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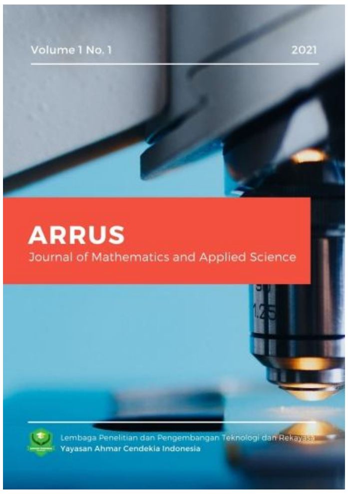

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RESEARCH ARTICLE

Factors Associated with Monocyte and SuPAR Levels in Pulmonary Tuberculosis Patients: A Longitudinal Study

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Abstract: Tuberculosis in Indonesia had the second highest TB burden globally, after India. 92% of the estimated cases were confirmed to be pulmonary tuberculosis. However, controlling pulmonary tuberculosis relies heavily on accurate diagnosis, appropriate treatment, effective monitoring, and evaluation. This study aims to model and investigate the most significant factor affecting monocyte and suPAR levels as a biomarker based on observation time, body mass index, and erythrocyte sedimentation rate. This study was a longitudinal study. 60 patients were involved every two weeks over 13 periods. Path analysis with the generalized linear mixed model (GLMM) approach and comparing three estimation methods to investigate the longitudinal relationship between variables and compare the best structure for modeling the relationship. The best model for describing the relationship between observation time, body mass index, and erythrocyte sedimentation rate on monocyte and suPAR levels is GLMM with unstructured covariance (R^2 = 0.977 and AIC = 0.052). A significant positive correlation between monocyte and suPAR levels further validates suPAR as a robust biomarker for monitoring treatment response. The study concludes that effective clinical management of pulmonary tuberculosis requires an integrated strategy that combines OAT with regular monitoring of BMI, ESR, and monocyte levels to optimize patient recovery.

Keywords: GLMM, Longitudinal Path Analysis, Pulmonary Tuberculosis, suPAR

1. Introduction

Tuberculosis (TB) is a leading contributor to the human disease burden and considered one of the deadliest infectious diseases, after coronavirus disease (COVID-19), and caused almost twice as many deaths as HIV/AIDS (WHO, 2024). World Health Organization (2023) also reported that tuberculosis disease in Indonesia had the second highest TB burden globally, after India. The number of tuberculosis cases in Indonesia is estimated at 1,090,000 cases. This is increasing from cases in 2022 with 969 thousand cases. Of the estimated tuberculosis cases reported in Indonesia, 92% were confirmed to be pulmonary tuberculosis.

However, controlling pulmonary tuberculosis relies heavily on accurate diagnosis, appropriate treatment, effective monitoring, and evaluation of treatment. In recent years, a biological marker called suPAR (Soluble Urokinase Plasminogen Activator Receptor) has been discovered for use in the monitoring stage. SuPAR is a soluble version of uPAR

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(Urokinase Plasminogen Activator Receptor). It has the potential to be a common biomarker in diagnosing, prognosing, and following up the lung diseases (Hussain, Mohammed, & Ali, 2023). Research conducted by (Enocsson, et al., 2021) also demonstrated that suPAR levels impact time. Another alternative that has long been used to diagnose and evaluate tuberculosis disease is the erythrocyte sedimentation rate. Testing the erythrocyte sedimentation rate is relatively easy and fast, making it suitable for use in areas with high tuberculosis cases (Ayatollahi, et al., 2022). The diagnosis and evaluation of the progression of Pulmonary Tuberculosis are also carried out by observing the monocyte levels in the body. Monocytes play a dual role in Tuberculosis infection, serving as an important anti-microbial defense through innate mechanisms and causing immunity to Tuberculosis disease. However, they can also trigger the spread of pathogens, inflammatory reactions, and tissue damage (Levalett, et al., 2020).

Furthermore, to address the limitation of cross-sectional studies, conducting longitudinal studies that capture the temporal sequence of measuring the relationship between exogenous on endogenous in cases of pulmonary tuberculosis seems to be appropriate. In health sciences, longitudinal studies are critical for enhancing the understanding of the development and persistence of disease. These studies can address fundamental questions by assessing within-individual changes in the response variable through repeated measurements of the same individuals over time (Fitzmaurice, et al., 2004). (Verbekke & Molenberghs, 2000) introduced the Generalized Linear Mixed Model (GLMM) analysis method for longitudinal data. The GLMM model calculates two effects: the initial one being a fixed effect, which analyzes the influence of treatment and concomitant variables. The second effect is random, accounting for individual subject differences (subject-specific). Finally, longitudinal methods and analysis can contribute to the monitoring and evaluation of patients with pulmonary tuberculosis.

2. Literature Review

2.1. *Longitudinal Data*

Longitudinal data is a type of data that incorporates both cross-sectional and time series components. It involves collecting observations from N independent subjects, with each subject being observed multiple times over T time periods. In contrast, cross-sectional studies collect only a single data point from each subject. Therefore, the primary distinction between longitudinal and cross-sectional data is that longitudinal data tends to be correlated within a subject and independent across different subjects, whereas cross-sectional data is typically independent.

In health sciences, longitudinal studies play an important role in enhancing the understanding of the development, and persistence of disease, and can address fundamental questions concerning the assessment of within-individual changes in the response variable by obtaining measurements of the same individuals repeatedly over time. The general structure of longitudinal data used in this study is presented in Table 1.

Table 1. General Structure of The Longitudinal Data

ID (i)	Time (t)	Endogenous variable(s)		Exogenous variable(s)
		Y_{1it}	Y_{2it}	X_{jit}
1	0	y_{110}	y_{210}	x_{j10}
	1	y_{111}	y_{211}	x_{j11}
	⋮	⋮	⋮	⋮
	12	y_{1112}	y_{2112}	x_{j112}
2	0	y_{120}	y_{220}	x_{j20}
	1	y_{121}	y_{221}	x_{j21}
	⋮	⋮	⋮	⋮
	12	y_{1212}	y_{2212}	x_{j212}
⋮	⋮	⋮	⋮	⋮

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N	0	y_{1N0}	y_{1N0}	x_{jN0}
	1	y_{1N1}	y_{2101}	x_{jN1}
	⋮	⋮	⋮	⋮
	12	y_{1N12}	y_{2N12}	x_{jN12}

2.2. *Path Analysis*

First developed by Sewall Wright (1918), path analysis is a statistical method for decomposing a total correlation between two variables into one direct effect and one or more indirect effects (Wooldredge, 2021). These relationships, also known as paths, can be distinguished as direct or indirect associations. A direct relationship occurs when one variable, such as reading news, is found to be associated with another variable such as learning. An indirect relationship occurs when a variable is connected to another variable through a third variable, which is directly associated with the outcome variable (Valenzuela & Bachmann, 2017). Path analysis enables the examination of numerous direct and indirect relationships. In comparison to typical regression analysis, path analysis is a more complex technique. To facilitate interpretation, the relationships found with a path analysis are usually presented in the form of a path diagram, with boxes representing variables and arrows representing paths of relationships. The simple path diagram is presented in Figure 1.

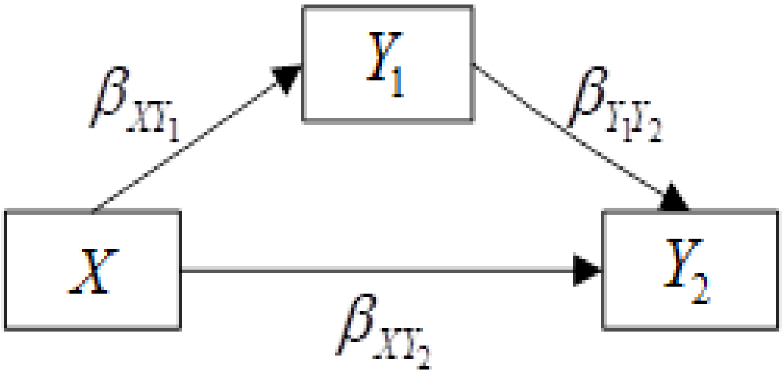

Figure 1: Simple Path Diagram

2.3. *Generalized Linear Mixed Effect Model (GLMM)*

The Generalized Linear Mixed Model (GLMM) derived from a two-stage analysis of the longitudinal data is presented below (Verbekke).

$$\underset{\sim}{Y}_{it} = \underset{\sim}{X}\underset{\sim}{\beta} + \underset{\sim}{Z}\underset{\sim}{\alpha} + \underset{\sim}{\varepsilon}$$

Description:

Y_{it}: Response variable matrix for subject i
$\boldsymbol{\beta}$: Fixed effect matrix
$\boldsymbol{\alpha}$: Random effect matrix $\alpha \sim N(0, D)$
$\boldsymbol{\varepsilon}$: residual component matrix $\varepsilon \sim N\left(0, \Sigma_i\right)$
D: General covariance matrix
$\boldsymbol{\Sigma_i}$: A covariance matrix that depends on i only in the T dimension

3. Research Method and Materials

This study was carried out using longitudinal path analysis with GLMM approach to investigate factors associated with monocyte and SuPAR levels in patients with pulmonary tuberculosis and determine the most significant factor between observation time, body mass index, and erythrocyte sedimentation rate on monocyte and suPAR levels. The data was

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analyzed using R Studio. Figure 2 illustrates the relationship between exogenous on endogenous variables.

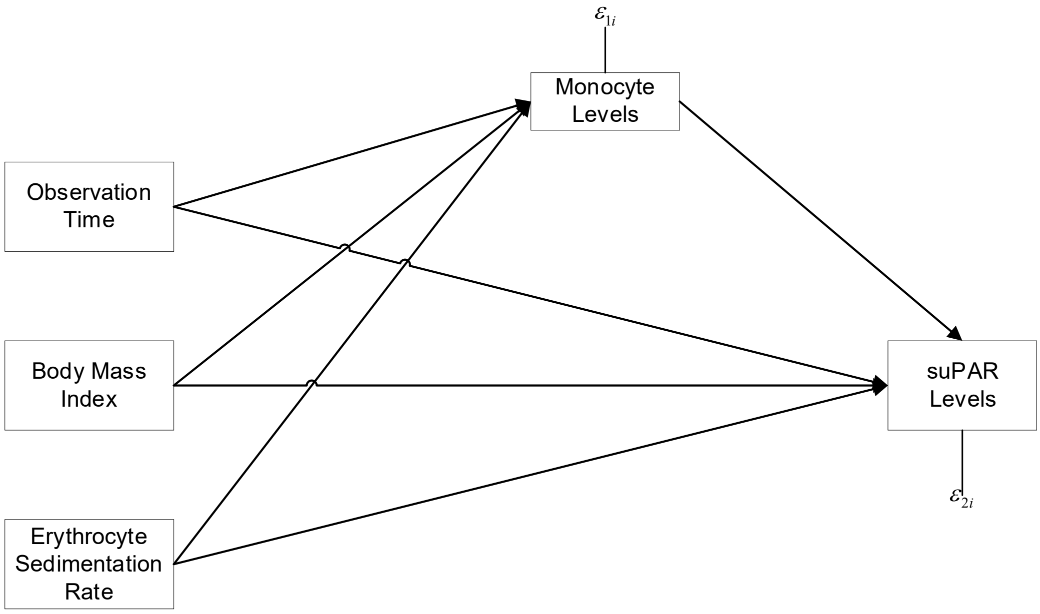

Figure 2: Path Diagram Used

The data in this study was collected over 13 periods. The patients were evaluated every 2 weeks during the 6-month treatments over 13 periods (weeks 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24). This longitudinal study involved 60 patients with pulmonary tuberculosis, for individuals who met the inclusion-exclusion criteria as follows:

1) The data is complete and balanced, indicating that patients were routinely monitored throughout the 13 observation periods
2) Only patients with new cases of pulmonary tuberculosis, not relapse cases, were included in this study
3) The patient is following anti-tuberculosis drug therapy
4) Patients aged between 25 – 50 years.

4. Results and Discussion

4.1. *Descriptive Statistics*

This study presents the development of path analysis using the Generalized Linear Mixed Model (GLMM) approach, which involves fixed and random effects on exogenous variables. The estimation is carried out using Weighted Least Squares (WLS) method. The data was collected for 6 months of treatment and employed observation time, body mass index, and erythrocyte sedimentation rate as exogenous variables, while monocyte levels and suPAR levels were used as endogenous variables. Table 2 provides the descriptive statistics of the variables.

Table 2. Descriptive Statistics

Variable	Min	Max	Average
BMI	15.57 kg/m²	28.31 kg/m²	22.26 kg/m²
ESR	3.00 mm/h	124.00 mm/h	33.55 mm/h
Monocyte Levels	0.34 103/μL	1.17 103/μL	0.75 103/μL
SuPAR Levels	0.33 μL	1.42 μL	0.78 μL

Table 2 presents a summary of the general characteristics of each exogenous and endogenous variable utilized in the study. The body mass index (BMI) average was 22.26 kg/m², which is generally considered to be within the normal range. In accordance with the World Health

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Organization (WHO, 2023), the body mass index for adults is defined as ranging from 18.5 to 24.9 kg/m². Moreover, the erythrocyte sedimentation rate yielded an average of 33.50 mm/h, which suggests an anomaly in the patient's sedimentation rate. Tishkowski and Zubair (2025) posited that the normal erythrocyte sedimentation rate in individuals under 50 years of age ranges from 15 to 20 mm/h, while in individuals over 50 years of age, the range is 20 to 30 mm/h. The elevated erythrocyte sedimentation rate observed in patients is indicative of inflammatory processes associated with the disease (Taye, 2020). Moreover, the monocyte level variable yielded an average of 0.75 $10^3/\mu L$, indicating that patients generally exhibit monocyte levels within the normal range. As stated by Mangaongkar et al. (2021), the normal range for monocyte levels is 0.2–0.8 $10^3/\mu L$. Moreover, the suPAR level variable yielded an average of 0.78 μL, which serves as a preliminary reference point for monitoring suPAR levels in patients throughout the treatment phase.

4.2. *Longitudinal Path Analysis with GLMM*

The generalized linear mixed model (GLMM) approach with three covariance structures was used, including compound symmetry, first-order autoregressive (AR(1)), and unstructured and compared the results with ordinary least square (OLS) result. Table 3 presents the hypothesis testing of the direct effect using OLS estimation compared to the other methods (compound symmetry, first-order autoregessive, and unstructured).

Table 3. Hypothesis Testing of The Direct Effect

Relationship	Estimation Method							
	OLS		CS		AR(1)		US	
	Path coeff	p-value	Path coeff	p-value	Path coeff	p-value	Path coeff	p-value
Time → Monocyte	-0.012	0.312	0.011	0.006***	-0.003	0.396	-0.095	<0.001***
BMI → Monocyte	0.062	0.138	0.024	0.019***	0.070	<0.001***	-0.052	<0.001***
ESR → Monocyte	-0.004	0.360	0.002	0.202	0.006	0.004***	0.034	<0.001***
Time → suPAR	0.001	0.396	0.011	0.009***	-0.005	0.152	-0.005	0.062**
BMI → suPAR	0.041	0.253	0.021	0.046***	0.028	0.003***	-0.026	0.001***
ESR → suPAR	-0.006	0.316	0.002	0.222	-0.007	<0.001***	0.013	<0.001***
Monocyte → suPAR	-0.115	0.304	0.001	0.397	-0.047	0.142	0.121	<0.001***

Note: *** and ** indicates significant at 1% and 5% level of significance based on t-statistics

As indicated in Table 3, the WLS model (CS, AR(1), and US) is generally more effective than the OLS model for depicting the relationship among variables. The direct effect of GLMM model tested using the OLS method yielded an insignificant relationship between the variables. This is evidenced by the p-values for each relationship, which are >0.05. This indicates that the variables of time, body mass index, and erythrocyte sedimentation rate do not significantly affect the development of monocyte and suPAR levels in patients with pulmonary tuberculosis. Moreover, the result of WLS models with different covarian structures (CS, AR(1), and US) will manifest different results. In the compound symmetry model, the variables that exert a significant influence on monocyte levels and suPAR levels are observation time and body mass index. Moreover, in the first-order autoregressive model, the variables that exert a notable influence on monocyte levels and suPAR levels are the variables of body mass index and erythrocyte sedimentation rate. In contrast, the unstructured model indicates that all variables exert a significant influence on monocyte levels and suPAR levels.

After obtaining the path model with the GLMM approach based on each estimation method – namely the OLS method, WLS with compound symmetry covariance model, first-order autoregressive (AR(1)), and unstructured – the most suitable model is selected based on the largest total determination coefficient value with the smallest AIC value. A comparison of the coefficient of total determination and the AIC value of the model for each estimation method is provided in Table 4.

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Table 4: Model Selection

Estimation Method	R^2	AIC
OLS	0.880	0.071
CS	0.884	0.094
AR(1)	0.913	0.061
US	0.977	0.052

As demonstrated in Table 4, the most suitable model to elucidate the impact of observation time, body mass index, and erythrocyte sedimentation rate on monocyte and suPAR levels in patients with pulmonary tuberculosis is the unstructured model. This model demonstrates the smallest AIC value is 0.052 with a coefficient of determination of 0.977, signifying that the model can elucidate the phenomenon by 97%, while the residual 13% is attributable to factors external to the model. The path diagram of the selected model (unstructured) is presented in Figure 3.

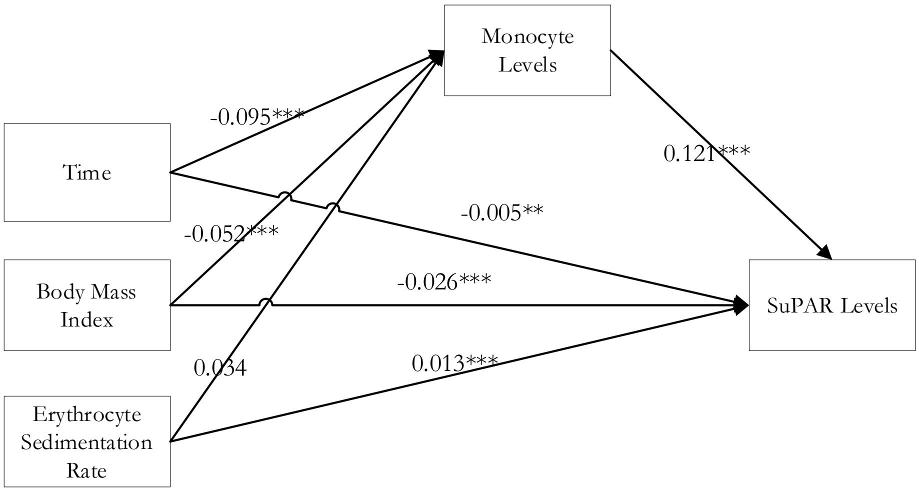

Figure 3: Path Diagram of The Unstructured Model

The indirect effects of the selected model (unstructured) were calculated by multiplying the coefficients of the direct effects of each variable. In contrast, total effects represent the sum of both direct and indirect effects, determined by adding the coefficients of these effects. The results of the tests for indirect and total effects are presented in Table 5 and Table 6, respectively.

Table 5: The Indirect Effect Results of The Unstructured Model

Path Relationship	Path Coeff	p-value
Time (X_1) → Monocyte Levels (Y_1) → suPAR Levels (Y_2)	0,011	<0,001***
BMI (X_2) → Monocyte Levels (Y_1) → suPAR Levels (Y_2)	-0,006	<0,001***
ESR (X_3) → Monocyte Levels (Y_1) → suPAR Levels (Y_2)	0,004	<0,001***

Note: *** indicates significant at 1% level of significance based on t-statistics

The indirect effect demonstrate that the impact of observation time on suPAR levels through monocyte levels indicates that regular OAT administration during the treatment period and a decline in monocyte levels will result in a reduction in suPAR levels by 0.011μL. Additionally, the indirect effect of body mass index on suPAR levels through monocyte levels demonstrates that a decrease in the patient's body mass index and an increase in monocyte levels will result in an increase in suPAR levels by 0.006μL. Finally, the indirect effect of erythrocyte sedimentation rate on suPAR levels through monocyte levels demonstrates that

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an increase in erythrocyte sediment rate, conco'itant with an increase in monocyte levels, will result in an increase in suPAR levels'in patients with pulmonary tuberculosis by 0.004μL.

Table 6: The Total Effect Results of The Unstructured Model

Path Relationship	Path Coefficient
Time (X_1) → suPAR Levels (Y_2)	0.006
BMI (X_2) → suPAR Levels (Y_2)	-0.033***
ESR (X_3) → suPAR Levels (Y_2)	-0.009***

Note: *** indicates significant at 1% level of significance based on t-statistics

According to Table 6, body mass index and erythrocyte sedimentation rate exert a significant combined effect on suPAR levels in patients with tuberculosis, with the erythrocyte sedimentation rate variable exerting the most substantial influence, as indicated by its coefficient of -0.009. This suggests that both body mass index and erythrocyte sedimentation rate should be considered in patients with pulmonary tuberculosis, as they have the potential to reduce suPAR levels.

4.3. *Factors influencing Monocyte and SuPAR Levels in Pulmonary Tuberculosis Patients*

The present study employs longitudinal path analysis to elucidate the progression of Pulmonary Tuberculosis disease in relation to observation time, body mass index, and erythrocyte sedimentation rate on monocyte levels and suPAR levels in patients. Monocyte levels and suPAR levels are biomarkers that are currently employed in monitoring and evaluating Pulmonary Tuberculosis disease. A decrease in monocyte levels and suPAR levels in patients is indicative of a positive progression of the disease, and vice versa (Rasmussen et al., 2021).

The findings of this study, based on the most suitable model – the US model – indicate that monocyte levels in patients are significantly influenced by observation time. In patients who routinely carry out controls and follow OAT (Anti-Tuberculosis Drug) therapy, monocyte levels will decrease in each observation period by 0.095 x 103/μL. Conversely, suPAR levels in patients undergoing OAT therapy exhibited a decline of 0.005 mL with each observation period, thereby underscoring the potential benefits of OAT in patients with pulmonary tuberculosis, including the enhancement of recovery and the reduction of the risk of tuberculosis.

Furthermore, body mass index is also one of the factors that can significantly affect monocyte levels and suPAR levels in patients, where decreasing the patient's body mass index by 1 unit will increase the chance of increasing monocyte levels by 0.052 x 103/μL. In a study by Nabilah (2020), it was observed that in patients with severe tuberculosis, a low body mass index was associated with a decrease in CD4+ and CD8+ levels in monocytes, suggesting a suppression of cellular immunity. This indicates an increase in monocyte levels within the body. Additionally, a decrease in the patient's body mass index by 1 unit was found to result in an increase in suPAR levels by 0.026 μL. This finding aligns with the research conducted by Choi et al. (2021), which demonstrated that body mass index exhibits an inverse correlation with the development of tuberculosis disease, suggesting that patients with overweight and obesity face a reduced risk of contracting tuberculosis compared to those with a normal body mass index.

The findings of the study demonstrate that the erythrocyte sedimentation rate exerts a substantial influence on the progression of monocyte levels and suPAR levels. It is observed that an elevated rate of erythrocyte sedimentation rate in patients leads to a concomitant increase in monocyte levels and suPAR levels by 0.034 x 103 / μL and 0.013 μL, respectively. This finding aligns with the research conducted by Levalett et al. (2020), which suggests that elevated monocyte levels in patients are indicative of an underlying inflammatory condition.

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Furthermore, monocyte levels have been demonstrated to exert a significant influence on the development of suPAR levels in patients during the treatment period. It has been observed that an increase in monocyte levels in the patient's body is concomitant with an increase in suPAR levels. This finding lends further support to the notion that suPAR levels serve as a robust biomarker in the monitoring and evaluation of pulmonary tuberculosis patients (Eugen-Olsen et al., 2002). Consequently, it is imperative to closely monitor patients during the treatment period, taking into account various parameters such as OAT administration, body mass index, erythrocyte sedimentation rate, and monocyte levels. This comprehensive approach is essential for the successful treatment of pulmonary tuberculosis.

5. Conclusion

This study demonstrates that longitudinal path analysis employing Generalized Linear Mixed Model (GLMM) is an effective approach for identifying determinants of monocyte and soluble urokinase plasminogen activator receptor (suPAR) concentrations in patients with pulmonary tuberculosis. Among the covariance structures assessed, the unstructured model provided the best fit, yielding the highest coefficient of determination ($R^2 = 0.977$) and the lowest AIC (AIC = 0.052).

The results indicate that observation time, body mass index (BMI), and erythrocyte sedimentation rate (ESR) are significant predictors of both monocyte and suPAR levels. Specifically, the standard anti-tuberculosis therapy (OAT) was associated eith a progressive decline in monocyte and suPAR concentrations across 24-wee treatment period, consistent with favorable clinical response. In contrast, low BMI and elevated ESR were positively associated with higher inflammatory marker levels, underscoring their importance as indicators of disease severity.

Additionally, a significant positive association between monocyte and suPAR levels was observed, supporting the utility of suPAR as a ribust biomarker for monitoring treatment response. These findings advocate for an integrated clinical monitoring strategy in pulmonary tuberculosis that couples OAT with routine assessment of BMI and ESR measurements to optimize patient management and evaluate therapeutic effectiveness.

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