Factors Associated with the Level of Non-Adherence to Take Antituberculosis drugs

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ABSTRACT

Non-adherence to take antituberculosis drugs is one of the causes of tuberculosis (TB) resistance. However, in Indonesia no study identified the factors associated with the level of non-adherence to take antituberculosis drugs in Multi-Drug Resistant Tuberculosis (MDR-TB) patients when they were still pulmonary drug-sensitive TB survivors. The aim of this study was to identify factors associated with the level of non-adherence to take antituberculosis drugs. This was a cross-sectional study which was conducted from October 2021 to December 2021 at Dr. Soetomo Hospital Surabaya. The dependent variable was the level of non-adherence to take antituberculosis drugs, while the independent variables were age, gender, education level, income, distance from home to health care service, role of health workers, role of superintendent of swallowing drugs (PMO), and side effects. Forty out of the 195 secondary-resistant MDR-TB patients were selected as subjects for this study based on their willingness. The instrument was questionnaire which had been tested for its validity and reliability. The results of bivariate analysis showed that gender, the role of PMO, and side effects had a significance of $p<0.05$. The results of the bivariate analysis indicated that gender, role of PMO, and side effects have significance value $p<0.05$. The conclusion of this study is gender, role of PMO, and side effects are associated with the level of non-adherence to take antituberculosis drugs.

1. Introduction

Resistance of tuberculosis bacteria to first-line antituberculosis drugs can be a problem in the process of eradicating TB. With this resistance, TB therapy takes longer to more than 36 months. Moreover, second-line or third-line drugs which are administered as substitutes are more toxic and more expensive than the first-line drugs [1]. In addition, the success of MDR-TB therapy can be said to be still quite low. Research conducted by Indarti *et al.* [2] showed that the success of MDR-TB therapy using the standard shorter regimen (STR regimen) and bedaquiline (BDQ)-containing individual regimen was only 35.4% and 52.9%, respectively. On the other hand, handling MDR-TB will be difficult to do in areas that have limited access to health care facilities. Therefore,

it requires sustainable effort, commitment, and collaboration between referral centers and primary health care, so appropriate management could be achieved [3].

WHO estimates that around half a million people in the world suffer from rifampicin-resistant TB (RR-TB) and 78% of them develop MDR-TB [4]. Globally, between 2017 and 2019 MDR-TB patients experienced an increase of 10% with 5 countries experiencing an absolute increase, including India, China, Russian Federation, Indonesia, and Angola [4]. Meanwhile, the number of MDR-TB in Indonesia in 2017 was estimated to reach 8,600 – 15,000 cases [5]. On the other hand, Research by Heriqbaldi *et al.* [6] held in Surabaya, Indonesia showed that the pattern of resistance of TB bacteria to anti-tuberculosis drugs was mostly resistance to isoniazid and rifampicin (HR), followed by rifampicin (R), and isoniazid, rifampicin, and ethambutol (HRE).

Patient non-adherence to take antituberculosis drugs for 6 months and/or physician error in therapeutic management which increases the risk of developing genetic resistance is one of the causes *M. tuberculosis* resistance [7]. On the other hand, some comorbid conditions can also reduce serum drug levels. Hopewell *et al.* in Broaddus [8] states that comorbid conditions such as malabsorption, diarrhea, and use of antifungal drugs. Not only that, suboptimal levels of isoniazid can occur in people who have the NAT2 gene with RA phenotype (Rapid acetylator or fast acetylator) [9]. Dwajani *et al.* [10] states that non-adherence to take antituberculosis drugs can lead to an increase in morbidity, mortality, and health care costs. This, of course, is not only detrimental to the patient, but also the patient's family, health care facilities, and the government. Therefore, the problem of non-adherence to take antituberculosis drugs in tuberculosis patients needs to be a concern so that the incidence of MDR TB cases can be suppressed.

One of the interesting studies is Wulandari's study [11] which aimed to evaluate the factors associated with adherence in to take antituberculosis drugs using Lawrence Green's theoretical basis. In this study, the research variables were divided into behavioral factors (predisposing, enabling, and reinforcing) and non-behavioral factors. As a result, several behavioral factors such as, the attitude of health workers, the patient's perception of TB, the distance from home to health care facilities, and the role of the PMO are associated with adherence to take antituberculosis drugs. On the other hand, non-behavioral factors such as side effects also showed an association with antituberculosis drugs adherence. In addition, there were several factors in the Wulandari's study [11] were associated with adherence to take antituberculosis drugs but were not associated in other studies, and vice versa. Therefore, the gap between Wulandari's study [11] and another study is interesting to be explored further.

In Indonesia, there is no study that aims to identify the level of non-adherence to take antituberculosis drugs in MDR-TB patients when they are still drug-sensitive pulmonary TB survivors. Based on this background, it is necessary to conduct study on the topic of factors associated with non-adherence to take antituberculosis drugs in MDR-TB patients when they are still drug-sensitive pulmonary TB survivors.

The aim of this study was to identify the factors associated with the level of non-adherence to take antituberculosis drugs. With this study, it is expected to be able to strengthen existing medical theory and study to develop science. Not only that, it is hoped that the results of this study will be useful as a form of evaluating factors associated with the level of non-adherence to take antituberculosis drugs so that these factors can be controlled. If these factors can be controlled, it is hoped that all TB patients adhere to antituberculosis drugs and the incidence of MDR-TB can be reduced.

2. Method

Research design

This study was an analytic observational study with a cross sectional design which was carried out at the MDR TB Polyclinic, RSUD Dr. Soetomo Surabaya from October to December 2021.

The Sample Population

The sample of this study were 40 secondary-resistance MDR-TB patients who had recovered or were undergoing the treatment process at the MDR-TB Polyclinic, RSUD Dr. Soetomo Surabaya based on MDR TB treatment card data which began to be diagnosed from January 1, 2019 to October 31, 2021. The sample inclusion criteria in this study were MDR-TB secondary resistant MDR-TB Poly TB patients at RSUD Dr. Soetomo. Soetomo Surabaya, which is known from the registration number and the results of the GeneXpert Molecular Rapid Test or drug sensitivity test listed on the MDR TB treatment card at the MDR TB Poly Hospital Dr. Soetomo Surabaya who can be contacted and replied to his statement of willingness to be a research subject via WhatsApp. The exclusion criteria for the sample were those who could not be contacted, could be contacted but did not respond, or were not willing to be the research sample. The sampling technique was using total sampling where the authors contacted all patients who met the inclusion criteria. Of the 195 patients who were contacted via WhatsApp, 155 patients were excluded, leaving 40 patients who were willing to be subjects in this study.

Data collection techniques and instrument development

The data taken in this study were data on age, gender, education level, income, distance from home to health care facilities, the role of health workers, the role of PMO, side effects as the independent variables and the level of non-adherence to take antituberculosis drugs as the dependent variable. The data was taken from a questionnaire made by the author. Before being used as a research instrument, the part of the questionnaire used to measure the level of non-adherence, the role of health workers, and the role of PMOs has been tested for validity and reliability to 30 MDR-TB secondary resistance patients at RSUD Dr. Soegiri Lamongan which is assumed to have the same characteristics as the research sample.

Measurement of the Role of Health Officers, the Role of PMOs, and the Level of Non-adherence to Take Drugs

Measurement of the role of health workers, the role of PMO, dan the level of non-adherence to take antituberculosis drugs was obtained from the questionnaire. The role of health workers is the role of health workers during routine examinations of research subjects when they are drug-sensitive pulmonary TB survivors. This role includes always being friendly, always listening to every complaint and providing solutions to the complaint, always providing an explanation of the rules and schedule for taking antituberculosis drugs, always giving advice to take antituberculosis drugs regularly until it runs out, always telling when to check regularly again, and always tell the side effects that may be experienced and how to overcome them. Data on the role of health workers are divided into: 1) Less supportive: if the sample scores 1-2; 3) Sufficiently supportive: if the sample gets a score of 3-4; 4) Support: if the sample gets a score of 5-6.

The role of PMO here is the role of PMO in supervising taking antituberculosis drugs research subjects when they are drug-sensitive pulmonary TB survivors. These

roles include always ensuring samples of taking antituberculosis drugs every day, always reminding to take antituberculosis drugs regularly, always ensuring the availability of antituberculosis drugs, always giving advice to go to health facilities regularly, always giving motivation if taking antituberculosis drugs regularly will get better quickly, and always providing information regarding TB to the research subject. Data on the role of PMO are divided into: 1) Less supportive: if the sample scores 1-2; 3) Sufficiently supportive: if the sample gets a score of 3-4; 4) Support: if the sample gets a score of 5-6.

The level of non-adherence with taking antituberculosis drugs is the level or degree of quality of the patient's non-adherence when a patient is a survivor of drug-sensitive pulmonary TB to take antituberculosis drugs prescribed by a doctor in terms of the regularity of the patient's drugs taking hours, the completeness of drugs consumption, (whether have forgotten or intentionally not taken the drugs), the completion of the redemption of drugs, and dose adequacy. The level of non-adherence is divided into: 1) Adherence: if the sample gets a score of 0; 2) Low degree of non-adherence: if the sample gets a score of 1-2; 3) Moderate degree non-adherence: if the sample gets a score of 3-4; 4) High degree of non-adherence: if the sample gets a score of 5-6;

Data analysis techniques

After the data was obtained, the data were analyzed by bivariate analysis. The statistical test used to analyze the bivariate is the Spearman rank correlation test, the chi-square test, and the fisher's exact test. Spearman correlation test was used to examine the association between age, education level, income, distance from home to health care facilities, and the role of PMO with the dependent variable. The chi-square test was used to examine the association between gender, the role of health workers, and side effects with the dependent variable. The fisher's exact test was used to examine association between the role of health workers with the dependent variable. The significance value used in the association test is 0.05.

Ethical clearance

Ethics clearance was obtained from the Study Ethics Committee of RSUD Dr. Soetomo Surabaya with the number 0873/127/3/VIII/2021 (version: 2)
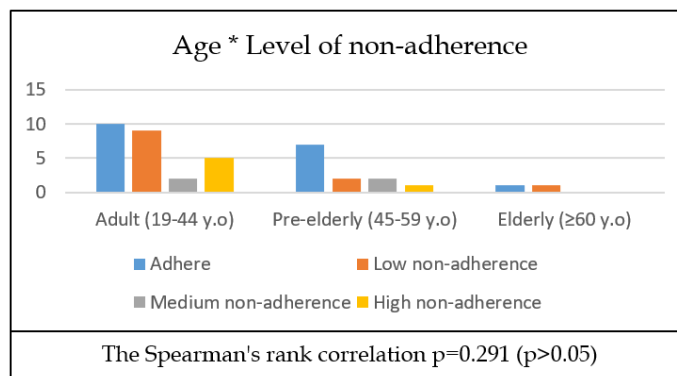
3. Results and Discussions

Association of Age with the Level of Non-adherence to take Antituberculosis Drugs

The distribution and association between age and the level of non-adherence to take antituberculosis drugs and the significance of the Spearman's rank correlation test result are shown in the figure 1 below. Age categories were divided into adults, pre-elderly, and elderly. From figure 1, it can be seen that the results of the Spearman's rank correlation test for age with the dependent variable had a significant correlation value of $p=0.291$ ($p>0.05$). This means that there was no association between age and the level of non-adherence to take antituberculosis drugs.

This result supported by the study of Erawatyningsih *et al.* [12] which states that age was not associated with non-adherence to take antituberculosis drugs. Furthermore, Erawatyningsih *et al.* [12] stated that both young and old individuals still have the motivation to live a healthy life and want to pay attention to their health. However, the awareness to have the motivation to live healthy is sometimes not carried out by all age groups. In the study conducted by the author, the study subjects who were relatively

young (aged 15-49 years) were adhere and some were not adhere, as well as the older study subjects (≥50 years).

Figure 1. Age distribution and association with the level of non-adherence to take antituberculosis drugs
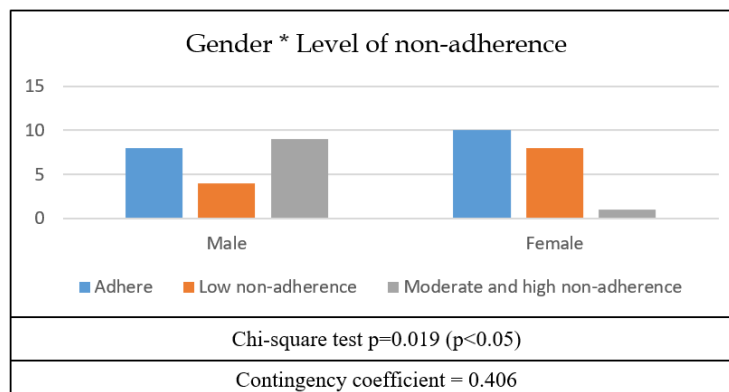
The result of the study conducted by the author showed different results from the study conducted by Fitriani *et al.* [13] and Furlan [14] which state that age was associated with adherence to take antituberculosis drugs. The difference may occur because of the age range of the study subjects in the study conducted by the author was more concentrated in adulthood, so that the number of study subjects with extreme age ranges (elderly age range) that has the potential to be non-adherent to take antituberculosis drugs was very small. This is reinforced by the results of study by Fitriani *et al.* [13] which states that adherence will decrease in individuals aged 65 years. In the study conducted by the author, the age of the oldest study subject was 62 years, so Fitriani *et al.* study [13] has not been proven yet.

Association of Gender with the Level of Non-adherence to take Antituberculosis Drugs

The distribution and association between gender and the level of non-adherence to take antituberculosis drugs and the significance of the Chi-square test results are shown in figure 2. Gender categories were divided into male and female. From figure 2, it can be seen that the results of the Chi-square test for sex with the dependent variable had a significant correlation value of $p=0.019$ ($p<0.05$). This means that there was a significant association between gender and the level of non-adherence to take antituberculosis drugs. On the other hand, the strong association that forms between the 2 variables was moderate based on the contingent correlation coefficient was 0.406.

This result supported by the studies of Ariani *el al.*[15], Fitriani *et al.*[13], and Herrero *et al.* [16] which states that gender was significantly associated with adherence to take ant-TB drugs. Fitriani *et al.* [13] stated that the female gender will tend to be less adhere to take antituberculosis drugs than men. Herrero *et al.* [16] stated that males tend to be non-adherence to take antituberculosis drugs due to their less interaction with health workers than females. In the study conducted by the author, it was found that the male gender works as a driver, entrepreneur, online motorcycle taxi driver, laborer, foreman, janitor, and odd jobs, while the female gender is mostly not working, being a housewife, and entrepreneur. This shows that male study subjects will have a tendency to interact less with health workers because if they leave their work in a day for routine

checks, their income will be threatened to decrease or even have no income at all on that day.
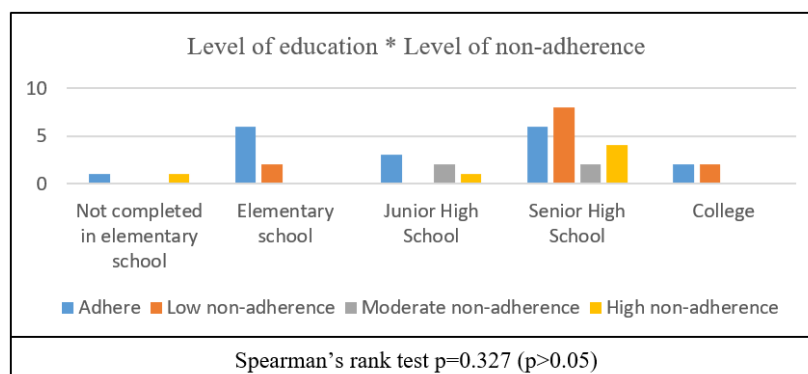

Figure 2. Gender distribution and association with the level of non-adherence to take antituberculosis drugs

The results of the study conducted by the authors differ from those of Kondoy *et al.* [17], Wulandari [11], and Rosadi [18] which stated that gender was not associated with adherence to take antituberculosis drugs and the results of the study by Erawatyningsih *et al.* [12] which states that gender is not associated with non-adherence to take antituberculosis drugs. All pulmonary TB patients, male or female, want to recover from their illness and do not want to transmit it to their families, so they adhere to follow the drug guidelines given even though it takes a long time [19]. However, in the study conducted by the author, it was found that men tend to be non-adherent to take antituberculosis drugs.

Association of Level of Education with the Level of Non-adherence to take Antituberculosis Drugs

The distribution and association between level of education and the level of non-adherence to take antituberculosis drugs and the significance of the Spearman's rank correlation test results are shown in figure 3. Education level categories were divided into not completed in elementary school, elementary school, junior high school, senior high school, and college. From figure 3, it can be seen that the results of the Spearman's rank correlation test for education level with the dependent variable had a significant correlation value of $p=0.327$ ($p>0.05$). This means that there was no association between the level of education and the level of non-adherence to take antituberculosis drugs.
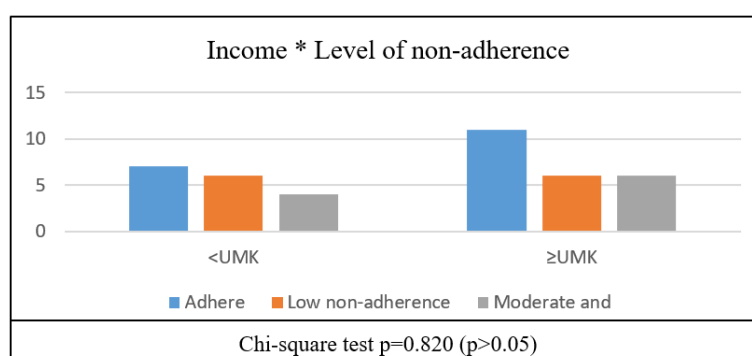

Figure 3. Level of education distribution and association with the level of non-adherence to take antituberculosis drugs

Wulandari's study [11] support this result which states that education is not associated with adherence to take antituberculosis drugs and the results of study by Fang *et al.* [19] which states that education is not associated with non-adherence to take antituberculosis drugs. On the other hand, the results of Kondoy *et al.* [17] and Soboka *et al.* [20] were different with the result of this study. Kondoy *et al.* [17] stated that non-adherence to take antituberculosis drugs was found in many people with low education, while Soboka *et al.* [20] explained that people with higher education tend to be non-adherence to take antituberculosis drugs. The study results of Kondoy *et al.* [17] showed that non-adherence to take antituberculosis drugs was more common in patients with low education, whereas Soboka *et al.* [20] explains that people with higher education tend to be busy with work so that they are not adhere with the TB treatment they are undergoing.

Association of Income with the Level of Non-adherence to take Antituberculosis Drugs

The distribution and association between income and the level of non-adherence to take antituberculosis drugs and the significance of the Chi-square test results are shown by figure 4. Income categories are divided into < regency/city minimum wage (UMK) and ≥ UMK. From figure 4, it can be seen that the results of the income Chi-square test with the dependent variable had a significant correlation value of p=0.820 (p>0.05). This means that there was no association between income and the level of non-adherence to take antituberculosis drugs.
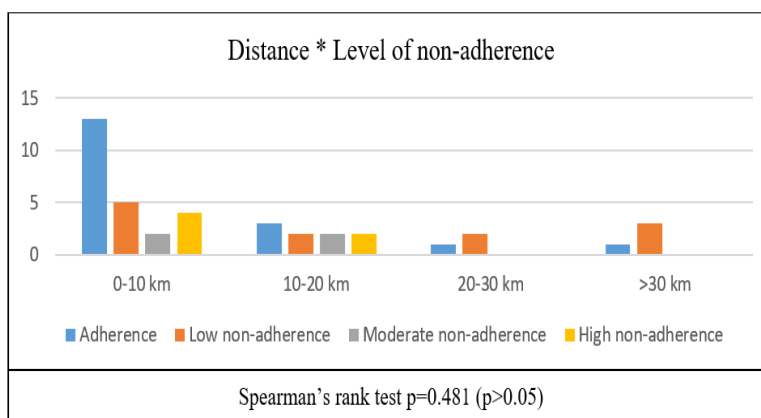

Figure 4. Income distribution and association with the level of non-adherence to take antituberculosis drugs

The results is supported by the study of Kondoy *et al.* [17] and Wulandari [11] which state that income is not associated with adherence to take antituberculosis drugs and the results of study by Ali and Prins [21] which state that income is not associated with non-adherence to take antituberculosis drugs. Kondoy *et al.* [17] stated that many pulmonary TB patients come from underprivileged circles but they can adhere to take antituberculosis drugs because it is free so that income is not a problem in adherence to take and redeem TB drugs. The results of the study conducted by the author showed different results from the study conducted by Erawatyningsih *et al.* [12]. Erawatyningsih *et al.* [12] stated that TB patients with low incomes will find it more difficult to access health services because in addition to meeting their daily needs they must set aside their income for transportation to health services. However, the study conducted by the

author shows that most of the study subjects go to health care facilities that are relatively close to their homes so they did not need to spend a lot of money on transportation.

Association of Distance from Home to Health Care Facilities with the Level of Non-adherence to take Antituberculosis Drugs

The distribution and association between distance from home to health care facilities and the level of non-adherence to take antituberculosis drugs and the significance of the Spearman rank correlation test result are shown by figure 5. Distance from home to health care facilities categories are divided into 0-10 km, 10-20 km, 20-30 km, and, >30 km. From figure 5, it can be seen that the results of the Spearman rank correlation test that the distance from home to health care facilities with the dependent variable had a correlation significance value of $p=0.481$ ($p>0.05$). This means that there was no association between the distance from home to health care facilities and the level of non-adherence to take antituberculosis drugs.

Figure 5. Distance distribution and association with the level of non-adherence to take antituberculosis drugs
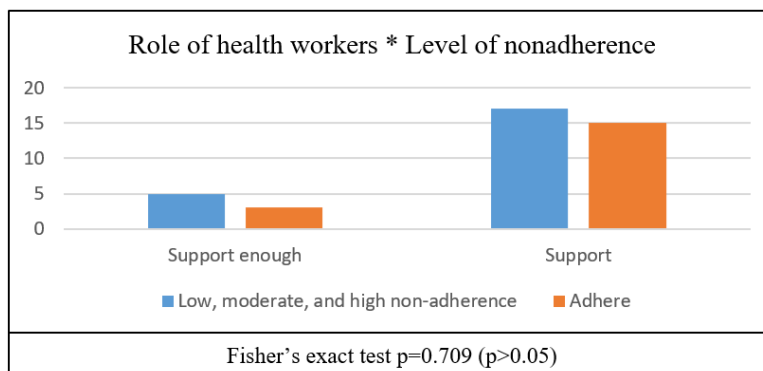
This result is supported by the study of Puspitasari et al. [22] stated that the distance from home to health care facilities is not associated with adherence to take antituberculosis drugs and the results of study by Erawatyningsih et al. [12] which states that the distance from home to health care facilities is not associated with non-adherence to take antituberculosis drugs. The results of the study by Erawatyningsih et al. [12] showed that most of the distance from the study subject's house to the health care facility where TB treatment was located was not a problem because the location of the health service facility was easily accessible. Most of the study subjects study conducted by the author went to health care facilities close to their homes (0-10 km) so it was easy to get treatment and redeem drugs.

The results of the study conducted by the authors showed different results from the study conducted by Wulandari [11] and Daksa et al. [23]. In their study in Ethiopia, Daksa et al. [23] explained that the distance from home to health care facilities is one of the reasons for non-adherence to take antituberculosis drugs because TB treatment requires DOT principles which make it difficult for patients to redeem drugs every day from health care facilities [23]. In practice, the DOT principle in Indonesia is not carried out by redeeming drugs every day from health care facilities but every few days.

Association of Role of Health Workers with the Level of Non-adherence to take Antituberculosis Drugs

The distribution and association between role of health workers and the level of non-adherence to take antituberculosis drugs and the significance of the Fisher's exact test results. Role of health workers categories were divided into support enough and support. From figure 6, it can be seen from the results of the Fisher's exact test on the role of health workers with the dependent variable had a significant correlation value of p=0.709 (p>0.05). This means that there was no association between the role of health workers and the level of non-adherence to take antituberculosis drugs.
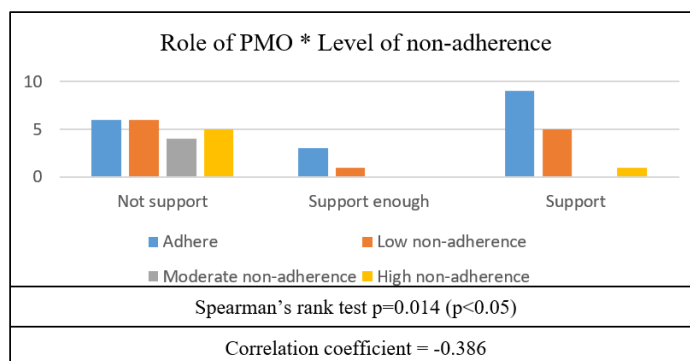

Figure 6. Role of health workers distribution and association with the level of non-adherence to take antituberculosis drugs

This result is supported by the study of Prayogo [24] which states that the role of health workers is not associated with adherence to take antituberculosis drugs and the results of study by Erawatyningsih *et al.* [12] which states that the role of health workers is not associated with non-adherence to take antituberculosis drugs. Erawatyningsih *et al.* [12] showed that the role of health workers in serving TB patients was not associated with non-adherence to take antituberculosis drugs because health workers had given special attention and provided as clear information as possible to patients. The results of the study conducted by the authors showed different results from the study conducted by Tukayo *et al.* [25]. Tukayo *et al.* [25] explained that an important role or emotional and cognitive support is given to patients. The role or emotional support aims to make patients feel comfortable, cared for, empathetic and feel accepted by health workers [25].

Association of Role of PMO with the Level of Non-adherence to take antituberculosis Drugs

The distribution and association between role of PMO and the level of non-adherence to take antituberculosis drugs and the significance of the Spearman rank correlation test results are shown in figure 7. Role of PMO categories was divided into not support, support enough, and support. From figure 7, it can be seen that the results of the Spearman rank correlation test for the role of PMO with the dependent variable had a significant correlation value of p=0.014 (p<0.05). This means that there was a significant association between the role of PMO and the level of non-adherence to take antituberculosis drugs. On the other hand, the value of the correlation coefficient of the PMO role variable and the level of non-adherence was -0.386. This value means that the strong relationship between the two variables was weak. The value of the coefficient formed between the PMO role variable and the level of non-adherence was negative. A

negative value on the correlation coefficient indicated a relationship between the two variables tested in opposite directions, that was, the greater the value of one variable, the smaller the value of the other variables. In this case it means that the higher the role of the PMO, the lower the level of non-compliance and vice versa.

Figure 7. Role of PMO distribution and association with the level of non-adherence to take antituberculosis drugs
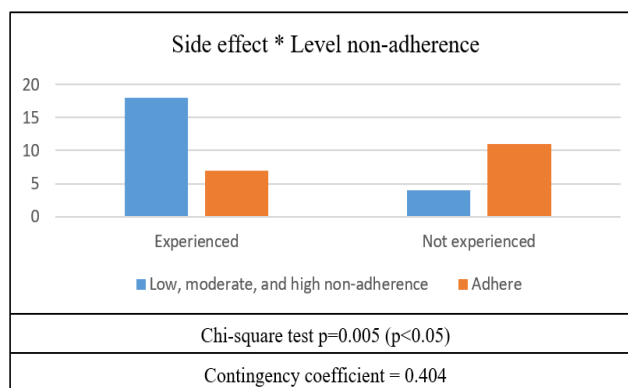
The role of PMO is associated with the level of non-adherence to take antituberculosis drugs. The result is supported by the study of Wulandari [11] which shows that the role of PMO is associated with adherence to take antituberculosis drugs. On the other hand, the results of the study conducted by the authors differ from those of Ariani *et al.* [15] stated that the role of PMO was not associated with adherence to take antituberculosis drugs. In addition, study on the association between the role of PMO and non-adherence to take antituberculosis drugs was conducted by Erawatyningsih *et al.* [12] showed that PMO was not associated with non-adherence to take antituberculosis drugs. Increasing the role of PMO in supervising TB patients can be done by increasing the PMO's knowledge about TB. This is supported by the study results of Manurung *et al.* [26] which shows that there is association between the level of knowledge and the success of TB treatment. The increase in knowledge can be done by means of lectures, discussions, and questions and answers that can be carried out by relevant stakeholders such as the Health Service [27].

In addition to increasing the PMO's knowledge of TB, the selection of the right PMO candidate should also be considered. The Indonesian Ministry of Health [28] explained that PMOs should be selected from people who are trained, can be well received by patients, and selected with patients. Furthermore, Harahap *et al.* [29] explained that close family members can be selected as PMOs because of their better emotional closeness than PMOs who do not come from close family so that PMOs do not hesitate to reprimand TB patients if the patient is non-adherence and the patient himself does not feel indebted to PMO for his services during the treatment period.

Association of Role of Side Effects with the Level of Non-adherence to take antituberculosis Drugs

The distribution and association between role of side effect and the level of non-adherence to take antituberculosis drugs and the significance of the Chi-square test results are shown by figure 8. From figure 8, it can be seen that the results of the Chi-square test of side effects with the dependent variable had a significant correlation value of p=0.005 (p<0.05). This means that there was a significant association between side

effects and the level of nonadherence to take antituberculosis. On the other hand, the strong relationship that forms between the two variables was a moderate association on the basis of a contingency correlation coefficient of 0.404.

Figure 8. Side effect distribution and association with the level of non-adherence to take antituberculosis drugs

The results of the study conducted by the authors are supported by the study of Wulandari [11] which states that side effects are associated with adherence to take antituberculosis drugs and the study of Erawatyningsih *et al.* [12] which states that side effects are associated with non-adherence to take antituberculosis drugs. Meanwhile, the results of the study conducted by the authors are not in line with the study of Kondoy *et al.* [17] and Fitriani *et al.* [13] stated that side effects were not associated with adherence to take antituberculosis drugs. Kondoy et al. [17] explained that the emergence of symptoms of side effects can make patients lazy to take antituberculosis drugs, especially in the early phase.

The Indonesian Ministry of Health [30] explained that information about side effects can be taught by health workers to TB patients so that these patients recognize the general symptoms of antituberculosis drugs side effects and report their condition to health workers. Patients with low side effects should continue their treatment and be given instructions on how to overcome these side effects or be given additional treatment to overcome existing complaints, while patients with high side effects should stop their treatment temporarily and then be referred to a doctor or referral health care facility for further management and should be treated in a hospital [30]. Therefore, the presence of side effects in TB patients needs to be watched out so that these side effects can be handled properly and do not cause TB patients to not adhere to take antituberculosis drugs.

4. Conclusion

The results of the bivariate analysis indicated that gender, role of PMO, and side effects are associated with the level of non-adherence to take antituberculosis drugs. Gender is associated with the level of non-adherence to take anti-tuberculosis drugs because men tend to work in the service sector so they interact less with health. Role of PMO is associated with the level of non-adherence to take antituberculosis drugs so that PMOs are needed who are trained, can be well received by patients, and selected with patients and if possible, come from the family. Side effect is associated with the level of non-adherence to take antituberculosis drugs, so monitoring of side effects needs to be done so that side effects can be handled properly.

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