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Correlation Between APTT and Anti-Tuberculosis Therapy Stages at Cempaka Health Center

***Anny Thuraidah, Neni Oktiyani, Nurlailah, Yayuk kustiningsih, Intan Meilinda**

Medical Laboratory Technology Poltekkes Kemenkes Banjarmasin
Mistar Cokrokusumo Street 4A Banjarbaru Indonesia.
*Email: thuraidahapt@gmail.com

Abstract: Tuberculosis (TB) is an infectious disease that is still a global health problem. TB treatment with anti-tuberculosis drugs can affect the hemostasis system, one of which is through changes in activated partial thromboplastin time (APTT). However, the relationship between APTT values and the phase of TB therapy is still not fully understood. This study aims to analyze the relationship between APTT values and the phase of TB therapy and patient characteristics, including age and gender. This study used a cross-sectional design with an accidental sampling technique involving 30 pulmonary TB patients undergoing anti-tuberculosis drug therapy at the Cempaka Health Center. APTT examination was performed using an automatic method with a normal value of 25–43 seconds. Statistical analysis used the Pearson correlation test for normally distributed data and the Spearman test for non-normally distributed data. The results showed that 63% of patients had normal APTT values (26.0–41.2 seconds; average 32.7 seconds), while 37% of patients experienced prolonged APTT (44.8–49.7 seconds; average 47.6 seconds). There was no significant relationship between APTT values and the TB therapy phase (p=0.165), age (p=0.249), and gender (p=0.630). There was no significant relationship between APTT values and TB therapy phase, age, and gender. However, these results indicate that some patients experience changes in the hemostasis system during TB therapy. This study suggests that monitoring APTT in TB patients undergoing anti-tuberculosis drug therapy is still needed to anticipate potential coagulation disorders. Further research with a larger sample size and control of nutritional factors and patient inflammation status is recommended to obtain a more comprehensive understanding of the effects of TB therapy on the hemostasis system.
Keywords: Activated partial thromboplastin time; pulmonary tuberculosis; tuberculosis drugs; tuberculosis treatment phase.

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis. Despite innovations in diagnostic methods and therapeutic strategies, this disease remains a major challenge in global health[1]. The World Health Organization (WHO) estimates that TB will affect 10.6 million people worldwide in 2022, equivalent to 133 cases per 100,000 population. Most major TB cases in that year occurred in Southeast Asia (46%), Africa (23%), and the Western Pacific (18%)[2].

Corresponding Author: Anny Thuraidah
Medical Laboratory Technology Poltekkes Kemenkes Banjarmasin.
Mistar Cokrokusumo Street 4A Banjarbaru Indonesia..
Email: thuraidahapt@gmail.com

According to data from the South Kalimantan Provincial Health Office, Banjarbaru City ranked 5th out of 13 districts in South Kalimantan with 463 TB cases in 2022[3]. From January to November 2023, there were 862 TB cases. The Cempaka Inpatient Health Center had the highest number of TB cases, 117.

Mycobacterium tuberculosis complex infection causes chronic granulomatous inflammation in TB patients[4]. This inflammation activates the hemostasis system, which then affects the balance of vascular homeostasis[5]. The hemostasis system functions to maintain the integrity of blood circulation. However, disorders of this system can increase the risk of morbidity and mortality. Uncontrolled inflammatory processes can cause hemostasis disorders that contribute to the progression and clinical course of TB. This occurs in the systemic inflammatory response to chronic infections, including tuberculosis[6].

Researchers have documented hematological disorders associated with mycobacterial infections for almost a century. Bacterial infections, including TB, activate the coagulation and fibrinolysis pathways as an immunopathological response. This activation plays a role in the pathogenesis of TB by forming granulomas and triggering thrombotic or bleeding complications that can save the patient's condition[7].

From the results of a comparative study of APTT values in tuberculosis patients with healthy people, the APTT value in healthy people was 34.63 seconds. In comparison, in tuberculosis patients, the APTT value in the intensive phase was 46 seconds, and in the advanced phase was 45.74 seconds. 6 Likewise, in other studies, tuberculosis treatment affects hemostasis so that APTT is prolonged compared to controls; for controls, it is 34 seconds, while in tuberculosis patients, it is 46 seconds[8]. There have been studies comparing APTT values in TB patients with healthy people[7,8], but there are still limited studies that identify the relationship between the anti-tuberculosis drugs treatment phase (intensive or advanced) with APTT values and explore the relationship with the age and gender of patients, so this study aims to determine the relationship between APTT values with the TB treatment phase, age, and gender of patients.

MATERIALS AND METHODS

Research Methods

This study is an analytical survey with a cross-sectional design. The study population consisted of pulmonary tuberculosis patients at the Cempaka Health Center who were undergoing treatment using anti-tuberculosis drugs. The study sample was taken using the accidental sampling technique, with a total of 30 respondents. This technique is used because it allows sampling from patients who come to the Health Center directly during the study period, making it more practical and in accordance with the limited time and resources available. The independent variables in this study include the duration of anti-tuberculosis drug treatment and the characteristics of the respondents (age and gender). In contrast, the dependent variable is the APTT value.

Materials and Tools

This study uses several materials and tools for laboratory examinations. The materials used include blue cap tubes, vacutainer needles, and holders, 70% alcohol swabs, dry cotton, wound dressings, tourniquets, masks, and sample labels. The tools used include Coatron M2, centrifuge, micropipette, yellow/blue pipette tips, timer, cuvette, plastic test tubes, and test tube racks. The reagents used in the examination include

citrate plasma, 0.025 M calcium chloride ($CaCl_2$) solution, and partial thromboplastin substrate containing an activator (APTT reagent).

Research Procedure

Respondents who came to the Cempaka Health Center were asked to listen to an explanation before the study was conducted. Respondents who were willing to participate signed an informed consent form and filled out a questionnaire. Blood was taken using a blue-capped vacuum tube containing 1.8 ml of 3.2% Sodium Citrate until the required blood volume was met. After that, the tube was inverted so that the blood sample was mixed homogeneously. The sample was then centrifuged for 30 minutes at 3000 rpm; then, the plasma was separated and put into a test tube. A total of 50 µL of plasma was taken and put into a coagulometer cuvette, and then 50 µL of APTT reagent (BioSystem COAX) was added and mixed until homogeneous. The mixture was incubated at 37°C for 3 minutes, then 50 µL of $CaCl_2$ was added, and the measurement was started by pressing the GO button on the device.

This study has obtained ethical approval from the Ethics Commission of the Poltekkes Kemenkes Banjarmasin, Indonesia, with the number 844/KEPK-PKB/2024. The data obtained were tabulated and presented in graphical form. The hypothesis was analyzed using the Pearson correlation test for normally distributed data, while for non-normally distributed data, the Spearman correlation test was used. Statistical analysis was carried out with the help of computer software to ensure more accurate and efficient calculations.

RESULTS AND DISCUSSION

Thirty respondents who had been diagnosed with pulmonary tuberculosis and were undergoing therapy using anti-tuberculosis drugs underwent an APTT examination using an automatic method. Normal APTT values ranged from 25 to 43 seconds, while values more than 43 seconds were categorized as abnormal. In addition to undergoing the APTT examination, respondents were also asked to complete personal characteristic data.

Respondent Characteristics

The respondents in this study consisted of men and women with a minimum age range of 17 years. The duration of anti-tuberculosis drug treatment varied between 1 and 6 months (Table 1).

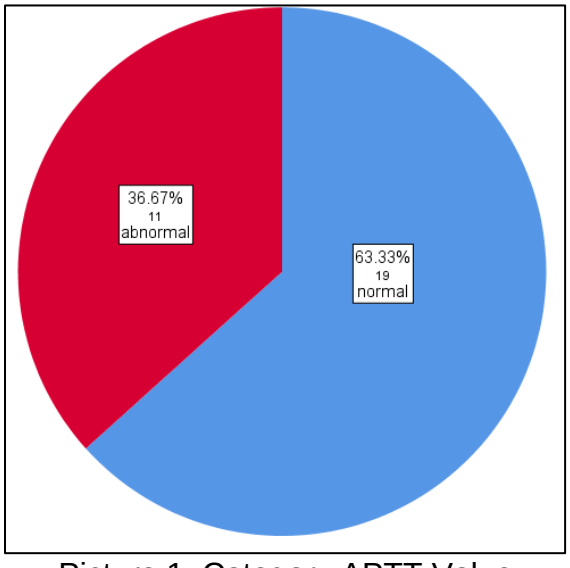
Based on the table above, the majority of respondents are in the category of 1–2 months of anti-tuberculosis drugs consumption (intensive phase) of 57%, the age group of 17–55 years of 80%, and male gender of 60%. Other characteristics show that 57% of respondents consume four types of anti-tuberculosis drugs, 100% are compliant in consuming anti-tuberculosis drugs, 90% have no comorbidities, and 63% have a habit of consuming foods or drinks containing vitamin K.

Results of Activated Partial Thromboplastine Time (APTT) Value Examination

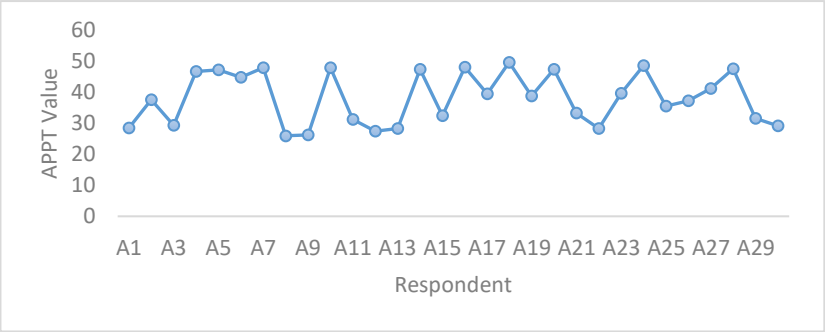
The results of the examination showed that 63% of respondents or 19 people had normal APTT values in the range of 26.0–41.2 seconds with an average of 32.7 seconds. Meanwhile, 37% of respondents or 11 people had abnormal APTT values with a range of 44.8–49.7 seconds and an average of 47.6 seconds (Figure1-2).

Table 1. Respondent Characteristics

Variabel	Frequence (N)	Percentage (%)
Treatment Phase		
1-2 (intensif)	17	57
3-6 (continued)	13	43
Age (years)		
17-55	24	80
>55	6	20
Sex		
Male	18	60
Female	12	40
TB drugs consumed		
4 types	17	57
2 types	13	43
TB drug adherence		
Compliant	30	100
Non compliant	0	0
Disease other than TB		
Hypertension	3	10
Non hypertension	27	90
Food/drink containing vit K consumption		
Yes	19	63
No	11	37



Picture 1. Category APTT Value



Picture 2. Graph APTT Value

Cross Table of Questionnaire with APTT Value Category

From Table 2. it is known that the analysis of 30 respondents. As many as 41% of respondents had abnormal APTT values in the intensive phase of TB therapy, while in the continuation phase, the percentage was lower, namely 31%. Respondents aged over 55 years showed a higher level of abnormal APTT, namely 67%, compared to other age groups.

In terms of gender, 28% of men had abnormal APTT values, while in women, this figure was higher, reaching 50%. Respondents who consumed four types of anti-tuberculosis drugs experienced abnormal APTT by 41%, while in those who only consumed two types of anti-tuberculosis drugs, this figure was lower, namely 31%. All respondents in this study were compliant with consuming anti-tuberculosis drugs, and as many as 37% of them had abnormal APTT values. In addition, only 5% of respondents who had a habit of consuming food and drinks containing vitamin K experienced abnormal APTT. In contrast, all respondents who did not have this habit experienced abnormal APTT.

Results of Statistical Analysis

The results of the Spearman Correlation test between APTT Values and Therapy Phase, Age, and Gender obtained p values above 0.05. So, it can be interpreted that there is no significant relationship between the APTT value and the therapeutic phase of the respondent's age and gender (Table 3).

The results of this study indicate that the majority of TB sufferers are male, which is 60% (Table 1). This is in line with the research of Sunarmi et al. (2022), which found that the prevalence of TB is higher in men, possibly due to smoking habits, which can reduce the immune system. Decreased immunity in the respiratory tract due to exposure to cigarette smoke toxins can damage mucocilia and inhibit antigen responses, thereby increasing the risk of pulmonary TB. In addition, the routine of men who are more often outside the home is also a risk factor for TB transmission[9].

In terms of age, this study also shows that most TB sufferers are in the productive age group of 17-55 years, as much as 80% (Table 1). These results are supported by research by Sutrisna et al. (2022), which states that TB occurs more often at the age of 15-58 years, possibly due to a busy lifestyle, lack of rest time, and a decreased immune system. These factors can increase the risk of infection because the body does not have enough time to regenerate cells and repair the defense system against pathogens[10].

Table 2. Frequency Distribution of APTT Values and Characteristic Respondent

Questionnaire	APTT Value Category				
	Normal	%	Abnormal	%	Total
Treatment Phase					
Intensif phase	10	59	7	41	100
Contued phase	9	69	4	31	100
Age (years)					
17- 55	17	73	7	27	100
>55	2	33	4	67	100
Sex					
Male	13	72	5	28	100
Female	6	50	6	50	100
TB drugs consumed					
INH, Rifampisin, Pyrazinamid, Ethambutol	10	59	7	41	100
INH, Rifampisin	9	69	4	31	100
TB drug adherence					
Compliant	19	63	11	37	100
Non compliant	0	0	0	0	0
Disease other than TB					
Hypertension	0	0	3	100	100
Non hypertension	19	70	8	30	100
Food/drink consisting vit K consumption habits					
Yes	19	95	1	5	100
No	0	0	10	100	100

Table 3. Spearman Correlation Results

APTT value with:	p-value	Conclusion
Treatmen phase	0,165	No correlation
Age	0,249	No correlation
Sex	0,630	No correlation

In addition to affecting the immune system, tuberculosis can also affect the blood clotting system through activation of the immune and coagulation systems. A study conducted by Suryakusumah et al. (2021) found that patients with advanced lung lesions had higher APTT levels compared to patients with mild lesions ($p<0.001$)[11]. Excessive immune system activation in TB can trigger the release of inflammatory cytokines such as IL-1, IL-6, and TNF-α, which increase the expression of tissue factor (TF) in endothelial cells, monocytes, and macrophages. This activates the intrinsic and extrinsic blood clotting pathways, which ultimately cause changes in coagulation protein levels

such as fibrinogen and factor VIII[12]. If inflammation persists, the blood clotting system can experience further disorders characterized by disseminated intravascular coagulation (DIC), where clotting factors are consumed excessively, causing prolonged PT and APTT values [7,13].

In this study, there was no significant difference between APTT values in the intensive phase and the continuation phase of TB therapy (p=0.165) (Table 3). Still, APTT results in the intensive phase with abnormal values were higher (41%) compared to the continuation phase (31%) (Table 2), so it can be stated that there is an improvement in the coagulation system after the continuation phase of treatment. A study conducted by Suryakusumah et al. (2021) showed that after the intensive phase of TB therapy, APTT results decreased significantly compared to before treatment, so it can be stated that improvements in the coagulation system occur along with a decrease in the bacterial load due to intensive therapy. Other studies also show that TB patients with positive sputum smears experience increased PT levels associated with more severe lung injury[14]. Excessive inflammation in this condition can trigger activation of the coagulation pathway, which, in some cases, disrupts the balance between coagulation and fibrinolysis.

Anti-TB therapy is known to play a role in improving the hemostasis system. A study conducted by Suryakusumah showed that after the intensive phase of therapy, there was a significant decrease in PT, APTT, fibrinogen, and D-dimer levels[15]. Another study conducted by Kutiyal et al. also found a decrease in PT and fibrinogen levels after TB therapy, although the decrease in APTT levels was not statistically significant. Similar findings were also reported in Akpan's study, which showed that fibrinogen levels decreased significantly after two months of anti-TB therapy. Still, changes in PT and APTT levels were not statistically significant. This decrease in fibrinogen levels occurred due to a decrease in the acute phase response of the liver after treatment[7]. With anti-TB therapy, repair of endothelium damaged by infection can reduce the production of plasminogen activator inhibitors and normalize fibrinolytic activity. This is indicated by a decrease in the accumulation of fibrin degradation products and D-dimer, indicating the recovery of the blood coagulation system after controlled TB infection[16]. In the examination of the Activated Partial Thromboplastin Time (APTT) value, 11 people (37%) obtained abnormal APTT values with an average value of 47.6 seconds, and for the results of normal APTT values, as many as 19 (63%) samples with an average value of 32.7 seconds. For abnormal APTT values of 11 samples in the intensive phase treatment, there were 7 samples (41%), and in the advanced phase, there were 4 samples (31%).

This study has several advantages that contribute to understanding the relationship between tuberculosis (TB) therapy and the hemostasis system. This study used a cross-sectional design, which allows simultaneous analysis of the relationship between variables. This study was conducted at the Cempaka Health Center, which has a high number of TB cases, so the data obtained are more representative. This study also measured Activated Partial Thromboplastin Time (APTT) as an indicator of changes in the blood coagulation system due to TB therapy, which is still rarely studied at the primary care level.

This study has limitations in the relatively small number of samples, namely 30 patients, which can affect the power of statistical analysis. The accidental sampling

technique used can also cause selection bias because it only involved patients who came to the health facility during the study period. Nutritional factors, especially vitamin K intake, were not analyzed in this study, although they have an important role in the blood coagulation system.

The results of this study have implications for clinical practice and further research. Health workers need to monitor the blood coagulation system in TB patients, especially those who experience prolonged APTT because they are at risk of hemostasis disorders. Evaluation of the impact of TB therapy on blood coagulation can be included in the monitoring of TB patients in primary health care. Further studies are recommended to use a larger sample size and longitudinal design and consider additional variables such as nutritional status, vitamin K levels, and inflammatory factors so that the results obtained are more comprehensive.

CONCLUSION

This study shows that APTT values do not have a significant relationship with the phase of TB therapy, age, and gender in pulmonary TB patients at the Cempaka Health Center. The results of this study indicate that some patients experience changes in the hemostasis system but are not strong enough to show a certain pattern based on the variables analyzed. Although the relationship is not significant, health workers need to monitor the blood clotting system in TB patients, especially those who experience prolonged APTT, because they are at risk of hemostasis disorders. Further research with a larger sample size and control for nutritional and inflammatory factors is needed to understand better the effect of TB therapy on the hemostasis system.

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CONFLICT OF INTEREST

The authors declare no conflict of interest and have not received any funds for this study.

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