

RESEARCH ARTICLE

RISK FACTORS OF ADVERSE EFFECTS IN ACTIVE PULMONARY TUBERCULOSIS PATIENTS WITH CATEGORY 1 TREATMENT

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ABSTRACT

Category 1 treatment of active pulmonary tuberculosis (TB) takes 6-8 months that can expose patients to adverse effects. The severity of adverse effects occur can affects patients adherence that lead to loss to follow-up. The recent study was aimed to analyze risk factors that might have contribution to the occurrence of adverse effects in active pulmonary TB patients received category 1 treatment. A cross sectional study with open questionnaire was conducted to active pulmonary TB patients who undergo treatment follow-up at RS Paru Karang Tembok Surabaya. Gender, ages, diabetes melitus status, body weight, and length of treatment were analyzed as potential risk factors of the number of adverse effects occur through poisson regression. The result derived from 41 patients analyzed showed that gender (OR: 0,842, 95% CI: 0,550-1,287, $p>0,05$), ages (OR: 0,997, 95% CI: 0,986-1,009, $p>0,05$), body weight (OR: 0,992, 95% CI: 0,976-1,010, $p>0,05$), diabetes melitus status (OR: 1,197, 95% CI: 0,773-1,856, $p>0,05$), and length of treatments (OR: 1,007, 95% CI: 0,989-1,025, $p>0,05$) have no significant risk to the number of adverse effects patients suffered from. In the present study, gender, age, body weight, diabetes mellitus status, and the length of TB treatments have being taken have no significant contribution to the number of adverse effects occurred. However, further study with higher sample size to confirm the result need to be conducted.

Keywords: Tuberculosis, Pulmonary tuberculosis, Adverse effect, Category 1, Risk factors.

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INTRODUCTION

Tuberculosis (TB) still remains a global health problem and still becomes one of the top 10 causes of death. The world health organization (WHO) predicted TB as the 7th highest morbidity disease in the world until 2020 (Mathew and Joseph, 2017). In 2018, 10.0 million people worldwide are infected with TB. Also, TB was related to 1.3 million

deaths around the world (WHO,2018). In Indonesia, total all forms of TB cases notified in 2016 were 139 cases per 100.000 inhabitants and the treatment success rate among new smear-positive was 85 percent for the cohort of patients registered in 2015 (WHO, 2017; Health Ministry of Indonesia, 2018). In 2017, the case notification rate increase to 161 cases per 100.000

inhabitants and the treatment success rate also slightly increase at 85,1 percent (Health Ministry of Indonesia, 2018). Morbidity and mortality caused by TB is not only related to the disease itself, but also related to the occurrence of adverse drug reactions (ADR) due to the use of antituberculosis agents. The most common symptom ADRs related to category 1 treatments are GI symptoms like nausea, vomiting, loss of taste, dyspepsia, abdominal pain, diarrhoea, jaundice, and others (Mathew and Joseph, 2017). The ADRs occur will affect patients adherence, while adherence related to the treatment failure and the increase of resistance (Bhattacharya et al, 2018). A research by Wohlleben et al mentioned that ADRs is one of the risk factors associated to loss to follow-up beside migration to another country, moving within country, being previously treated for TB, patient refusal, stigma and family problems (Wohlleben et al, 2017). Hence, it is essential to conduct preventive and curative actions regarding the occurrence of ADRs. Risk factors analysis of the ADRs is one of the important point in order to prevent ADRs.

Brazilian guidelines on TB state that many factors caused ADRs on antituberculosis drugs. The major determinants of ADRs to antituberculosis drugs are age, organs function such as liver and kidney, the doses, the time of day at which the drugs are administered, nutritional status related to body weight loss >15%, alcohol daily intake >101 mL, and co-infection with HIV (Brasil. Ministério da Saúde, 2002,2011; Conde et al, 2009). Moreover, treatment regimens, anemia, sodium, iron, and albumin deficiency also contributed to the incidence of ADRs (Resende and Dos Santor-Neto, 2015). In Indonesia, there is a lack of data documented about risk factors analysis related to antituberculosis drug. This study aimed to

analyze a number of risk factors that might related to the ADRs of antituberculosis drugs category 1.

METHODS

A cross sectional study based on opportunity sampling technique was conducted in March-May 2018 at RS Paru Karang Tembok Surabaya. The respondents eligible for the study were all of the pulmonary TB outpatients received category 1 TB treatments who undergo treatments follow up during the study periods. A questionnaire consists of open-ended questions was used to observe symtomatical adverse effects experienced among the respondents during the treatments. Gender, ages, diabetes melitus status, body weight, and length of treatment were also recorded. The uncompleted questionnaires were excluded.

Gender, ages, diabetes melitus status, body weight, and length of treatment have being taken were analyzed as risk factors that might have contribution to the occurrence of adverse effects. Statistical analysis by SPSS 20 using poisson regression was used to evaluate the correlation of the potential risk factors mentioned and the number of adverse effects experienced. Odd ratio use to determine how strong the risk factors associate to the number of adverse effects and the p-value <0,05 use to determine statistical significance of the correlation.

RESULTS AND DISCUSSION

A total of 41 eligible active pulmonary TB patients were enrolled in this study. Among them, 58,54% were female and 24,39% of them were in the age range of 16-25 and 46-55 years. There were only 9 patients who have diabetes mellitus comorbid. The average of body weight among them was

48,42+11,486 kg while the average length of treatments has being taken was 13,85+10,150 weeks (Table 1). aspartam, dan akuades (derajat farmasetis).

Table 1. Respondents' Demographics

	n=41	Percentage (%)
Gender		
Male	17	41,46
Female	24	58,54
Age		
16-25	10	24,39
26-35	6	14,64
36-45	9	21,95
46-55	10	24,39
56-60	3	7,31
>60	3	7,31
Comorbids		
Diabetes Mellitus	9	21,95
Non-Diabetes Mellitus	32	78,05
Body Weight in kilograms (Average±SD)		
	48,42 ± 11,486	
Length of treatments in weeks (Average±SD)		
	13,85 ± 10,150	

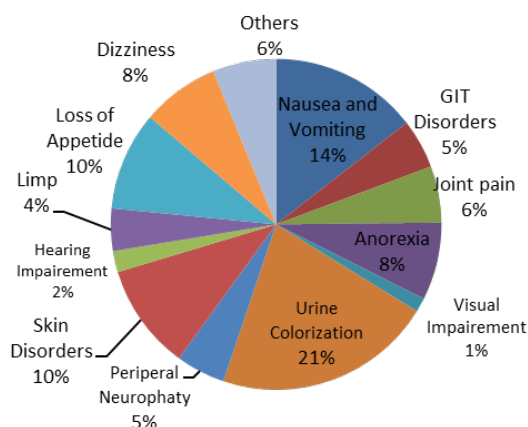


Figure 1. Symptomatic ADRs observed

Various symptomatic ADRs have observed in this study (Figure 1). In general, the ADRs are not life threatening, however it have affect on patients adherence (Castelnuovo,

2011). The most frequent ADRs occur was urine colorization (21%). Urine colorization is a manifestation of rifampicin usage that has no harmful effect (Sweetman, 2009). The other symptomatic ADRs observed were nausea-vomiting (14%), skin disorder (10%), loss of appetite (10%), anorexia (8%), dizziness (8%), etc. The similar prevalence pattern of ADRs in category 1 TB treatment mentioned in the study by Mathew dan Joseph (2017) that are nausea (56%), vomiting (30%), loss of taste (14%), dyspepsia (24%), abdominal pain (20%), diarrhea (4%), jaundice (8%), malaise (16%) dan skin rash (2%)(Mathew and Joseph, 2017).

Table 2 shows a number of risk factors that might contributed to the occurrence of ADRs in TB patients received category 1 TB treatments. The result showed among five factors analyzed, no significant correlation found to the number of ADRs incidence (p-value >0,05). However, if we criticize the Odd ratio value, all the five factors have different association to the number of ADRs.

Table 2. Analysis of ADRs Risk Factors

	Odd Ratio	95 % CI	p-value
Gender			
Male	0,842	0,550-	0,426
Female*	1	1,287	
Age			
	0,997	0,986-1,009	0,619
Body weight			
	0,992	0,976-1,010	0,389
Co-morbids			
Diabetes	1,197	0,773-	0,420
Non-diabetes*	1	1,856	
Length of treatments			
	1,007	0,989-1,025	0,469

*Referennce

The data showed that among five factors analyzed (gender, age, diabetes comorbid, and the length of treatments) have no significant correlation to the number of ADRs incidence. Gender factor showed that male patients have 0,842-fold lower risk than female of developing ADRs (Odd ratio <1). This phenomenon may associated to the influence of androgen that increase hepatic microsomal enzym activity. Hence, male are more effective in drug metabolism than female (Resende and Dos Santor-Neto, 2015).

Age determinant has Odd ratio 0,997 that explain that older age is not correlated to the number of ADRs experienced. However, A study by Ai et al (2010) and Baghaei et al (2010) said that elderly age (>60 or >65 years old) will be more likely to be exposed to ADRs (Ai et al, 2010; Baghaei et al, 2010). This difference might caused by patients' age distribution in this study that dominated by less than 60 years old of age (Table 1).

The same result as analyzed in age factor showed in body weight factor. In this study, body weight does not correlate to the number of ADRs incidence (Odd ratio 0,992). This founding may caused by low average of patients' body weight. A study by Chung-Delgado et al (2011) stated that the ADRs related to antituberculosis drug are associated to the obesity status of patients. The patients who suffer from obesity have a-2,13 fold risk of ADRs (Chung-Delgado et al, 2011).

Higher risk of ADRs observed in patients with diabetes comorbid (Odd ratio 1,197). This result confirmed by the study by Siddiqui et al (2016) that the prevalence of ADRs related to TB treatments in India is 3,578 fold higher in TB patients with diabetes. This phenomenon might be caused by potential drug interaction. However, it still need a further analysis.

The length of treatments factor also showed the same result as age and body weight which has no correlation to the number of adverse effect occurred (Odd ratio 1,007). This result indicate that the occurrence of adverse effects is not evolved by different length of treatments has being taken. The similar result also mentioned in the study by Siddiqui et al (2016) that the adverse effects could happen any time during the treatments period and it is not specified at the some point of time.

CONCLUSION

In the present study , gender, age, body weight, diabetes mellitus status, and the length of TB treatments have being taken have no significant contribution to the number of adverse effects occurred. However, further study with higher sample size to confirm the result need to be conducted.

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REFERENCES

- Ai, X., Men, K., Guo, L., Zhang, T., Zhao, Y., Sun, X., et al. 2010. Factors associated with low cure rate of tuberculosis in remote poor areas of Shaanxi Province, China: a case control study. *BMC Public Health*. 10:112.
- Baghaei, P., Tabarsi, P., Chitsaz, E., Saleh, M., Marjani, M., Shemirani, S., et al. 2010. Incidence, clinical and epidemiological risk factors, and outcome of drug-induced hepatitis due to antituberculous agents in new tuberculosis cases. *Am J Ther*. 11:17-

22. 1.
- Bhattacharya, T., Ray, S., Biswas, P., Das, DK. 2018. Barriers to treatment adherence of tuberculosis patients: A qualitative study in West Bengal, India. *International Journal of Medical Science and Public Health*. 7: 396-402. 5.
- Brasil Ministério da Saúde. Secretaria de Políticas de Saúde. Departamento de Atenção Básica. 2002. Manual técnico para o controle da tuberculose: cadernos de atenção básica nº6. Brasília: Ministério da Saúde.
- Brasil Ministério da Saúde. Secretaria de Vigilância em Saúde. 2011. Departamento de Vigilância Epidemiológica. Manual de recomendações para o controle da tuberculose no Brasil. Brasília: Ministério da Saúde.
- Castelnuovo, B. 2010. A review of compliance to anti tuberculosis treatment and risk factors for defaulting treatment in Sub Saharan Africa. *Afr Health Sci*. 10: 320-4. 4.
- Chung-Delgado, K., Revilla-Montag, A., Guillen-Bravo, S., Soria-Montoya, A., Nunez-Garbin, A., Silva-Caso, W.. 2011. Factors Associated with Anti-Tuberculosis Medication Adverse Effects: A Case-Control Study in Lima, Peru. *PLoS One*. 6 : e27610. 11.
- Conde, M.B., Melo, F.A., Marques, A.M., Cardoso, N.C., Pinheiro, V.G., Dalcin Pde, T., et al. 2009. III Brazilian Thoracic Association Guidelines on tuberculosis. *J Bras Pneumol*. 35 :1018-1048.10.
- Health Ministry of Indonesia. 2018. Infodatin Tuberkulosis. Jakarta : Center of Data and Information.
- Mathew, S., Joseph, A. 2017. Adverse effects of antituberculosis drugs in patients under DOTS category-1. *J. Evid. Base Med. Health*. 4: 415-22. 8.
- Resende, L.S.O., dos Santor-Neto, E.T., 2015. Risk Factors associated with adverse reactions to antituberculosis drugs. *J Bras Pneumol*. 41:77-89. 1.
- Siddiqui, A.N., Khayyam, K.U., Sharma, M. 2016. Effect of Diabetes Mellitus on Tuberculosis Treatment Outcome and Adverse Reactions in Patients Receiving Directly Observed Treatment Strategy in India: A Prospective Study. *Biomed Res Int*. 2016: 7273935.
- Sweetman, S.C. 2009. Martindale. 36th edition. London : Pharmaceutical Press.
- Wohleben, J., Makhmudova, M., Saidova, F., Azamova, S., Mergenthaler, C. and Verver, S., 2017. Risk factors associated with loss to followup from tuberculosis treatment in Tajikistan: a case-control study. *BMC Infectious Disease*. 17:2-8. 543.
- World Health Organization. 2018. Global Tuberculosis Report 2018. France: World Health Organization.
- World Health Organization. 2017. Indonesia TB situation update 2017 [downloaded in 13 Februari 2019]. Available from: <http://www.searo.who.int/indonesia/topics/tb/en/>