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A Joint Model for Possibly Multivariate Longitudinal End Point in Clinical Cohort Study

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Abstract

This paper is motivated in modeling a joint mixed effect model incorporating random effects with independent measurement error for both end points. Both the association in the evolution (AOE) for two or possibly multiple outcomes and evolution in the association (EOA) are expected to be assessed by joint mixed effect model. The proposed model is further trustful of grasping the problem of nonlinearity and absence of normality assumption and in turn is to predict the effect of associated covariates in the progressive evolution of longitudinal outcomes throughout the given time interval. As case study the two outcomes Systolic Blood Pressure (SBP) and Diastolic Blood Pleasure (DBP) of hypertensive patients are considered. The summary statistics of the two end points are included in this context. Thus, the average follow-up is 4.21(0.088) months, the average SBP and DBP of hypertensive patients are 136.12(0.367) and 85.13(0.273) respectively and the standard deviation of SBP and DBP are 16.21 and 12.06 respectively. Moreover, the average age of the hypertensive patients is 50.63(0.315) years old. The values inside the brackets refer the standard errors. Finally, the straight lines on the two plots indicate the normality of the two outcomes. This study suggests for the further work to the extended non-linear mixed effect model for correlated multivariate repeated measure data usually called longitudinal data. Moreover, the study can incorporate the joint model of multivariate longitudinal outcome with time to event outcomes. In order to come up with flexible and robust models, the authors can further extend these models to non-parametric smoothing models of longitudinal endpoints and survival times.

Keywords: Blood pressure; End points; Joint mixed effect models; Longitudinal data; Multivariate models

Introduction

A joint mixed effect model

In cohort studies the individuals' clinical progress is being checked throughout the entire follow up time. Thus, it is fact to have multiple outcomes in many fields of experimental studies including biomedical, agricultural, public health, epidemiological studies, engineering science and other life science including behavioural sciences researches. Obviously, several questions arise upon the researchers' mind in context that how to model the shared evolution of multivariate longitudinally followed clinical end points. That is the reason for many researchers to be motivated in modelling the correlated outcomes jointly.

In such experimental results the multivariate longitudinal data are unique in the sense that they allow the researchers to study the joint evolution of the outcomes over time. When individual study units are followed from clinical admission until the determination of sure event of interest, loss to follow-up study or the pre-specified time for end of study, whichever condition comes first a progressive study is said to be longitudinal or a follow-up study. Epidemiologists and social scientists usually call the longitudinal studies as cohort studies and panel studies respectively [1]. According to Toh and Hernán [1], once the foremost concern is estimating the causal effect of certain action on the outcome, longitudinal studies are usually ideal and favoured over cross-sectional or non-longitudinal studies for possibly unclear sequential order of treatments and outcome.

- Frequently, multiple response variables are possibly tracked in clinical follow-up of various longitudinal settings. Thus, analysing all settings jointly is much worthier than analysing separately [2]. However, years gone these types of data were being analysed.
- Using simple approaches in which each outcome is analysed separately or by using data reduction approaches like factor analysis and/or principal components to reduce the dimension of several correlated outcomes. Separate analysis approach is practically easier yet it does not able to handle the correlation between longitudinal outcomes and/or other possibly existing features like measurement errors either in one or more responses [3].
- Due to the clear limitations of the two mentioned approaches, since over recent years several researchers have given attention how to model the multivariate outcomes jointly. Consequently, joint mixed effect model for continuous outcomes and joint GEE for discrete longitudinal outcomes have been given high attention to model the joint evolution of two or more longitudinally measured outcomes.

Modelling bivariate continuous longitudinal outcomes jointly

The commonly used bivariate linear mixed effect models are convenient while analysing longitudinal outcomes of two allied end points. In this paper, the motivation is to model a joint linear mixed effect model incorporating random effects with independent measurement error for both endpoints. Regularly longitudinal data are collected in epidemiological studies specially to study the evolution of biomedical endpoints.

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Experimental

For the elegant analysis the standard statistical packages are available in several software; particularly, freely accessible software R, which is good to model the linear mixed effect model easily handling intra-subject correlation [4]. Furthermore, out of several authors those have modelled the bivariate mixed effect to investigate the joint evolution of two longitudinally measured outcomes, the authors [5,6] recently have published the joint mixed effect models for longitudinal outcomes Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) of hypertensive patients and Heart Rate (HR) or Pulse Rate (PR) and Respiratory Rate (RR) of congestive heart failure patients respectively.

Thus, the two longitudinally measured endpoints of vector $Y_i(t)$, at each occasion which is designed in below are supposed to be modelled jointly.

Suppose the vector $Y_i = \begin{bmatrix} Y_{1i} \\ Y_{2i} \end{bmatrix}$ be the response vector for the individual i, with Y_{Ki} the n_{ki} vector of the end points k (k=1, 2) with $n_{1i}=n_{2i}=n_i$, hence possibly proposed model for bivariate longitudinal data with assumption of Gaussian process is

$$\begin{cases} Y_{1i}(t) = \mu_1(t) + a_{1i} + b_{1i}t + \varepsilon_{1i}(t) \\ Y_{2i}(t) = \mu_2(t) + a_{2i} + b_{2i}t + \varepsilon_{2i}(t) \end{cases}$$

Where, $\mu_1(t)$ and $\mu_2(t)$ refer to the population means at time t.

The association between the possible evolution of Y_1 and Y_2 is given by

$$r_E = \frac{\operatorname{cov}(b_1, b_2)}{\sqrt{\operatorname{var}(b_1) \times \operatorname{var}(b_2)}} = \frac{\sigma_{b_1 b_2}}{\sqrt{\left(\sigma^2_{b_1} \times \sigma^2_{b_2}\right)}}$$

The conceivable marginal association between 1Y and 2Y at time t is given by

$$r_M(t) = \frac{\operatorname{cov}\left(Y_{1i}(t), Y_{2i}(t)\right)}{\sqrt{\operatorname{var}\left(Y_{1i}(t)\right) \times \operatorname{var} Y_{2i}(t)}} = \frac{\sigma_{a_1 a_2} + t\sigma_{a_1 b_2} + \sigma_{a_2 b_1} + t^2\sigma_{b_1 b_2} + \sigma_{12}}{\sqrt{\left(\sigma^2_{a_1} + 2t\sigma_{a_1 b_1} + t^2\sigma^2_{b_1} + \sigma^2_1\right) \times \left(\sigma^2_{a_2} + 2t\sigma_{a_2 b_2} + t^2\sigma^2_{b_2} + \sigma^2_2\right)}}$$

Obviously, it is easy to realize the raise of problems and difficulties in estimating covariance parameters due to the existence of exponential high dimensional covariance parameters with the increase of number of response variables. Therefore, it is true to choose the techniques intuitively.

Case Study

The case study was done on hypertension patients at Mekelle Ayder Referral Hospital of Mekelle University, Tigray, Ethiopia. The cohort data about SBP and DBP of hypertensive patients is obtained from the hospital. Mekelle University is one of the highly recognized learning and medical training University with enough laboratory equipment which is located in north Ethiopia in Tigray regional state.

Study variables

- Response variables: Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP)

- Covariates (Independent variables): Age, Sex, Time, Place of Residence, Family history, type of treatment.

Results

Results of descriptive statistics

According to the follow up the minimum and maximum age of hypertensive patients are 20 yrs and 86 yrs old respectively. Likewise, the minimum number of SBP and DBP are 90 and 50 respectively and the maximum number of SBP and DBP are 230 and 130 respectively. The maximum follow-up time in months are 18 months and the average follow-up is 4.21(0.088) months. Furthermore, the average SBP and DBP of hypertensive patients in this follow-up report are 136.12(0.367) and 85.13(0.273) respectively. The total follow-up is 1950 repeated measures.

Additionally, the rounded standard deviation of SBP and DBP are 16.21 and 12.06 respectively. Moreover, the average age of the hypertensive patients is 50.63(0.315) yrs old. The values inside the brackets refer the standard errors (Table 1).

Both Figures 1 and 2 shows straight line on points indicating that the data fit the normality assumptions.

Discussion

Summary report

In these report 354 adolescent hypertensive patients with age greater than or equal to 18 yrs, who were on treatment, and who had measured at least three times are considered. The data were extracted from the patient card charts with the guidance of physicians and nurses. The data extraction and clinical follow-up has been taken from August 01, 2017 tod September 30, 2017.

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			Descriptive statistics				
	N Statistic	Minimum statistic	Maximum statistic	Sum statistic	Mean statistic	Mean std. error	Std. deviation statistic
Time old age	1950	0	18	8200	4.2051	0.08783	3.87847
Hypertensive patients	1950	20	86	98719	50.6251	0.31535	13.92568
Systolic blood pressure	1950	90	230	265430	136.1179	0.36701	16.20661
Diastolic blood pressure	1950	50	130	166010	85.1333	0.27303	12.05672
Valid N (list wise)	1950						

Table 1: Summary statistics.

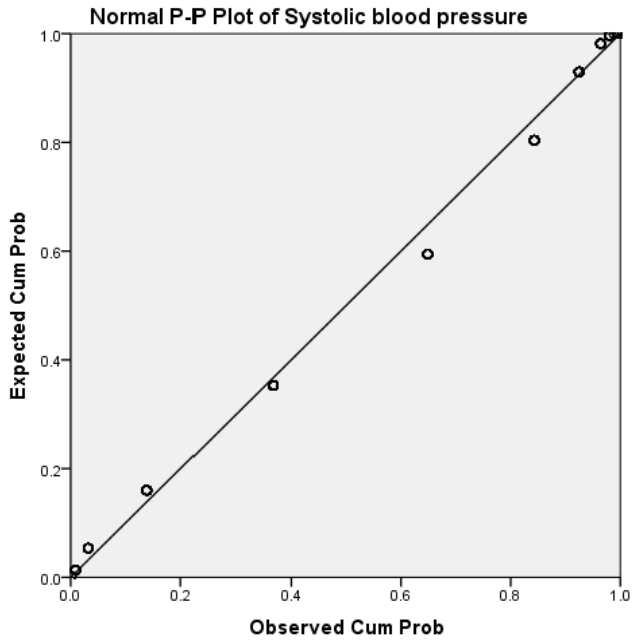

Figure 1: Normal P-P Plot of systolic blood pressure.

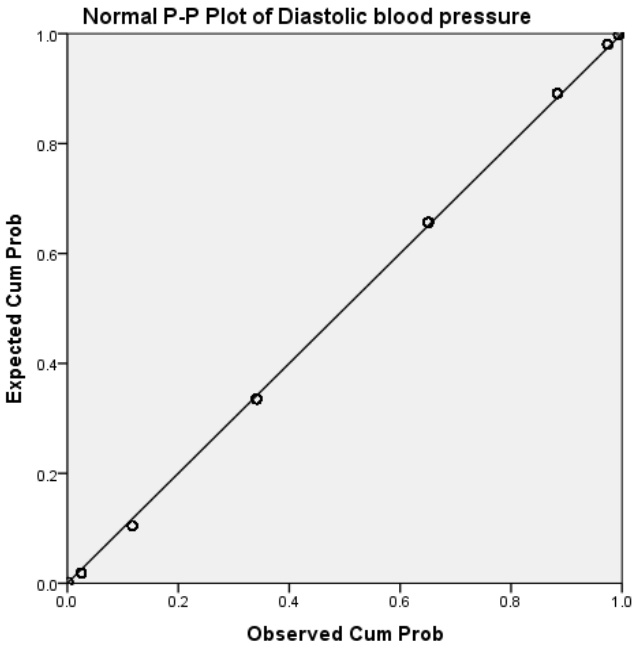

Figure 2: Normal P-P Plot of diastolic blood pressure.

Conclusion

This study models the mixed effect with the concept of both association in the evolution (AOE) of the two or more responses and the evolution in the associations (EOA) under usual joint linear mixed effects model to grasp the problem of nonlinearity and absence of normality assumptions then to predict the effect of associated factors in the evolution of longitudinal end point through the given time interval.

In all fields of studies such as art, science, engineering and biological or life sciences, especially clinical and epidemiological research, it is usually known to perceive multivariate longitudinal end points. As a result of either experimental or observational outcomes, multivariate longitudinal study initiates the potential researchers to deal with the shared evolution of several outcomes throughout the time. Therefore, the author proposed the joint mixed effect model for multivariate or correlated longitudinal outcomes.

The commonly known assumptions of linear regressions model linearity and normality assumption may not always plausible due to the result of sparse and unbalanced data. Therefore, applying more flexible joint mixed model so-called joint nonlinear mixed effects model for several longitudinal endpoints is more suitable and efficient.

For future work, this can be extended to non-linear mixed effect model for multivariate longitudinal data. Moreover, the study can incorporate the joint model of multivariate longitudinal outcome with time to event outcomes. In order to come up with flexible and robust models, the authors can further extend these models to non-parametric smoothing models of longitudinal end points and survival times.

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