widehat{\beta}$. Note that these residuals are deviations from the observed data, because the model is a normal linear mixed model, and hence it does not involve pseudo-data. Whenever the random-effects solutions $\widehat{\gamma}$ are involved in constructing residuals, the title of the residual graphics identifies them as conditional residuals. The predictor takes on only six values for the marginal residuals, corresponding to the combinations of three response variables with two levels. The assumption of a zero mean for the visiting time random effect seems justified; the marginal residuals in the upper-left plot of Figure 3 do not exhibit any trend. The conditional residuals in Figure 3 are smaller and somewhat closer to normality compared to the marginal residuals.

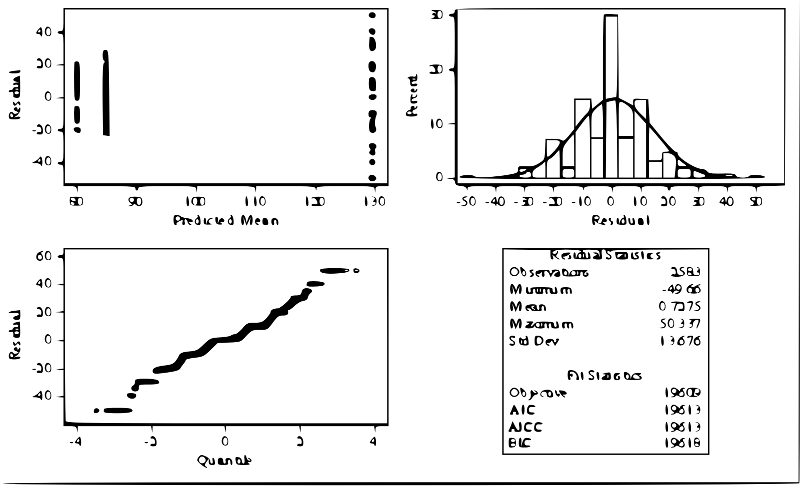


Fig. 3: Marginal Residuals Plots

4.1 Discussion of the Results

Longitudinal data were collected from the diabetic patients' card having three minimum visiting times and thirteen maximum visiting times from Jimma University Specialized Hospital during the period of September11, 2018 up to October 11, 2021. Of 861 observations were considered to evaluate the multivariate effect of potential factors on the multivariate responses of pulse rate, systolic and diastolic blood pressure. In this study multivariate multilevel model were best to fit the longitudinal data than uni-variate model. This is supported by[20]. Based on this multivariate analysis the association between systolic and diastolic blood pressure were decrease over a time. The variation of pulse rate, systolic and diastolic blood pressure between patient level and variation existing within patients was 45.8% and 54.2% respectively and likelihood ratio test also equal to 1231.89. This implies the study didn't needs more observations to achieve the same power as when there is little variation at the higher level which confirmed with study [21].

Based on the log-likelihood method time varying and invariant covariate model was fit the data well having smallest -2log-likelihhod value 18798.3 and used to model the pulse rate, systolic and diastolic blood pressure of diabetic patients. Our result showed that gender was an important demographic predictor for systolic blood pressure that revealed males are more affected in hypertension. The multivariate effect of diabetic patients' pulse rate, systolic and diastolic blood pressure were explained by gender which is significantly associated with them having (p-value=0.0488) since the multivariate responses had strong correlation as stated in intra-class correlation. This study confirmed with previous study which suggested that male patients' had greater hypertensive rate and higher blood pressure than female hypertensive[22,23,24,25]. A study conducted in north western Ethiopia also supported that male patients have higher risk of hypertension and diabetes as compared to females' patient[26]. In addition, there is significant mean difference systolic and diastolic blood pressure for male and female diabetic patients'[27,28].

Another demographic variable associated with systolic blood pressure were residence of patients' which revealed that living in urban area reduce the average systolic blood pressure as compared to rural area. This result confirmed with previous[29,30,31]which in other way implies living in urban were less likely hypertensive than rural area due to availability treatments and health sectors. However, the result contradict with the study done in northwest Ethiopia that reported the patients from urban areas were more likely to have hypertension as compared to patients from rural areas[32,33].These differences may occur due to the geographical location, whether condition and dietary diversity practice of the patients. Subjects with systolic blood pressure had significantly higher glucose concentrations among diabetic patients (p-value≐0.0001). Level of glucose concentration was a clinical risk factor that determines the effect of blood pressure on the hypertension patients in correlation with pulse rate. The result supported by study that concluded mean of glucose concentration had significantly associated with systolic blood pressure and higher in hypertensive men at all body mass index of blood pressure[34].On the top of this, level of glucose had significant association higher prevalence of hypertension and independent risk factors for systolic and diastolic blood pressure[35].Being hypertensive was an important factor that associated with diabetic systolic blood pressure of patients' (p-value less than 0.001).This result consistent with the study done by[33].

More important potential determinants that associated with multivariate response in this study in addition to the above were weight of patients, fasting blood sugar, having complication and type of complication at the baseline significance level (5%).Those factors had significant effect on diabetic patients pulse rate, systolic and diastolic blood pressure that needs attention for intervention. As indicated in the Table 5 an increment in the weight of patient indicated that the change of rate 0.1609 times in the diastolic blood pressure of patients. Since the pulse rate, systolic and diastolic pressures have strong correlation to each other the effect of weight, fasting blood sugar, complication status and type of complication on one of them determining the other multivariate outcomes. The result confirmed with study done in[36].

5 Conclusions

Multivariate multilevel analysis was employed on repeated measurements of longitudinal data of diabetic patients considering between and within variation of the subjects at a time and over time. Based on the result of log-likelihood test of random intercept both time varying and invariant covariate model was an appropriate model to predict the common effect of diabetic patient's level of pulse rate, systolic and diastolic blood pressure. The correlated responses of pulse rate, systolic and diastolic blood pressure of diabetic patients were associated with gender, glucose level, residence, weight, baseline fasting blood sugar, hypertension status, complication status, and type of complications at 5% level of significance. Moreover, the multivariate mean level of pulse rate, systolic and diastolic blood pressure for the male diabetes patients' was higher than female by keeping all other predictors constant. The weight, and level of glucose of patients increased then the multivariate mean level of pulse rate, systolic and diastolic blood pressure were increased whereas the baseline fasting blood sugar increment showed the multivariate mean level of pulse rate, systolic and diastolic blood pressure were decreased. On the other side, the multivariate mean level of pulse rate, systolic and diastolic blood pressure for diabetes patients' having hypertension, living in urban area, and long type of complication were decreased than those patients who was not hypertension history, lived in rural and no type of complication treatments. These variations occurred between and within the subjects who revealed change over time for diabetic patients' and needs better intervention to reduce the effect of the multivariate response to survived the patients.

Abbreviations

HF: Heart failure, PR: Pulse rate, DBP: Diastolic Blood Pressure, SBP: Systolic Blood Pressure, SAS: Statistical Analysis System, ART: Antiretroviral Therapy,WHO: World Health Organization, FBS: Fasting Blood Sugar, BMI: Body Mass Index, LMM: Linear Mixed Model, LDL: Low Density Lipoprotein, HDL: High Density Lipoprotein, ICC: Infra Class Correlation Coefficient, AIC: Akaike information criteria, BIC: Bayesian information criteria, and DIC: Deviance Information Criteria,LRT:Likelihood Ratio Test,SD:Standard Deviation,SE:Standard Error.

Ethics approval and consent to participate

Letter of ethical clearance was obtained from Jimma University, Department of Epidemiology and submitted to the Jimma University Specialized Hospital to get permission to conduct this research. This study was developed in accordance with established legislation and complies with the norms of good clinical practice, and informed consent was being not necessary as personal identifying information was kept separate from this research data. Finally, the study protocol was approved by the ethics committee or medical directors of the Hospital.

Consent for publication

This manuscript has not been published elsewhere and is not under consideration by any other journal. All authors approved the final manuscript and agreed with its submission.

Availability of data and materials

The raw data used in this study can be accessed from Jimma University Specialized Hospital.

Competing interests

The authors declare that they have no competing interests.

Table 5: Parameter Estimation of Random intercepts both time varying and invariant covariate model

Variables (reference)	Levels	Response	Estimate	SE	P-Value	Lower	Upper
Intercept	Continues	PR	77.8855	7.4497	0.0001	63.2772	92.4939
Intercept	Continues	SBP	127.07	7.4497	0.0001	112.46	141.68
Intercept	Continues	DBP	64.9441	7.4497	0.0001	50.3358	79.5525
Age group(18-49)	50-65	PR	1.7781	2.7990	0.5253	-3.7105	7.2666
	50-65	SBP	0.3210	2.7990	0.9087	-5.1676	5.8095
	50-65	DBP	-0.1977	2.7990	0.9437	-5.6863	5.2908
	≥65	PR	0.1684	2.5460	0.9473	-4.8242	5.1610
	≥65	SBP	2.5090	2.5460	0.3245	-2.4836	7.5016
	≥65	DBP	0.01215	2.5460	0.9962	-4.9804	5.0047
Gender(female)	Male	PR	0.8866	2.1030	0.6734	-3.2373	5.0106
	Male	SBP	4.1453	2.1030	0.0488	0.02139	8.2693
	Male	DBP	3.5352	2.1030	0.0529	-0.5887	7.6592
Weight	Continues	PR	0.09172	0.08346	0.2719	-0.07195	0.2554
	Continues	SBP	0.1414	0.08346	0.0904	0.02228	0.3051
	Continues	DBP	0.1609	0.08346	0.0439	0.00273	0.3246
Fasting blood sugar level	Continues	PR	0.01361	0.004360	0.0018	0.005058	0.02216
	Continues	SBP	-0.00609	0.004360	0.1629	-0.01464	0.002464
	Continues	DBP	-0.00525	0.004360	0.2289	-0.01380	0.003302
Level of glucose	Continues	PR	0.01029	0.01175	0.3814	-0.01275	0.03332
	Continues	SBP	0.04555	0.01175	0.0001	0.02251	0.06859
	Continues	DBP	0.007196	0.01175	0.5403	-0.01584	0.03023
level of LDL	Continues	PR	-0.02208	0.02754	0.4229	-0.07609	0.03194
	Continues	SBP	-0.01824	0.02754	0.5079	-0.07225	0.03577
	Continues	DBP	0.01460	0.02754	0.5961	-0.03941	0.06861
Cholesterol level	Continues	PR	-0.00852	0.02248	0.3459	-0.05261	0.03557
	Continues	SBP	-0.02061	0.02248	0.3594	-0.06470	0.02348
	Continues	DBP	0.02120	0.02248	0.3459	-0.02289	0.06529
Residence(rural)	Urban	PR	0.9147	1.9799	0.6441	-2.9677	4.7971
	Urban	SBP	-10.0856	1.9799	0.0001	-13.9680	-6.2032
	Urban	DBP	-2.8164	1.9799	0.1550	-6.6988	1.0660
Hypertension status(no)	Yes	PR	-1.9080	1.9057	0.3168	-5.6449	1.8289
	Yes	SBP	-8.3920	1.9057	0.0001	-12.1289	-4.6551
	Yes	DBP	-0.9315	1.9057	0.6250	-4.6684	2.8054
Complication status(no)	Yes	PR	5.4646	6.8136	0.4226	-7.8964	18.8256
	Yes	SBP	-41.6479	6.8136	0.0001	-55.0089	-28.2869
	Yes	DBP	0.05763	6.8136	0.9933	-13.3034	13.4186
Types of complication (no)	short term	PR	-7.9016	7.2302	0.2746	-22.0794	6.2763
	short term	SBP	32.7822	7.2302	0.0001	18.6043	46.9600
	short term	DBP	-0.9826	7.2302	0.8919	-15.1605	13.1952
	long term	PR	1.6723	3.3001	0.6124	-4.7990	8.1436
	long term	SBP	-9.6801	3.3001	0.0034	-16.1514	-3.2088
	long term	DBP	-1.0861	3.3001	0.7421	-7.5574	5.3852

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Authors' contributions
MWD and KKG was involved in the conception and design of the study, drafting the manuscript, review of protocol development, interpretation of the data and review of the manuscript. HAG and ALS were participated in data collection and entry, and review of the manuscript. All authors read and approved the final manuscript.

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Appendix

SAS Codes for Data Analysis

```
Data var0;
set dm;hyper='SBP';BP=BSBP;
run;
Data var1;set dm; hyper='DBP';BP=DBP;run;
Data var2;set dm;hyper='PR';BP=PR;run;
Data long;
set var0 var1 var2 ;run; * Creating the dummies for the response variables
data multi;
```

```
set long
;if hyper='SBP' then d1=1; if hyper='DBP' then d1=2;else if hyper='PR' then d1=0;
run; * Random intercept with both time varying and invariant covariate model proc mixed data=multi noclprint noitprint;
class id time gender HT Complication Type of complication age group Residence d1;
model BP =d1 d1*age group d1*HT d1*Complication d1*Type of complication d1*gender d1*Weight d1*Residence d1*cholestrol level d1*LDL d1*Glucose d1*FBS /s cl noint;
random intercept/sub=id type=un;
run;
```