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Modeling of Multi-Response Longitudinal DataUsing Linear Mixed Modelin Patient with Pulmonary Tuberculosis in Syaiful Anwar Hospital Malang

Adji Achmad Rinaldo Fernandes*, Solimun

[1]Department of Statistics, Faculty of Natural Sciences, University of Brawijaya, Malang, Indonesia & Jl MT Haryono 169 Malang 65145, Indonesia

Abstract : In medical research, eventually researcher using the longitudinal data dealing with repeated measurement in each patient as a subject in several period of time with the quantitative response. Longitudinal data is data that has two characteristics which repeated measurements on the same subjects during a certain period and there is a relationship between the studied observations from time to time. In the longitudinal data is often found to observations that have more than two response variables are inter-connected and quantitative. Because the study was repeated in time on the same subject then the longitudinal data analysis are always correlated, corresponding to the analysis using multi-response longitudinal mixed model. This study aimed to establish the model of multi-response longitudinal data in medical research, using the Mixed Model. Data to be modeled is a secondary data on the effects of Anti Tuberculosis Drug therapy in patients with pulmonary tuberculosis, Syaiful Anwar Hospital Malang. Variable responses were observed, among others, BMI (Body Mass Index), LED (erythrocyte sedimentation rate), monocytes, and levels of Supar (soluble urokinase plasminogen activator receptor). Final model is formed in patients with pulmonary tuberculosis showed that during the treatment period increased Body Mass Index (BMI), decreased erythrocyte sedimentation rate (LED), decreased monocyte and decreased levels of soluble urokinase plasminogen activator receptor (Supar). This demonstrates the success of Anti Tuberculosis Drug therapy in patients with pulmonary tuberculosis. Increased Pulmonary Tuberculosis patient age resulted in increased Body Mass Index (BMI), erythrocyte sedimentation rate (LED), monocytes and levels of soluble urokinase plasminogen activator receptor (Supar). The gender difference in patients with Pulmonary Tuberculosis only affects the response variable is Body Mass Index (BMI), whereas the other response variables are not influenced by gender differences.
Keywords : Longitudinal, Multi-response, Mixed Model.

Introduction

Longitudinal data is data that has two characteristics which repeated measurements on the same subjects during a certain period and there is a relationship between the studied observations from time to time[1]. In general, studies to determine the explanatory variables that most influence on more than one response using Multivariate Analysis of Variance (MANOVA) model. The correlation between observations within the same unit on longitudinal data lead MANOVA procedure can not be applied, so that appropriate methods for the analysis of longitudinal data with more than one response variable using the Mixed Models[2].

In the longitudinal data is often found to observations that have more than two response variables are interconnected and quantitative. This research will form a model of multi-response longitudinal data on health

using the Mixed models[3]. The research objective is to establish a data model of pulmonary tuberculosis patients using multi-response mixed model.

Material and Methods

1. Longitudinal data

Longitudinal data is data that has two characteristics which repeated measurements on the same subjects during a certain period and there is a relationship between the studied observations from time to time. Research data in which the number of time units for each unit of the same cross-sectional data are called balance longitudinal data[4]. The framework of balanced longitudinal data show the same measurement unit (fixed) and the number of observations for the cross-sectional units (subjects) is the same in all subjects was observed. The framework of balanced longitudinal data as follows:

Table 1 Balance Longitudinal Data Framework

i	t	Y_{it}	X_{it}
1	1	Y_{11}	X_{11}
	2	Y_{12}	X_{12}
	⋮	⋮	⋮
	T	Y_{1T}	X_{1T}
2	1	Y_{21}	X_{21}
	2	Y_{22}	X_{22}
	⋮	⋮	⋮
	T	Y_{2T}	X_{2T}
⋮	⋮	⋮	⋮

where

i : i^{th}*cross-sectional* unit i (i : 1,2,…, S)
t : t^{th} time unit t (t : 1,2,…, T)
$\mathbf{Y_{it}}$: Response variable value for i^{th}*cross-sectional* i and t^{th} time.
$\mathbf{X_{it}}$: Predictor variable value for i^{th}*cross-sectional* i and t^{th} time.

2. Two Stage Analysis

Verbeke and Molenberghs[4] explains that in practice, the longitudinal data using linear regression function on each subject (subject-specific). This method is called with two-stage analysis.

a. First Stage

At this stage,response variables Y_{ij} indicates that the response to be observed, for the i-th individual, at time j-th, where i = 1, ..., S, and j = 1, ..., n_i

Models in the first stage is defined as:

$$\mathbf{Y_i} = \mathbf{Z_i\beta_i} + \boldsymbol{\varepsilon_i}, \quad (1)$$

$$\mathbf{Y_i} = \begin{bmatrix} y_1 \\ y_2 \\ y_3 \\ \vdots \\ y_{n_i} \end{bmatrix}_{n_i x 1}, \mathbf{Z_i} = \begin{bmatrix} 1 & t_1 & t_1^2 & \cdots & t_1^r \\ 1 & t_2 & t_2^2 & \cdots & t_2^r \\ 1 & t_3 & t_3^2 & \cdots & t_3^r \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 1 & t_{n_i} & t_{n_i}^2 & \cdots & t_{n_i}^r \end{bmatrix}_{n_i x q},$$

$\boldsymbol{\beta_i} = \begin{bmatrix} \beta_{1i} \\ \beta_{2i} \\ \beta_{3i} \\ \vdots \\ \beta_{qi} \end{bmatrix}_{qx1}$, dan $\boldsymbol{\varepsilon_i} = \begin{bmatrix} \varepsilon_1 \\ \varepsilon_2 \\ \varepsilon_3 \\ \vdots \\ \varepsilon_{n_i} \end{bmatrix}_{n_i x1}$

where:

$\mathbf{Y_i}$: response variable
$\mathbf{Z_i}$: predictor variable
$\boldsymbol{\beta_i}$: subject-specific coefficient
$\boldsymbol{\varepsilon_i}$: error model, $\boldsymbol{\varepsilon_i} \sim N(\mathbf{0}, \sigma^2 \boldsymbol{I}_{n_i})$
$\boldsymbol{I}_{n_i}$: identity matrix

b. Second Stage

In the second stage, the regression model used to explain the diversity of each patient associated with regression coefficients $\boldsymbol{\beta_i}$ specific subject, with the form:

$$\boldsymbol{\beta_i} = \mathbf{K_i}\boldsymbol{\beta} + \mathbf{b_i} \quad (2)$$

where:

$\mathbf{K_i}$: predictor variable
$\boldsymbol{\beta}$: unknown parameter regression
$\mathbf{b_i}$: residual, $\mathbf{b_i} \sim N_q(\mathbf{0}, \mathbf{D})$
$\mathbf{D}$: covariance matrix of response variable

3. Mixed Model

According to Verbeke and Molenberghs[4], the combination of the two-stage analysis into a single statistical model, which combines $\boldsymbol{\beta_i}$in equation (2) into equation (1) will be obtained Mixed Model as follows:

$$\mathbf{Y_i} = \mathbf{X_i}\boldsymbol{\beta} + \mathbf{Z_i}\mathbf{b_i} + \boldsymbol{\varepsilon_i} \quad (3)$$

The model assumes the vector of repeated measurements followed the linear regression model with population-specific parameter, β (same for all subjects) and subject-specific parameters $b_i$assumed to be random so-called random effects.

According to Hedeker and Gibbons[5], the excess Mixed Model in longitudinal data modeling are: (1) Model the evolution time response on the subject clearly, (2) More flexible in terms of repeated measurements, by not requiring the same number of observations for each subject and time can be a continuous value, (3) Specifications of covariance are more flexible structure in repeated measurements, and (4) The model can be expanded into a higher level, repeated measurements of each subject in the group.

4. Mixed Model in Multi-Response Variables

Thiebaut, et al.[6] defines the Mixed Models in birespon variables with Gaussian mixture model of the component is random, order to-1 from the auto-regressive, AR (1) and remnant components. The expansion of the model into a multi-response model, suppose $\mathbf{Y_i} = \begin{bmatrix} \mathbf{Y_{1i}} \\ \mathbf{Y_{2i}} \\ \vdots \\ \mathbf{Y_{ki}} \end{bmatrix}$, is the response vector for i^{th}subject, with Y_{ki} is the measurement vector n_{ki}, then k (k = 1,2 ,...,.) with $n_{1i} = n_{2i} = n_{ki}$. Mixed Models in multi-response variables that can be used are as follows:

$$\begin{aligned} Y_{1i} &= X_{1i}\beta_1 + Z_{1i}b_{1i} + W_{1i} + \varepsilon_{1i} \\ Y_{2i} &= X_{1i}\beta_2 + Z_{1i}b_{1i} + W_{2i} + \varepsilon_{2i} \\ &\vdots \\ Y_{ki} &= X_{1i}\beta_k + Z_{1i}b_{1i} + W_{ki} + \varepsilon_{ki} \end{aligned} \qquad (4)$$

where

$\varepsilon_{ki} \sim N(0, \sigma^2_{\varepsilon_k} I_{n_1})$, $b_{1i} \sim N(0, G_1)$, $W_{ki} \sim N(0, R_{ki})$

X_{1i} :predictor variable for fixed effect

β_k :fixed effect

Z_{1i} : predictor variable for random effect

b_{1i} :random effect

I_{n_1} :identity matrix

ε_{ki} : error model

$\sigma^2_{\varepsilon_k} I_{n_1} = \begin{bmatrix} \sigma^2_{\varepsilon_1} & 0 & 0 & 0 \\ 0 & \sigma^2_{\varepsilon_2} & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \sigma^2_{\varepsilon_1} \end{bmatrix}$: error covariance matrix

$W_{ki}(t)$: $\begin{bmatrix} w_{1i}(t) \\ w_{2i}(t) \\ \vdots \\ w_{ki}(t) \end{bmatrix}$ covariance function

Suppose that in a longitudinal data set has three response variables at three time iteration:

$w_{\downarrow}ki\ (t) = R_{\downarrow}i \otimes ($

$$W_{ki}(t) = \begin{bmatrix} \sigma^2_{w_1} & \sigma_{w_1w_2} & \sigma_{w_1w_3} \\ \sigma_{w_1w_2} & \sigma^2_{w_2} & \sigma_{w_2w_3} \\ \sigma_{w_1w_3} & \sigma_{w_2w_3} & \sigma^2_{w_3} \end{bmatrix} \begin{bmatrix} 1 & \rho & \rho^2 \\ \rho & 1 & \rho \\ \rho^2 & \rho & 1 \end{bmatrix}$$

5.Parameter Estimate for Mixed Model forMulti-response

5.1 Estimation of Marginal Model

Thiebaut, et al.[6] describes the marginal Mixed models in longitudinal multi-response data are given:

$$\begin{aligned} Y_{1i} &\sim N(X_{1i}\beta_{1i}, Z_{1i}G_1Z^T_{1i} + R_i + (_{\downarrow}1i) \\ Y_{2i} &\sim N(X_{1i}\beta_{2i}, Z_{1i}G_1Z^T_{1i} + R_i + (_{\downarrow}2i) \\ &\vdots \\ Y_{ki} &\sim N(X_{1i}\beta_{ki}, Z_{1i}G_1Z^T_{1i} + R_i + (_{\downarrow}ki) \end{aligned}$$

If $\alpha$is variance component as variance parameter in $V_i = Z_iG_iZ_i^T + R_i + \Sigma_i$, then $\alpha$is thus composed of q(q+1)/2 distinct elemen in **G** and all parameter in Σ_i. Thus $\theta = (\beta', \alpha')'$ is parameter estimates of marginal model Y_i, and $\Theta : \Theta_\beta \times \Theta_\alpha$ as parameter space for θ, then **G** and all $\Sigma_i$assemidefinit positive matrix.

a. *Maximum Likelihood* (ML) Estimation for Fixed Effect

According Molenbergh and Verbeke[4], the classical approach to obtain a conclusion based on the expected value of fixed effects parameters β obtained by maximizing the marginal likelihood function:

$$L_{ML}(\theta) = \prod_{i=1}^{s} \left\{ (2\pi)^{-\frac{n}{2}} |V_i(\alpha)|^{-\frac{1}{2}} \exp\left(-\frac{1}{2}(Y_i - X_i\beta)' V_i^{-1}(\alpha)(Y_i - X_i\beta) \right) \right\} \qquad (6)$$

Based θ and assuming $\alpha$is known. *Maximum Likelihood* (ML) estimation for fixed effect β, obtained by maximizing (6), conditional on variance components of $\alpha$is:

$$\hat{\boldsymbol{\beta}}(\alpha) = \left(\sum_{i=1}^{S} \mathbf{X}_i' \mathbf{W}_i \mathbf{X}_i\right)^{-1} \sum_{i=1}^{S} \mathbf{X}_i' \mathbf{W}_i \mathbf{y}_i \quad (7)$$

Where $\mathbf{W_i} = \mathbf{V_i^{-1}}(\alpha)$, as covariance matrix for $\hat{\boldsymbol{\beta}}$ as follow:

$$var\left(\hat{\beta}\right) = \left(\sum_{i=1}^{s} X_i' W_i X_i\right)^{-1} \left(\sum_{i=1}^{s} X_i' W_i var(Y_i) W_i X_i\right) \left(\sum_{i=1}^{s} X_i' W_i X_i\right)^{-1} \left(\sum_{i=1}^{s} X_i' W_i X_i\right)^{-1} \quad (8)$$

Then $\hat{\boldsymbol{\beta}}(\alpha) \sim N(\boldsymbol{\beta}, var(\hat{\boldsymbol{\beta}}))$.

Solve the equations such as likelihood function can also use the Newton-Raphson iteration method. Newton-Raphson iteration method is a method for determining the value of a parameter estimator is repeated until converges at a certain value. $T_1 = (T_{11}, T_{12}, \ldots, T_{1k})$ is a k-dimensional vector statistic obtained from the trial solution. Tr is a vector view of the rth iteration. $\hat{\theta} = (\hat{\theta}_1, \ldots, \hat{\theta}_k)$ is the maximum likelihood estimator. Where ε_r is the error in the rth iteration is obtained from the difference between Tr and $\hat{\theta}$. To achieve a convergent then the value of $\hat{\theta}$ if $\varepsilon_r \leq 10^{-6}$ for $r \rightarrow \infty$[4].

b. *Restricted Maximum Likelihood* (REML) Estimation for Variance Component

Estimation of variance components using the Maximum Likelihood method produces the expected value is not valid, so use REML estimators (Diggle, *et. Al*[7]).

$$\mathbf{Y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{b} + \mathbf{W} + \boldsymbol{\varepsilon}, \quad (9)$$

S is a combination of subject-specific regression model (4) and (5), where **Y**, **b**, and **ε**, and the matrix **X** is obtained from the stacking vectors $\mathbf{Y_i}$, $\mathbf{b_i}$, $\boldsymbol{\varepsilon_i}$, and $\mathbf{X_i}$ matrix, while **Z** is diagonal-block by $\mathbf{Z_i}$ on the main diagonal and zero otherwise, while **W** is the realization of order-1 vector of auto-regressive of $\mathbf{W_i}$. **Y** with $\sum_{i=1}^{S} n_i$ dimension, and is denoted by n.

Thus $\mathbf{Y} \sim \mathbf{N}(\mathbf{X}\boldsymbol{\beta}, \mathbf{V}(\alpha))$, $\mathbf{V}(\alpha)$ is a diagonal matrix with the Vi-block on the main diagonal and zero otherwise.

REML estimators for the variance components **α**of obtained by maximizing the likelihood Error contrast **U = A'Y**, where A is any matrix ofLikelihood Function Error Contrasts U = A full order with columns orthogonal to the column matrix **X**. **U** ~ N(**0**, **A'V(α)A**), does not depend on **β**. According to Verbeke and Molenberghs[4], Contrasts Error Likelihood function can be written as:

$$L(\alpha) = \pi^{\frac{n-p}{2}} \left|\sum_{i=1}^{S} X_i' X_i\right|^{\frac{1}{2}} \left|\sum_{i=1}^{S} X_i' V_i^{-1} X_i\right|^{-\frac{1}{2}} \prod_{i=1}^{S} |V_i|^{-\frac{1}{2}} \exp\left\{-\frac{1}{2}\sum_{i=1}^{S} (Y_i - X_i\beta)' V_i^{-1} (Y_i - X_i\beta)\right\} \quad (10)$$

Where $\hat{\boldsymbol{\beta}}$ obtained in equation (7). REML estimator for **α** and **β** obtained by maximizing the likelihood function of REML as follow:

$$L_{REML} = \left|\sum_{i=1}^{S} X_i' W_i(\alpha) X_i\right|^{-\frac{1}{2}} L_{ML}(\theta) \quad (11)$$

For **β** dan **α** parameter simultaneously, where $\mathbf{W_i} = \mathbf{V_i^{-1}}(\alpha)$ and L_{ML} (**θ**) as function of *MaximumLikelihood* in equation (6).

5.2 Subject Specific Estimation

Random effects $\mathbf{b_i}$reflect subject-specific deviations from the overall average profile, so it is important prediction of the value of $\mathbf{b_i}$. Estimation of random effects is done by assuming the model (9), $\mathbf{Y_i} = \mathbf{X_i}\boldsymbol{\beta} + \mathbf{Z_i b_i} + \mathbf{W_i} + \boldsymbol{\varepsilon_i}$ better fit than the marginal model. The posterior density function:

$$f(\mathbf{b_i}|\mathbf{y_i}) = f(\mathbf{b_i}|\mathbf{Y_i} = \mathbf{y_i}) = \frac{f(\mathbf{y_i}|\mathbf{b_i})\, f(\mathbf{b_i})}{\int f(\mathbf{y_i}|\mathbf{b_i})\, f(\mathbf{b_i})\, d\mathbf{b_i}} \quad (12)$$

where:

$f(\mathbf{b_i})$: prior density function, $\mathbf{b_i} \sim N(\mathbf{0},\mathbf{G})$

$\mathbf{y_i}$: observer value of $\mathbf{Y_i}$

$\mathbf{b_i}$estimated as an average of posterior distribution. According Molenbergh and Verbeke[4] estimator for the random effects $\mathbf{b_i}$are:

$$\hat{\mathbf{b}}_i = E(\mathbf{b_i}|\mathbf{Y_i} = \mathbf{y_i}) = \int \mathbf{b_i} f(\mathbf{b_i}|\mathbf{y_i})\, d\mathbf{b_i} = G\, Z_i' V_i^{-1}(\alpha)(\mathbf{y_i} - \mathbf{X_i}\beta) \quad (13)$$

$\mathbf{b_i}$estimators in equation (13) is also called empirical Bayes estimator (EB) with the covariance matrix of these estimators as follow:

$$Var\left(\hat{b}_i(\theta)\right) = GZ_i' \left\{ V_i^{-1} - V_i^{-1}X_i \left(\sum_{i=1}^{s} X_i' V_i^{-1} X_i \right)^{-1} X_i' V_i^{-1} \right\} Z_i G \quad (14)$$

6. Hipothesis Testing of Fixed Effect

Testing the hypothesis of fixed effects parameters are used to select the appropriate fixed effects model. Fixed effect parameters in the test ie intercept, slope of linear time, and the parameters of fixed effects of concomitant variables. There are two approaches to hypothesis testing that can be used.

1. T-test

Testing hypotheses on each parameter vector $\boldsymbol{\beta}_j$, j = 1,2,..., p, in general for any matrix **L** is known is as follows:

H_o: $\mathbf{L}\boldsymbol{\beta} = 0$ melawan H_1: $\mathbf{L}\boldsymbol{\beta} \neq 0$ (15)

T test approach and confidence intervals obtained through the distribution approaches

$$t_{observed} = (\hat{\beta} - \beta_j)/s.\hat{e}(\hat{\beta}), \text{ with } s.\hat{e}(\hat{\beta}) = \sqrt{\mathbf{var}\,\hat{\boldsymbol{\beta}}} \quad (16)$$

and $\mathbf{var}\,\hat{\boldsymbol{\beta}}$ obtained from the main diagonal matrix $\beta = (X'V^{-1}X)^{-1}$, with corresponding t distribution, where degrees of freedom t test suspected from observational data and $\beta = (X'V^{-1}X)^{-1}$ is the inverse of $\mathbf{var}\hat{\boldsymbol{\beta}}$.

2. F-test

According to Verbeke and Molenberghs[4], hypothesis testing (15) simultaneously based on the approach to the F distribution with first degrees of freedom is the rank (L), and the second degrees of freedom suspected of observational data.

$$F_{observed} = \frac{\left(\hat{\beta} - \beta\right)' L' \left[L \left(\sum_{i=1}^{s} X_i' V_i^{-1}(\hat{\alpha}) X_i \right)^{-1} L' \right]^{-1} L\left(\hat{\beta} - \beta\right)}{\text{rank}(L)} \quad (17)$$

According Rutletge[1], degrees of freedom in the t test and two degrees of freedom for testing fixed effects in the F test is calculated as the minimum contribution to the rank (**XZ**) of the random effects containing the fixed effects. If there are no random effects then the two degrees of freedom equal to the residual degrees of freedom (Np-1).

Result and Discussion

1. Soure of Data

In this study, data to be modeled is a secondary data obtained from Chozin[8] on the effect of OAT therapy in patients with pulmonary tuberculosis. Variable responses were observed, among others, BMI (Body Mass Index) Y_1, LED (erythrocyte sedimentation rate) Y_2, monocytesY_3, and Supar levels at month 0, 2, and 6 after treatment, Y_4. Subject of study of 5 patients with pulmonary tuberculosis with characteristics: (1) KP Miller, (2) Far Advance, (3) Minimal Lession, (4) Mod Advance, and (5) Destroyed Lung.

2. Selection of Mixed Effect Component

Firsty, selection the fixed effect. The test results of selected fixed effect that affect the response variables in five patients with pulmonary tuberculosis are shown in Table 2.

Table 2: Selection ofFixed Effect

Fixed Effect	**AIC**	**P-value of Parameter Est.**		
		Time	**Time^2**	**Time^3**
Time Linear	2227.1	0.001*		
Time Quadratic	2212.3	0.014*	0.001*	
Time Cubic	2233.7	0.027*	0.202	0.399

* Significant at 5% level of significance

From table 2 shows that the smallest value of Akaike Information Criterion (AIC) indicate the selected fixed effect is time quadratic. This also indicate that the component of quadratic trend of time are significant at 5% significance level.

Second, selection the random effect. Tentative model for the longitudinal multi-response data show that the random effects included intercept and random effects coefficient of linear time. The results of random testing selection effects are presented in Table 3.

Table 3: Selection of Random Effect with fixed effect time Quadratic

Random Effect	***-2 Res Log Likelihood***	**$-2\ln\lambda_N$**	**P-value**
Intercept, Slope Time, Slope Time^2	Not convergence		
Intercept, Slope Time	2188.8	93.3	0.001*
Intercept Only	2095.5	93.3	0.001*
No Random Effect	2188.8		

* Significant at 5% level of significance

The results of random effects selection in Table 3 shows a significant p-value on the model, indicate that therandom intercept and random slope time linearinclude in the selection. So the final mixed model is for time quadratic fixed effect, and time linear fixed effect.

3. Formulation of Final Model

Final Mixed Models in multi-response variables include fixed effects time quadratic with random effectstime linear. Table 4 below shows the parameter estimates for selected model.

Table 4:Parameter Estimation of Fixed Effect

Response	Parameter	Estimate	Std.Error	$t_{observed}$	P-value
Supar	Intercept	14.082	0.934	15.08	0.000*
	Time	-1.603	0.654	-2.45	0.026*
	$Time^2$	0.077	0.016	4.80	0.000*
Monocyte	Intercept	1160.970	114.850	10.11	0.000*
	Time	-82.624	37.735	-2.19	0.044*
	$Time^2$	2.369	2.622	0.90	0.367
BMI	Intercept	17.140	1.980	8.66	0.000*
	Time	0.938	0.870	1.08	0.297
	$Time^2$	-0.050	0.043	-1.16	0.245
LED	Intercept	78.200	9.079	8.61	0.000*
	Time	-7.060	3.038	-2.32	0.034*
	$Time^2$	0.239	0.207	1.15	0.249

* Significant at 5% level of significance

Table 4 shows that the fixed effects model with linear time significant at all four response variables. The final model of multi-response Mixed Modelsubstitude by the parameter estimators marginal fixed effects model to obtain the final model of multi-response Mixed Model following equation (19):

(a) $Y_{1i} = (14.082 + b_{01i}) – (1.603 + b_{11i})\ t + 0.077\ t^2$
(b) $Y_{1i} = (1160.9 + b_{02i}) – (82.62 + b_{12i})\ t + 2.369\ t^2$
(c) $Y_{1i} = (17.140 + b_{03i}) + (0.938 + b_{13i})\ t – 0.050\ t^2$
(d) $Y_{1i} = (78.200 + b_{04i}) – (7.060 + b_{14i})\ t + 0.239\ t^2$ (19)

Where t indicates variables fixed time (a half month). Parameter estimation of random effect based on empirical bayes are shown in Tabel 5.

Table 5:Parameter Estimation of Random Effect

Response	Parameter	*Estimation*				
		Pat1	Pat2	Pat3	Pat4	Pat5
Supar	b_{01i}	0.954	0.557	-0.157	-1.634	0.280
	b_{11i}	-0.091	-0.043	-0.024	0.064	0.094
Monocyte	b_{02i}	0.065	0.136	-0.128	-0.189	0.116
	b_{12i}	0.459	0.517	-0.397	-0.591	0.012
BMI	b_{03i}	-0.893	-0.935	0.589	2.228	-0.989
	b_{13i}	-0.011	-0.399	0.227	0.497	-0.315
LED	b_{04i}	1.006	0.721	-0.715	-0.978	-0.034
	b_{14i}	3.499	0.678	-1.589	-1.558	-1.030

Based on the parameter estimation of fixed and random effect, subject specific prediction are shown in figure below (dot shows observation value, and line shows prediction value):

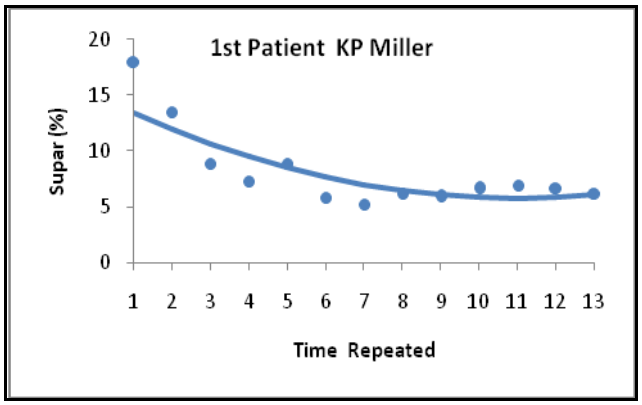

Figure 1: Supar Prediction of First Patient: KP Miller

From the figure shows that the supar level of patient with KP Miller were decrease from the first period until period 11 (after 5 month treatment), and will be increasing until the end of period. The separated figure of other patient shows in Appendix 1. The overlaid figure of each patients are shown in figure below:

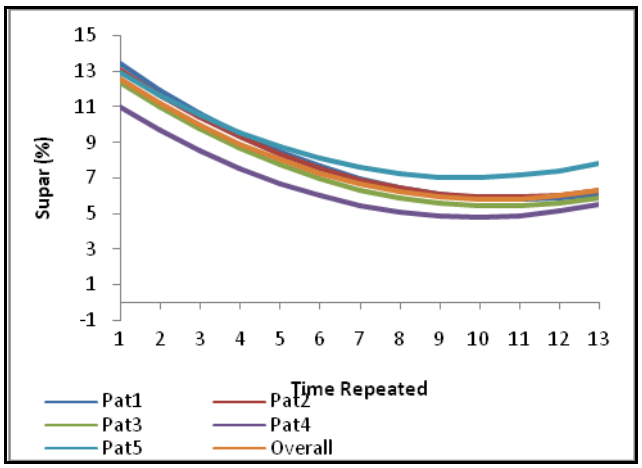

Figure2: Supar Prediction of Each Patient

From the figure above shows that the response of Supar in patients with type of Supar KP Miller and Far Advance is a quadratic pattern with the lowest levels of Supar in the period to 11 (after 5 months of treatment), while the three other types with the lowest levels in the period to 10 Supar (after 4.5 months of treatment).

4. Goodness of Fit model

Goodness of fit Mixed Model in equation (19) is obtained by calculating the value adjusted R-square values obtained for 0.8174. So it can be concluded that the variable responses of BMI, LEDs, monocytes and levels Supar 81.74% can be explained by the model include time quadratic fixed effect, and time linear random effect.

Conclusion and Reccomendation

Final model is formed in patients with pulmonary tuberculosis using the Mixed Model is a multi-response given in equation (19). Pulmonary Tuberculosis patients during treatment with anti-tuberculosis drug therapy (OAT) has increased Body Mass Index (BMI), decreased LED, decreased monocyte and decreased levels of soluble urokinase plasminogen activator receptor (Supar). This demonstrates the success of OAT therapy in patients with pulmonary tuberculosis.Increased Pulmonary Tuberculosis patient age resulted in increased Body Mass Index (BMI), LED, monocytes and levels of soluble urokinase plasminogen activator

receptor (Supar).The gender difference in patients with Pulmonary Tuberculosis only affects the response variable is Body Mass Index (BMI), whereas the other response variables are not influenced by gender differences.Future studies are advised to examine the longitudinal multi-response data in the form of non-parametric such us spline estimator for longitudinal multi-response data.

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