

## NON-ADHERENCE FACTORS TO TUBERCULOSIS TREATMENT IN PULMONARY TUBERCULOSIS PATIENTS IN SURAKARTA CENTRAL GENERAL HOSPITAL, INDONESIA

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🌐 <https://doi.org/10.31603/pharmacy.v9i2.9109>

### Article info:

Submitted : 13-05-2023

Revised : 03-07-2023

Accepted : 12-07-2023



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### Publisher:

Universitas Muhammadiyah  
Magelang

### ABSTRACT

Tuberculosis is an infectious disease that must be treated in the long term. One of the therapeutic efficacy factors in tuberculosis treatment is medication adherence by patients. Non-compliance to treatment leads to no achievement of treatment goals, increasing the risk of resistance, mortality, and morbidity. This study analyzed association factors that predicted the influence of the pulmonary tuberculosis patient's non-adherence to anti-tuberculosis medicines in Surakarta Central General Hospital, Indonesia. The research was analytical research with a cross-sectional approach. The study samples were 80 respondents. The inclusion criteria were patients diagnosed with pulmonary tuberculosis in Surakarta Central General Hospital, aged >17 years old, and patients who received Anti-Tuberculosis Drugs for at least two months. This study used a questionnaire that has been validated. Data were analyzed by bivariate analysis (chi-square or Fisher) and continued by multivariate logistic analysis. Of 80 respondents, there were 30 respondents (37.5%) were non-adherence to taking Tuberculosis (TB) drugs. The predicted factors that influenced non-adherence in taking anti-tuberculosis drugs were beliefs about the medicine of the harm subscale ( $p = 0.001$ ; OR = 8.167), suffering from drug side effects ( $p = 0.022$ ; OR = 4.222), and beliefs about the medicine of overuse subscale ( $p = 0.038$ ; OR = 3.504). The wrong beliefs of patients and side effects may influence patients' adherence to TB medicines. Counseling and education are needed to improve patients' beliefs and manage medicines' side effects.

**Keywords:** Non-adherence; Pulmonary Tuberculosis; Cross-Sectional; TB drugs

## 1. INTRODUCTION

Pulmonary tuberculosis (TB) is one of the most contagious infectious diseases that are a public health problem worldwide. Pulmonary TB ranks second after HIV infection disease, which causes millions of deaths annually. Pulmonary tuberculosis is caused by *Mycobacterium tuberculosis* which is transmitted by a droplet of sputum from positive TB patients (Ministry of Health of the Republic of Indonesia, 2014). The World Health Organization's 2015 report estimates that the global level is 9.6 million new TB cases. In Indonesia, the number of TB cases is estimated to be 1 million new TB cases yearly (399 per 100,000 populations), with 100,000 deaths per year (41 per 100,000 populations). TB in Indonesia ranks third after India and China, with 824 thousand cases and 93 thousand deaths per year, or 11 per hour. In Indonesia, most TB cases are in the productive age group, especially at 45 to 54 years old (Karuniawati et al., 2015, 2019; Karuniawati, Sudjono et al., 2017; Ministry of Health of the Republic of Indonesia, 2023).

TB treatment requires several drugs for a long-term minimum of six months. TB patients must be treated, finish the medicine, and take TB drugs exactly as prescribed or comply with their TB drugs (CDC, 2016). Compliance is consuming anti-tuberculosis medicine prescribed by a

doctor at the right time, frequency, and dose. Compliance is very important. Treatment will be effective if the patient complies with drug use rules (WHO, 2003).

If patients stop taking TB drugs too soon, they can become sick again; if they do not take the drugs correctly, the TB bacteria still alive may become resistant to TB drugs. In addition, if the treatment is not done regularly and not following the specified time, it will lead to the failure of treatment of patients, thus increasing the risk of illness and death and can lead to resistance. Resistance can be to several drugs simultaneously, called Multi Drugs Resistance (MDR) and Extended Drugs Resistance (XDR). In addition, TB bacteria resistant to TB drugs are harder and more expensive to treat (CDC, 2016). This will complicate eradicating pulmonary tuberculosis in Indonesia and exacerbate the burden on the government (Ministry of Health of the Republic of Indonesia, 2014).

According to the National Agency of Drug and Food Control (BPOM) of the Republic of Indonesia (2006), many factors related to TB treatment adherence include economic factors, patient characteristics, the relationship between health care providers and patients, therapeutic regimens, and health services. In addition, belief is also one of the many influencing adherence factors. However, comprehensive research on factors affecting non-adherence in tuberculosis patients has never been done. Therefore, it is necessary to research analysis factors that possibly affect non-adherence to tuberculosis treatment in pulmonary tuberculosis patients in Surakarta. The Surakarta Central General Hospital, previously known as the Surakarta Community Pulmonary Health Center, is one of the referral hospitals for respiratory and other diseases in Surakarta and Central Java. Through this research, a percentage of non-adherence patients and predict factors that may influence non-compliance in tuberculosis treatment can be obtained. Data also can be used as a recommendation for health workers or policymakers to improve patient adherence. Furthermore, the morbidity and death caused by tuberculosis could be decreased, and the incidence of drug resistance could be prevented.

## **2. METHODS**

### **2.1. Study Setting**

This study was conducted at the Surakarta Central General Hospital, Central Java, Indonesia referral hospital.

### **2.2. Research Design and Sampling**

This study was analytical research, and the data were collected cross-sectional approach. This study aimed to assess the degree of non-compliance and the factors associated with non-adherence in tuberculosis patients taking TB drugs. The population of this research was outpatients of pulmonary TB. Sampling was non-probability sampling with purposive sampling that met inclusion criteria. Inclusion criteria were patients diagnosed with pulmonary tuberculosis with age > 17 years old, patients with pulmonary tuberculosis who have received TB drug for at least two months, and willing to be a respondent and follow the research procedure from January to June 2018. Patients suffering from two or more bacterial infectious diseases were excluded. Independent variables were patients' demographics, type of medicine, income, level of knowledge, belief in medication, side effects, comorbidity, medicine, transportation availability, distance from home to hospital, and family and healthcare support. The dependent variable was adherence to TB medicine.

### **2.3. Ethical Consideration**

Approval of the study was obtained from The Health Research Ethics Committee, Faculty of Medicine of Universitas Muhammadiyah Surakarta, number 732/C.1/KEPK-FKUMS/IX/2017 before the commencement of the study. Informed consent was done, and participants' confidentiality was maintained during and after collecting data.

#### 2.4. Tool

There were five questionnaires for the test of adherence, knowledge, belief, family support, and healthcare support questionnaire, which were modified from the previous questionnaires. Adherence, knowledge, belief, family support, and healthcare support questionnaire were reviewed qualitatively by panel experts consisting of two academics with clinical pharmacy backgrounds, a community pharmacist, and a physician in infectious disease. The researchers revised the questionnaires based on the experts' suggestions. Believe questionnaire used Believe About Medicine Questionnaire (BMQ) (Horne et al., 1999). Patients are categorized as adhering if the score is  $\geq$  eight and non-adherent if it is  $<$  8. A score  $\geq$  7 is categorized as high knowledge and vice versa. Patients with a score  $\geq$  4 are categorized as having good support from family and health care and vice versa. Assessment of drug side effects based on patient information stating that the patient feels drug side effects, not assessed with special tools such as the Naranjo algorithm.

All questionnaires were pretested on thirty respondents as a pilot study to clarify ambiguities and test for validation and reliability. The validation and reliability of the questionnaires were then analyzed statistically with Pearson Correlation and Cronbach Alfa, respectively. The questionnaires were valid because the r-count (ranging from 0.365-0.955) was more than the r-table (0.301) or p-value  $<$ 0.05, and the questionnaires were reliable because the Cronbach Alfa (ranging from 0.719-0.779) were more than 0.6 (Riwidikdo, 2007).

#### 2.5. Data Collection

Primary data resulted from a patient's interview, and secondary data came from patients' medical records. During the research, 80 participants met the inclusion and exclusion criteria. After completing the informed consent sheet, patients were interviewed by the researchers about demographic data patients, adherence questionnaire, knowledge about their disease and their treatment, beliefs in their medicine, the experience of side effects, family support questionnaire, and healthcare support questionnaire.

#### 2.6. Data Analysis

Normality data was analyzed by the Kolmogorov-Smirnoff test. If the p-value  $>$ 0.05, the data was normal distribution and vice versa. Because this study's data was not normally distributed, non-parametric analysis was approached. Chi-square or Fisher test to analyze the association of one independent variable and one dependent variable. Variables with a P value  $<$  0.25 were analyzed by multivariate (logistic regression) (Dahlan, 2017).

### 3. RESULTS AND DISCUSSION

The population of TB patients in Surakarta Central General Hospital from January to June 2018 was 288, and 80 tuberculosis patients met the inclusion criteria. The baseline characteristic of tuberculosis patients can be seen in [Table 1](#).

The number of male patients was more than women. Male respondents were 52.5% and 47.5% female. In (Karuniawati, Sudjono, et al., 2017), man patient was 59%, and women were 41%. Men are more susceptible to pulmonary TB disease. This is due to their heavy workload, lack of rest, and unhealthy lifestyle of smoking and drinking alcohol. Characteristics of patients by age, for the age category 17-55 years, 63 respondents (79.5%), while age  $>$  55 years and 17 respondents 21.5%. According to the National Guidelines for Tuberculosis Control, about 79.5% of TB patients in Indonesia are in the most economically productive age group (15-55 years). This may result in the household's annual income since an adult TB patient is predicted to lose an average of 3 to 4 months of working time and a loss of 20-30% of annual household income (Ministry of Health of the Republic of Indonesia, 2014).

**Table 1.** Baseline characteristics of tuberculosis patients (N=80)

No.	Patient profile	Number	Percentage (%)
1.	Gender		
	Man	42	52.5
	Woman	38	47.5
2.	Age (year old)		
	17-25	16	20
	26-35	18	22.5
	36-45	14	17.5
	46-55	15	18.75
	56-65	14	17.5
	> 65	3	3.75
3.	Level of education		
	No education	6	7.5
	Primary school	15	18.75
	Junior high school	18	22.5
	Senior high school	33	41.25
	Diploma	8	10
4.	Occupation		
	Self-employment	38	47.5
	housewife	14	17.5
	Employee	8	10
	Labor	8	10
	Farmer	5	6.25
	student	4	5
	Unemployment	2	2.5

Based on [Table 1](#), it is known that respondents who have self-employment jobs have a high incidence of tuberculosis. From interviews with respondents, most work in the same place where TB bacteria is likely to be transmitted by contact or droplet infection with fellow workers. If workers work in an environment exposed to a lot of dust will affect the occurrence of interference in the respiratory tract. Chronic exposure to air pollution can increase morbidity, especially respiratory disease symptoms and pulmonary tuberculosis (Lin et al., 2019).

Of 80 respondents who met the inclusion criteria, 50 respondents (62.5%) were obedient, while 30 respondents (37.5%) did not adhere to tuberculosis drugs. Based on the patient's interview, patients obey because of some reason. Firstly, patients believe they will cure if they take tuberculosis drugs regularly; they get family support for completing treatment, and they get complete information about their disease and treatment from professional health care. On the other hand, non-adherence of pulmonary tuberculosis patients is related to several problems, such as patients sometimes forgetting to take medication, patients did not take medication intentionally, patients reducing the number of drugs and stopping taking the medication without the advice of doctors, forgetting to take drugs when traveling far, and feeling disturbed with their medication.

The biggest reason for non-adherence was as many as 23 (28.75%) patients forgot to take tuberculosis drugs. They forgot to take the tuberculosis drug was because of busy. Therefore, tuberculosis drugs should be taken in the morning before meals. This is not only because of good absorption on an empty stomach but also for the patient not to forget in taking the medicine (Ministry of Health of the Republic of Indonesia, 2014). Furthermore, respondents who had reduced the amount of the drug, as many as four respondents (5%), revealed that they did so because of the difficulty swallowing the drug. This is presumably because tuberculosis tablets are relatively larger than the size tablets in general, so some people find it difficult to swallow. In addition, four respondents (5%) did not complete their medication because they felt better. Feeling better is one reason for patients not adhering to their medication (Karuniawati, Ikawati, et al., 2017). It was the same as WHO (2003) stated that after taking tuberculosis drugs for 2 or 3 months, the symptoms disappear, and patients feel healthy and stop their treatment (WHO, 2003).

### 3.1. Bivariate Analysis

The bivariate analysis in this study was conducted to analyze the relationship between independent and dependent variables, as shown in [Table 2](#).

**Table 2.** Results of the analysis of the relationship of some variables to non-adherence of pulmonary tuberculosis patients in taking tuberculosis drugs

	Non-adherence		Adhere		P	OR	CI 95%	
	Number	%	Number	%			Min	Max
<b>a.</b> Gender								
Man	18	22.5	25	31.25	0.385	1.500	0.600	3.753
Women	12	15	25	31.25				
<b>b.</b> Age								
Non-productive	0	0	4	5	0.146	-	-	-
Productive	30	37	46	57.5				
<b>c.</b> Employment								
Work	25	31.25	37	46.25	0.333	1.757	0.557	5.545
Unemployed	5	6.25	13	16.25				
<b>d.</b> Level of education								
Low	11	13.75	30	37.5	0.043*	0.386	0.152	0.982
High	19	23.75	20	25				
<b>e.</b> Type of medicine								
Anti-TB drug	10	12.5	11	13.75	0.265	1.773	0.644	4.876
FDC	20	25	39	48.75				
<b>f.</b> Insurance								
No	18	22.5	16	20	0.014*	3.188	1.243	8.173
Yes	12	15	34	42.5				
<b>g.</b> Income								
Low	23	28.75	42	52.5	0.416	0.626	0.201	1.946
High	7	8.75	8	10				
<b>h.</b> Level of knowledge								
Low	7	8.75	10	12.5	0.724	1.217	0.408	3.634
High	23	28.75	40	50				
<b>i.</b> Belief <i>Necessity</i>								
Low	16	20	24	30	0.644	1.338	0.500	3.066
High	14	17.5	26	32.5				
<b>j.</b> Belief <i>Concerns</i>								
Low	12	15	25	31.25	0.385	0.667	0.266	1.668
High	18	22.5	25	31.25				
<b>k.</b> Belief <i>Harm</i>								
High	23	28.75	18	22.5	0.000*	5.841	2.097	16.269
Low	7	8.75	32	40				
<b>l.</b> Belief <i>Overuse</i>								
High	14	17.5	9	11.25	0.006*	3.986	1.441	11.025
Low	16	20	41	51.25				
<b>m.</b> Side effect								
Yes	24	30	26	32.5	0.012*	3.692	1.289	10.580
No	6	7.5	24	30				
<b>n.</b> Comorbidity								
Yes	5	6.25	10	12.5	0.712	0.800	0.245	2.614
No	25	31.25	40	50				
<b>o.</b> Medicine availability								
No	0	0	0	0	-	-	-	-
Yes	30	37.5	50	62.5				
<b>p.</b> Distance home to hospital								
Far	20	25	32	40	0.809	1.125	0.433	2.920
Near	10	12.5	18	22.5				
<b>q.</b> Transportation availability								
No	0	0	1	1.25	0.625	-	-	-
Yes	30	37.5	49	61.25				
<b>r.</b> Family support								
No	2	2.5	4	5	0.598	0.821	0.141	4.780
Yes	28	35	46	57.5				
<b>s.</b> Healthcare services								
Low	1	1.25	5	6.25	0.264	0.310	0.034	2.793
High	29	36.25	45	56.25				

FDC=Fixed-Dose Combination

\*Statistically significant

### 3.2. Multivariate Analysis

The multivariate analysis was done by logistic regression test because the dependent variable was categorical. Based on the bivariate analysis in **Table 2**, the variable which has  $p < 0.25$  (level of education, insurance, belief harm, belief overuse, and side effect) were analyzed by multivariate analysis.

**Table 3** revealed three independent variables as predicted factors associated with non-adherence to TB drugs statistically significantly. Those variables were believing harmful ( $p = 0.001$ ; OR = 8.167), drug side effects ( $p = 0.022$ ; OR = 4.222), and believe overuse ( $p = 0.038$ ; OR = 3.504).

**Table 3.** Multivariate analysis results

	Non-adherence		Adhere		P	OR	CI 95	
	Number	%	Number	%			Min	Max
<b>a.</b> Belief <i>Harm</i>								
High	23	28.75	18	22.5	0.001*	8.167	2.510	26.568
Low	7	8.75	32	40				
<b>b.</b> Side effect								
Yes	24	30	26	32.5	0.022*	4.222	1.230	11.450
No	6	7.5	24	30				
<b>c.</b> Belief <i>overuse</i>								
High	14	17.5	9	11.25	0.038*	3.504	1.072	14.492
Low	16	20	41	51.25				
<b>d.</b> Level of education								
Low	11	13.75	30	37.5	0.337	0.557	0.188	1.772
High	19	13.75	20	25				
<b>e.</b> Insurance								
No	18	22.5	16	20	0.188	2.066	0.702	6.078
Yes	12	15	34	42.5				

\*Statistically significant

### 3.3. Factors Association on Non-adherence of Pulmonary TB Patients in Taking TB Drugs

The belief subscale harm represents the patient’s opinion of the dangers of general drug use, consisting of 5 questions such as “Most drugs are addictive” or “All drugs are essentially toxic”. In this research, based on **Table 3**, of 30 patients who did not adhere to medication, 23 (28.75%) believed their medication was dangerous or harmful to them. Generally, a high score of believing harm indicates a patient’s negative perception of the medicines (Alhewiti, 2014; Sjölander et al., 2013). Based on the multivariate test, it was found that there was a significant influence of belief to sub-treatment of harm scale on patient compliance in taking TB drugs in pulmonary tuberculosis patients ( $p = 0.001$ ) with OR 8.167. This proves that patients with pulmonary tuberculosis with a negative perception or belief about the harm of medicines used had a higher odds of being non-adherence of 8.167 times compared with patients with a positive perception or belief about the use of medicines.

According to (Gatti et al., 2009), patients with low adherence indicate concerns about drug addiction. The result of the patients’ interview during this study, some patients said that during the therapy period, they occasionally discontinued treatment and switched to natural healing with herbal medicines. They believed natural herbs were safer than tuberculosis drugs that they accepted from hospitals or doctors. They switched their treatment to herb medicines because some had side effects experiences while taking conventional medicine. Of 80 respondents, 49 (61.25%) experienced side effects, and 31 (38.75%) did not experience side effects—the types of side effects found in **Table 4**.

The most side effect suffered by patients was itchy or rash (38.75%). Those side effects were highly predicted because of isoniazid, rifampicin, and pyrazinamide and could be handled by an antihistamine. Patients should be monitored closely. The second highest side effect was a tingling



/ burning sensation in the legs. These side effects are likely caused by isoniazid and can be treated with vitamin B6 (pyridoxine) 50-75 mg daily. Joint pain caused by using pyrazinamide can be minimized with aspirin, paracetamol, or Non-Steroid Anti-Inflammatory drugs (NSAIDs). Some patients also have flu syndrome (fever, shiver, headache, joint muscle), which is most likely caused by intermittent rifampicin doses, which can be replaced with daily doses of rifampicin. Hearing loss and balance may be caused by the use of streptomycin. These side effects can be managed by stopping streptomycin (Ministry of Health of the Republic of Indonesia, 2014). 26.25% of patients suffered from abdominal pain, nausea, and vomiting. A previous study revealed that around 23% of TB patients suffered from nausea (Fortuna et al., 2022). This study is in line with the previous studies on side effects associated with non-compliance (Zegeye et al., 2019; Zhang, 2022).

**Table 4.** Side effects experienced by TB patients

Side effect	Number	(%) N = 80
Itchy/ rash	31	38.75
Abdominal pain/ nausea/ vomit	21	26.25
Tingling and burning sensation in the feet	17	21.25
Headache/ dizzy	13	16.25
Muscle pain/ joint	13	16.25
Balance disorders	11	13.75
Fever/ Shiver	6	7.5
Vision Impairment	5	6.25
Hearing disorders	3	3.75

Due to an association between suffering side effects and adherence, it is necessary that the medical staff, especially the pharmacist, build a positive perception about the use of drugs to improve patient compliance in taking the drug. In addition, the side effects of drugs should be predicted, known, and handled as soon as health care by medical personnel to avoid discomfort for patients experiencing side effects. The pharmacist’s role for TB patients is to provide the best service, including counseling, so the patient gets the best and correct or appropriate medical information. So that patients know more about their disease and medication, and they can feel comfortable about their medication and improve their quality of life. In addition, the pharmacist must understand the patient’s knowledge of TB and medication and build their knowledge and belief, counsel patients on how to take medication, possible interactions and side effects of TB drugs, and how to handle side effects and drug interactions to achieve therapeutic goals (Ministry of Health Republic of Indonesia 2005). Several studies showed a significant relationship between knowledge and treatment adherence in pulmonary tuberculosis patients (Mekonnen & Azagew, 2018; Prihantana & Wahyuningsih, 2016; Ruru et al., 2018).

An overuse subscale addresses the patient’s consideration of over-treatment, such as a lack of confidence in drugs or over-administration. For example, they believed “Doctors use too many drugs”. A high score of belief overuse indicates a negative perception of the use of drugs prescribed by the physician used during the treatment (Annisaa’ et al., 2015). Based on the multivariate test, it was found that there was a significant association between the treatment belief of the subscale overuse and patient compliance in OAT treatment in pulmonary tuberculosis patients (p = 0.038) with OR 3.504. Patients who felt or believed they were taking too many drugs had higher non-adherence 3.504 times than patients who felt that their drugs were not too many.

According to (Gatti et al., 2009), patients with low adherence feel that doctors prescribe too much medicine for them. They believed if doctors spent more time paying attention to patients, the number of prescription drugs would decrease. To handle this problem, medical health care must build patients’ confidence and belief about the prescribed drugs by the doctors following the therapy guideline. As a result, patient compliance with taking TB drugs will increase. The difference between the subscale of harm and overuse is the harm subscale assesses the patient’s

beliefs about the hazards and the use of drugs in general. In contrast, the overuse scale assesses beliefs about the number of drugs physicians prescribe.

#### 4. CONCLUSION

Of 80 respondents, 50 (62.5%) were obedient, and 30 (37.5%) disobeyed taking TB drugs. The prediction factors associated with non-adherence to TB drugs were beliefs about the medicine of the harm subscale ( $p = 0.001$ ; OR = 8.167), drug side effects ( $p = 0.022$ ; OR = 4.222), and beliefs about the medicine of overuse subscale ( $p = 0.038$ ; OR = 3.504). Therefore, compliance of pulmonary tuberculosis patients in taking TB drugs needs to be improved by health care staff, including pharmacists, in providing drug information about the use and dangers or side effect, how to handle side effects, and the information about drugs prescribed by doctors.

#### 5. ACKNOWLEDGMENT

This study was financially supported by Lembaga Penelitian dan Pengabdian kepada Masyarakat (LPPM) Universitas Muhammadiyah Surakarta. The authors also would like to thank the Rumah Sakit Umum Pusat Surakarta staff and all respondents who participated in this study.

#### 6. CONFLICT OF INTEREST

All authors declare no conflict of interest.

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