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Separate longitudinal Analysis on the Progression of Systolic and Diastolic Blood Pressure with Hypertensive Patients Receiving Treatment: In case of Debre Berhan Referral Hospital

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Abstract

Background: Hypertension is a sever illness causing from high blood pressure through the arteries during circulation. Clinically, if the individual's systolic blood pressure is greater than or equal to 140 mmHg and/or diastolic blood pressure is greater than or equal to 90 mmHg then a person is said to be hypertensive.

Methods: A retrospective study was conducted to obtain secondary data among hypertensive patients receiving antihypertensive treatment in between1st September 2014 to30th August 2016 in Debre Berhan referral hospital. Demographic covariates and clinical factors like age, gender, marital Status, residence, educational status, family history, alcohol status, salt use, time, body mass index and regime were considered. The data was extracted from the patient record cards. Patients, who have fulfilled the inclusion criteria, were included in the study. The data consists of 300 individuals. The average follow-up time was six month gap in order to see the difference clearly.

Results: Unstructured variance covariance structure was computed for the separate longitudinal analyses. The variability of the two biomarkers between individuals seems higher at baseline and appears to decrease over time after patients were initiated on treatment. In final saturated linear mixed model for systolic blood pressure the main effects BMI, Age (40-60), Residence (Urban), Salt (Yes) and Alcohol (Yes) were significant. And also for diastolic blood pressure the main effects BMI, Age (40-60), Residence (Urban), Salt (Yes), Regime (Hydrocholorothizide + Enalapril) and Alcohol (Yes) were significant at the 0.05 significance level.

Conclusions: In this study, two models were considered for fitting two response variables measured longitudinally. Based on the separate analysis the progression of SBP and DBP measures were significantly differ with respect to the main effect independent variables time, sex(female), Age(40-60), residence, salt, alcohol and their interaction time.

Keywords: Debre Berhan • Diastolic Blood Pressure • Ethiopia • Hypertension • Systolic Blood Pressure

Introduction

Hypertension is one of the most common non-communicable diseases. According to the WHO, it is determined raised of systolic or diastolic blood pressure equal to or more than 140/90 mmHg in adults aged 18 years and above. It is cause for the prevalence of cardiovascular diseases (CVDs) such as myocardial infarction, congestive heart failure and complications like stroke and chronic kidney disease (CKD). Hypertensive patients often have no clinical symptom till organ damage begins and its exact causes are not known well, but there are several factors and conditions may play a role in its development. Due to these reasons, it is the main cause for morbidity and mortality among other non-communicable diseases, which ranks third as a means of a reduction in disability-adjusted life years [1-4].

Approximately one billion people have hypertension from these two-thirds are in developing countries. The new epidemic of hypertension and cardiovascular diseases isn't only a crucial public ill health, but it will even have vast economic impact due tohigh proportion of the productive population becomes persistently ill or die, leaving their families in poverty. Because of high blood pressure 7.5 million (12.8% of all cause s of death) deaths per year was estimated. The prevalence of hypertension varies among nations and sub-populations within a nation though generally lower among high-income populations [5-8].

In Sub Saharan Africa (SSA), a systemic review of seventeen studies pertaining to eleven countries revealed that prevalence rate of hypertension in Sub Saharan Africa in 2008 was at 16.2%, ranging from 10.6% in Ethiopia to 26.9% in Ghana. The total number of hypertensive in Sub Saharan Africa was estimated at 75 million in 2008 and at 125.5 million by 2025. According to the Global burden of hypertension analysis of worldwide data indicated that more than a quarter of the world's adult population totaling nearly one billion 26.4% had hypertensive. The rapid rise in the mortality of cardiovascular disease over a fairly short period is attributable mainly due to changes in lifestyle changes such as diet and physical activity.

In low and middle-income countries there is a high prevalence of hypertension in comparison with high-income countries. The exact causes of high vibrant sign aren't well identified, but different factors and conditions may play a role in its development. Few studies indicate that the disease has become a significant public health problem especially in the major cities of Ethiopia. Earlier reports from Ethiopia on the prevalence of hypertension were as high as 31.5% and 28.9% among males and females respectively in Addis Ababa and 28.3% from Gondar as estimated based on clinical record. On the other hand, a study based on Joint modeling of longitudinal systolic and diastolic blood pressure measurements of hypertensive patients receiving treatment age of the patient was strongly associated with the progression of systolic and diastolic blood pressure. Despite that different researchers had been done on the progression of two biomarkers and associated risk factor for the prevalence of hypertension among hypertensive patients in Ethiopia. For instance, the association of the risk factor for the prevalence of hypertension among hypertensive patients at the hypertension clinic of Jimma University Specialized hospital using binary logistic regression analysis by ignoring follows up time for Systolic and

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Diastolic blood pressure level of patients. Therefore, to address this gap this study was mainly concerned on the progression of both biomarkers (SBP and DBP) and their association with other risk factors by considering follow up time and major determinant factors for the progression of systolic and diastolic blood pressure of patients using separate longitudinal analysis model with appropriate covariance structure. The principal aim of this study was to explore the longitudinal analysis on the progression of systolic and diastolic blood pressures on hypertension patients in Debre Berhan referral hospital. Among them how the average progression of two blood pressure biomarkers (SBP and DBP) for hypertensive patients following treatment changes over time. And also which factors like age, gender, marital status, residence, educational status, family history, alcohol status, salt usage, body mass index (BMI) and regime of patients were strongly correlated with the progression of blood pressure level [9-11].

Methods

Source of data and description of the study area

The data for this study was obtained from Debre Berhan referral hospital, located in Debre Berhan town,North Shewa Zone of the Amhara Region. In the town there is only one government, one private hospital, two government health centers, five health posts, and 18 private clinics. Debre Berhan referral hospital is the only government hospital in the city and it is Zonal referral hospital serving to population residing in the north shewa zone and surrounding.

Retrospective study was conducted to obtain secondary data among hypertensive patients attending antihypertensive treatment from 1st September 2014 up to 30th August 2016 at Debre Berhan Referral Hospital. The data was extracted from the patient record cards. A longitudinal data on two biomarkers of hypertension which are Systolic and Diastolic blood pressure, various demographic covariates and clinical factors were considered. It contains eligible clinical information of all hypertensive patients receiving treatments in follow-up between ages 20 to 80 years old. And also, patients who have high blood pressure level above normal level of SBP and DBP take follow up. The data in this study consists of 300 patients with SBP and DBP above the normal level. The average follow-up time was six month gap.

Variables in the study

The descriptive statistics such as frequencies and percentage for baseline categorical covariates used to summarize the distribution of selected background characteristics of the sample. And to estimate the effect of each demographic covariates and clinical factors on the progression of systolic and diastolic blood pressure linear mixed model was fitted. Generalized linear mixed model based on random effects incorporate correlation between the repeated observations within each individual and variation between individuals. The goodness of fit test was checked using the likelihood ratio test (LRT), Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC).

Results

The brief description of the patients included in the study was given in Table 2. From a total of 300 hypertensive patients included in the dataset, the percentages of hypertensive female patients were 55% while the percentages of 45% were male patients.

Regarding age distribution 28.3% of patients were in the age group 20-40, 32.3% were 40-60 and 39.3% were in the category 60-80. About 60% of hypertensive patients, under follow up were married while the remaining 11% were single, divorced, or widowed. More than half of respondents used salt (56%) in their food items whiles the remaining and 43.7% were not used salt. And also 38.7% of patients use different alcoholic beverage and the remaining 61.3% weren't used alcoholic beverages in their day to day activity.

Half of 51.1% of respondents had a family history and the other 48.7% of patients hadn't a family history of the disease. Results show that about 44.7% of respondents were illiterate while the remaining 16% and 7% were accomplished primary, secondary, and above; respectively. The majority of patients living in urban areas 69.7% and the remaining 30.3% were living in the rural area. Concerning regime type, about 42.7% had used Hydrocholorothizide + Enalapril and the remaining, 31.6% and 25.7% and of patients had used Hydrocholorothizide and Enalapril; respectively (Table 1).

Results of linear mixed model

According to Table 2 BMI, age, residence, salt, and alcohol status were found significant. And also the interaction terms time by age, time by BMI, time by Residence, time by Salt, and time by Alcohol were significant at 0.05 level of significance associated with systolic blood pressure. Likewise, diastolic blood pressure reveals that interaction terms of time by age, time by BMI, time by residence, time by salt, and time by alcohol are significant at the 0.05 significance level. And also the main effects BMI, Age (40-60), Residence (Urban), Salt (Yes), Regime (Hydrocholorothizide + Enalapril), and Alcohol (Yes) were found significant (Table 2).

Selection of random effects

The estimated variance of random intercept was 102.62 and variance of random slope (time) was 3.3048 for systolic blood pressure while the covariance between random intercept and a random slope for the same patients was −20.4284. Similarly, for diastolic blood pressure, the estimated variance of random intercept was 17. 9492 and variance of random slope (time) was 0.6044 whereas the covariance between random intercept and a random slope for the alike patients was -3.6715 (Table 3).

Generalized linear mixed model

All fixed effects parameters in GLMM have subject-specific interpretation, unlike the marginal model. Thus, given the random effects (b_{1i}); the intercept ($e^{\beta 0} = e^{148.48}$=3.04) in GLMM is an estimate of the male subject average SBP provided that the individual married, secondary and above, urban and Regime (Hydrocholothiazide+Enalapril). Similarly, Time ($e^{\beta 1} = e^{1.4912} = 4.44$, implies the mean SBP increases 4.44 times per month for the male individual when the remaining variables kept constant and it is significantly different from zero (p<0.0001) at a 5% significance level. And also, the coefficient for residence (β_7=−7.8484) verifies that the mean SBP for the female individual is 0.538 times higher than the rural individual with the same random effects(b_i) at baseline and their difference is found to be statistically significant (p-value=0.0398) at 5%. Other parameters are interpreted in the same way (Table 4).

Similarly, in Table 7 given the random effects (b_{1i}; the intercept ($e^{\beta 0}$= $e^{93.6332} = 4.45$) in GLMM is an estimate of the female subject average DBP provided that the individual married, secondary and above, urban and Regime (Hydrocholothiazide+Enalapril). And also for Time ($e^{\beta 1} = e^{-4.5951} = 0.010$),

Table 1. Categorization of independent variables used in the study.

NO	Description	Variable Code (if any)
1	Gender of patients	1=Female, 2=Male
2	Baseline Age of Patients in Years	1=60-80, 2=40-60, 3=20-40
3	Marital status of patients	1=Married, 2=Others (single, widowed or Divorced)
4	Body Mass Index of Patients Kg/m^2	
5	Time in month	
6	Residence of patients	1= Urban, 2=Rural
7	Education Level of patients	1= Illiterate, 2=Primary, 3=Secondary and above
8	Alcohol status of patients	1= Yes, 2= No
9	Family history of patients	1= Yes, 2=No
10	Salt usage of patients	1= Yes, 2=No
11	Regime of patients	1=Hydrocholothiazide+Enalapril 2=Hydrochlorothiazide, 3=Enalapril

Table 2. Parameter estimates for the reduced fixed effect linear mixed model for systolic blood pressure and diastolic blood pressure.

	SBP				DBP			
Effect	Estimate	Std error	t-value	Pr> | t |	Estimate	Std.error	t-value	Pr> | t |
Intercept	148.38	5.7799	25.67	< .001*	93.8013	3.5980	26.07	< .0001*
Time	3.2744	1.2070	2.71	< .001*	1.0946	0.4295	0.93	< .0001*
Sex (Female)	2.2626	1.9727	1.15	0.0512	0.0498	1.2219	0.04	0.3213
BMI	0.4443	0.2133	2.08	0.0274*	0.1612	0.1173	1.37	0.0395*
Age (60-80)	-3.4932	2.4868	-1.40	0.1603	2.5582	1.3159	1.94	0.0521
Age (40-60)	4.7952	2.1174	-2.26	0.0237*	1.4968	1.0687	-1.40	0.0174*
Marital Status(Married)	-1.2397	1.1515	-1.08	0.2819	-1.0080	1.0929	-0.92	0.0548
Residence(Urban)	5.0777	2.1457	-2.37	0.0181*	2.9511	1.1961	-2.47	0.0137*
Educ_lev(Illiterate)	1.3392	1.3947	0.96	0.5371	-0.6187	1.2584	-0.49	0.1612
Educ_lev(Prim)	0.1388	1.4054	0.10	0.3570	0.3234	1.4421	0.22	0.6231
Regime(HCT+Enalapril)	-1.7486	1.0976	-1.59	0.1114	-0.7277	1.2107	-0.60	0.0017*
Regime (HCT)	0.4286	1.3124	0.33	0.7441	-1.8039	1.0884	-1.66	0.5479
Salt (Yes)	1.6222	1.8694	0.87	0.0059*	0.2370	0.5456	-0.43	0.0461*
Alcohol (Yes)	0.5754	1.9275	0.30	0.0323*	0.1438	0.5443	0.26	0.0279*
Time*Age (40-60)	-1.0011	0.6461	1.55	0.0097*	-0.3059	0.3471	0.88	0.0110*
Time*BMI	-0.0975	0.0653	-1.49	0.0362*	0.2136	0.0384	-0.36	0.0219*
Time* Resi(Urban)	-1.6458	0.5988	2.60	0.0093*	0.6045	0.3495	1.73	0.0112*
Time* Salt(Yes)	-0.4597	0.5504	-0.84	0.0437*	0.1266	0.3453	0.37	0.0141*
Time*Alco(Yes)	0.3661	0.5725	-0.64	0.0227*	0.2914	0.3466	0.84	0.0036*

* Significance (P-value < 0.05).

Table 3. Comparison of variance component models with different random effects using mixture chi-square test for systolic blood pressure and diastolic blood pressure.

	SBP			DBP		
Parameter	**No Random**	**Random intercept**	**Random intercept + time**	**No Random**	**Random intercept**	**Random intercept + time**
Var(intercept)	-	23.5421(7.1076)	102.62(23.5558)	-	3.6652(1.9387)	17.9492(6.3960)
Var(intercept ,slope)	-	-	-20.4284(8.4925)	-	-	-3.6715(1.8459)
Var(slope)	-	-	3.3048(2.0920)	-	-	0.6044(0.6457)
Var(residual)	-	320.23(12.1891)	310.15(13.0990)	-	102.07(3.8783)	100.12(4.2506)
Loglikilihood	14626.5	14654.5	14592.9	12668.3	12688.6	12698.2

Table 4. Final model for GLMM and Covariance parameter estimates for Systolic Blood Pressure and Diastolic Blood Pressure.

	SBP				DBP			
Effect	Estimate	S.E	t-value	Pr>| t |	Estimate	S.E	t-value	Pr>| t |
Intercept	148.48	6.265	23.7	<0.01*	93.633	3.596	26.04	<0.001*
Time	1.4912	4.049	-0.00	<0.01*	-4.595	3.267	-1.41	<0.001*
BMI	0.4592	0.215	2.13	0.033*	0.163	0.117	1.40	0.675
Sex(Female)	1.9052	2.243	0.85	0.396	-1.066	2.545	-0.42	0.018*
Age(60-80)	-3.0196	2.676	-1.13	0.259	2.577	1.317	1.96	0.050
Age(40-60)	-4.5184	2.160	-2.09	0.036*	-1.507	1.066	-1.41	0.017*
Mar_Stat(M)	-1.7316	1.958	-0.88	0.376	-0.992	1.093	-0.91	0.040*
Residence(U)	-7.8484	2.346	-2.06	0.039*	-2.944	1.190	-2.47	0.013*
Educ_lev (I)	1.7443	2.745	0.64	0.023*	-0.551	1.246	-0.44	0.658
Educ_lev (Prim)	0.6634	2.651	0.25	0.802	1.444	0.845	0.20	0.364
Regime(HCT+ E)	-2.6553	2.122	-1.25	0.031*	-1.833	1.107	-1.65	0.013*
Regime(HCT)	0.7381	2.352	0.31	0.753	-0.757	1.212	-0.62	0.272
Salt(Yes)	1.6959	1.897	0.89	0.003*	0.015	0.991	0.02	0.253
Alcohol(Yes)	-0.5099	0.989	-0.52	0.606	3.593	3.143	1.14	0.014*
FamHis	2.5284	1.940	1.30	0.019*	0.247	0.950	0.26	0.029*
Time*Time	-0.3388	0.166	-2.04	0.000*	-0.165	0.100	-1.65	0.000*
Time*Age(40-60)	0.8501	1.765	0.48	0.008*	0.777	1.156	0.67	0.006*
Time* BMI	-0.1086	0.065	-1.67	0.003*	0.699	0.699	0.48	0.008*
Time*Educ_lev (I)	-0.1217	0.852	-0.14	0.006*	1.839	1.034	1.78	0.016*
Time*Reside(U)	1.4496	0.697	2.08	0.038*	0.074	0.309	0.24	0.022*
Time*Regim(HCT+ Enalapril)	0.3988	0.629	0.63	0.004*	0.835	0.644	1.30	0.005*

*Significance (P-value <0.05)

implies the mean DBP increases 0.010 times per month for the male individual when the remaining variables kept constant and it is significantly different from zero ($p < 0.0001$) at a 5% significance level. And also, the coefficient for residence (β_7=−2.9440 verifies that the mean DBP for the female individual is 0.0526 ($e^{\beta 2} = e^{-7.5262} = 0.052\acute{6}$) times higher than the rural individual with the same random effects (b_i) at base line and their difference is highly significant (p-value=0.0135) at 5% level of significance.

Discussions

In this study, separate longitudinal analysis for two continuous longitudinal outcomes systolic blood pressure (SBP) and diastolic blood pressure (DBP) from Debre Berhan referral hospital hypertensive patients follow up is presented. Since the data was correlated and continuous the method of linear mixed model and generalized linear mixed model that includes fixed effects and random effects used for the two longitudinal outcomes are considered.

The covariance structure selected for this study is the unstructured based on the AIC, BIC and Log likihood for a final model, only covariance structures that make sense for the data should be considered. In the Linear mixed effect model (LMM) and Generalized linear mixed effect model (GLMM) unstructured was selected after taking into account all possible covariance structures due to, its smallest AIC and BIC value. This is supports the result of who put the appropriate covariance structure for their hypertensive data was unstructured as compared to the rest covariance structure.

Variables such as BMI, sex, age (40-60), residence (urban), salt and alcohol were significant effect with systolic blood pressure. And also BMI, age (40-60), residence(urban), education level (illiterate), regime (HCT+Enalapril), salt and alcohol were significant from main effect. The linear mixed model showed that, the interaction term of age with time was significant which indicates that a significant effect on the progression of systolic blood pressure and diastolic blood pressure [13-14].

From the final generalized linear mixed model for systolic blood pressure BMI (Body Mass Index), Age (40-60), Residence (urban), education level (Illiterate), regime (HCT+Enalapril), Salt (p=0.0336, p=0.0367, p=0.0398, p=0.0253, p=0.0315, and p=0.0031; respectively) and time by age, time by education level, time by BMI, time by regime and time by residence are significant predictors of systolic blood pressure at 5% significance level. And also the final generalized linear mixed model for diastolic blood pressure sex, age, marital status, residence, regime (HCT+Enalapril), alcohol and family history (p=0.0184, p=0.0179, p=0.0405, p=0.0135, p=0.0130, p=0.0148 and p=0.0290; respectively) and age by time, marital status by time, residence by time, family history by time, regime by time are significant predictors of diastolic blood pressure at 5% significance level. It supports baseline diastolic blood pressure, sex, age, time were significant determinants diastolic blood pressure, but contradicts family history, which were not significant but significant in our case [15].

Conclusions

This study evaluated the progression of systolic and diastolic blood pressures in hypertensive patients based on measured blood pressure levels using longitudinal analysis methodologies. The aim of the study was to investigate the progression and determinant factors that influence the progression of systolic and diastolic blood pressure in hypertensive patients using different statistical methodologies like the linear mixed model and generalized linear mixed model analysis. Based on the result the progression of systolic blood pressure and diastolic blood pressure measures were significantly different with respect to the main effect independent variables time, sex(female), Age(40-60), residence, salt, alcohol, and their interaction time. The average measure for both biomarkers measures decreases in a linear pattern over time after patients initiated antihypertensive treatment.

Competing Interests

The authors declare that they have no competing interests.

Authors' Contribution

WK had made substantial contribution to conception and design, or acquisition of data, or analysis and interpretation of the data; YB had been involved in drafting the manuscript or revising it critically for important intellectual content; AT had given final approval of version to be published.

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Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

Ethical clearance was taken from Debre Berhan University, school Post Graduate coordination ethical review board and official letter was written by the department of statistics to the Debre Berhan referral hospital in order to obtain the data from the hospital before planning and starting data collection. Official letter was given for concerned bodies and then confidentiality of the information was assured from all aspects.

Consent for Publication

Not applicable.

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