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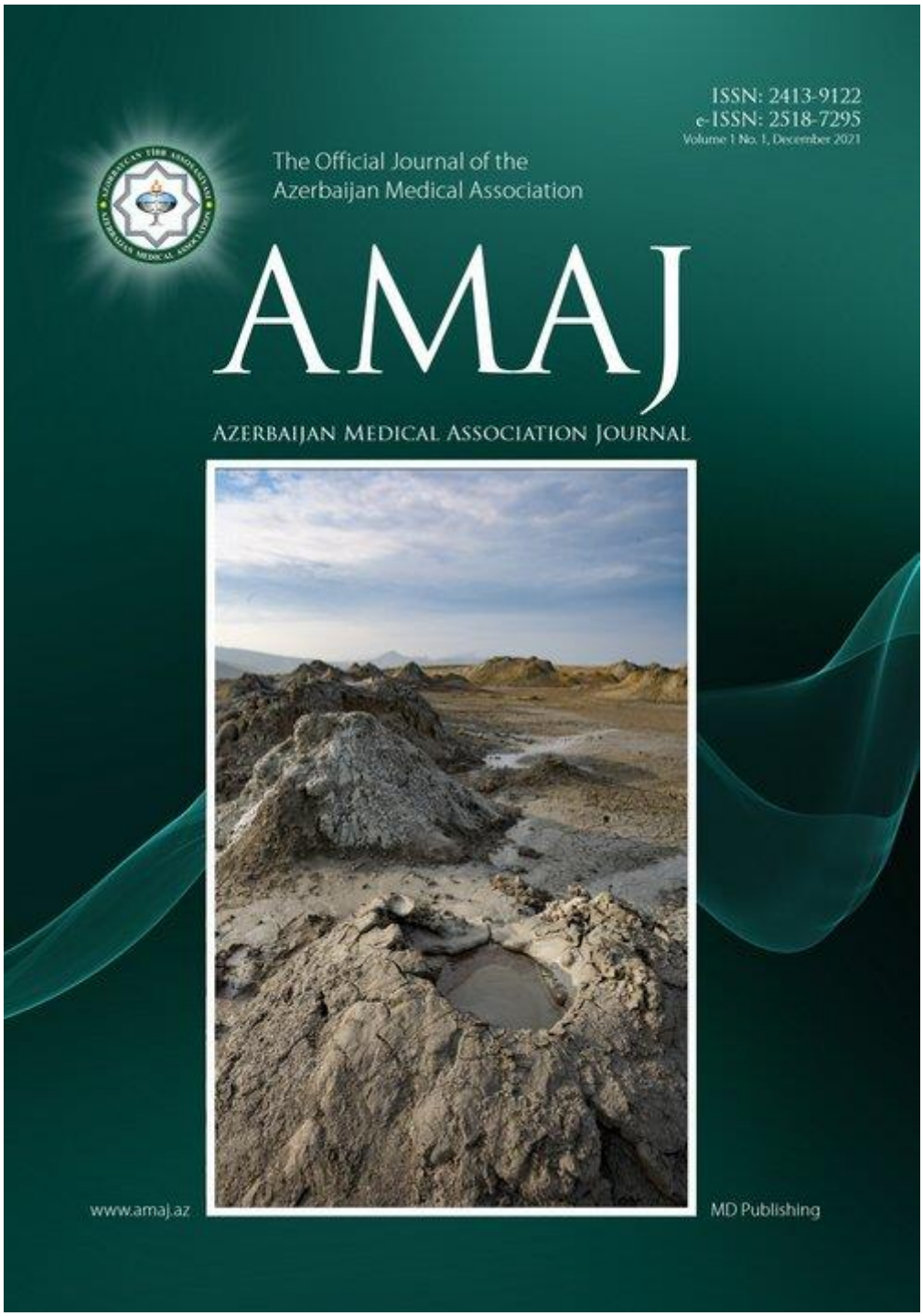

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Exploring the Determinants of Adherence to Pulmonary Tuberculosis Treatment During 2018-2023 in Indonesia: A Literature Review

Meiyanti[1,2*], Adang Bachtiar[3], Yohana[4], Eveline Margo[5], Lie Tanu Merijanti[6], Alvina[7], Pusparini[7]

Doctoral Student at the Faculty of Public Health, Universitas Indonesia, Depok, Jawa Barat, Indonesia[1]
Department of Pharmacology and Pharmacy, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia[2]
Department of Administration and Policy, Faculty of Public Health, Universitas Indonesia, Depok, Jawa Barat, Indonesia[3]
Departement of Biochemistry, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia[4]
Departement of Physiology, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia[5]
Department of Occupational Medicine, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia[6]
Clinical Pathology Department, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia[7]

Corresponding author: 1,2*

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ABSTRACT

Indonesia's tuberculosis treatment success rate currently stands at 86.5%. Medication adherence is an important key to achieving treatment success. This literature review aims to provide an overview of factors contributing to medication adherence. Articles were obtained from the Scopus database, and a manual review was conducted using Google Scholar for accredited national journals in Indonesia in 2018-2023. A literature review was conducted on quantitative studies to identify factors associated with tuberculosis treatment adherence. The keywords used for the search were "determinants" AND "adherence" OR "compliance" OR "treatment dropout" OR "lost to follow-up" and tuberculosis OR TB OR TBC. A total of 25 articles were obtained for the literature review of treatment adherence factors extracted and synthesized into the five World Health Organization adherence dimensions. The main dimension contributing to TB treatment adherence in Indonesia was socio-economic. Other factors associated with treatment adherence were distance to health facilities, transportation costs, residence location, and residence distance. Successful treatment of this disease is a complex and multi-dimensional problem with many factors involved. It requires integrated treatment from health services, access to health facilities, socioeconomic support, and family and neighborhood support to achieve successful treatment outcomes.

1. Introduction

Tuberculosis (TB) is a health problem that is still faced by various countries in the world including

Indonesia. Based on data from the Global Tuberculosis Report in 2022, the number of TB cases in Indonesia was 969,000 cases (354 per 100,000 population), currently, Indonesia is the second largest TB burden after India [60]. This is a challenge for Indonesia and requires attention from various parties, TB infectious disease cases currently provide a high burden of morbidity and mortality. The Indonesian government is currently committed to achieving TB elimination by 2030. In line with the sustainable development goals (SDGs) target for TB in 2030 is a 90% reduction in the number of deaths from TB and an 80% reduction in TB incidence [8].

Data from the World Health Organization (WHO) shows that TB is the 2nd cause of death from infectious diseases in the world, after the Covid-19 pandemic. In 2020, it is estimated that the number of people infected with TB will reach 10 million in the world. Even in developed countries, the morbidity and mortality rates due to TB are in line with the increase in cases of HIV/AIDS infection [61]. The high number of TB cases has an impact on the economic burden on the state, Global Fund data reports that global economic losses due to tuberculosis amount to 12 billion USD every year for the cost of treating cases of drug-sensitive TB and drug-resistant TB, this is due to unproductivity due to TB treatment and due to the development of TB disease. These costs are exacerbated in economically disadvantaged groups as patients who are the breadwinners lose their jobs due to a history of therapy or long-term TB treatment [53].

Adherence to TB medication is critical to achieving a cure. TB treatment is carried out using a combination of several drugs and given over a while, so patient compliance with taking medication is required. The success rate of TB treatment in Indonesia based on the annual report of the Ministry of Health's TB program in 2022 only reached 86.5%, still below the expected target of more than 90%. Based on these data, the estimated number of TB patient dropouts in Indonesia is still high at more than 10% [8]. Various reasons for patient dropouts such as drug side effects, economic conditions, lack of psychosocial support, and others have an impact on increasing cases of drug-resistant TB with the consequence that sufferers must undergo TB treatment for a longer time, more drug combinations, higher costs and an increased risk of morbidity and mortality due to TB disease [22], [46], [9], [34], [43].

Incomplete TB treatment puts patients at risk of recurrence, increases the severity of the disease, and results in hospitalization due to deterioration in health and complications of the disease. Previous studies conducted in Indonesia and other countries have concluded that many factors play a role in TB patient adherence. The importance of conducting a literature review on factors influencing pulmonary tuberculosis treatment adherence in Indonesia between 2018-2023 is that it will help formulate more effective control strategies to address the burden of disease, understand the impact of social and economic contexts on adherence, identify barriers and opportunities in treatment practices, and provide a basis for developing locally of each region in Indonesia appropriate interventions. The purpose of this literature review is to identify literature related to causal factors associated with medication adherence among TB patients in Indonesia.

2. METHOD

This study used a literature review approach to provide information on treatment adherence among TB patients and the determinants that contribute to it. The literature search was limited to the period between 2018 and 2023. The Scopus and Google Scholar databases were used for the literature search using the following keywords: 'determinants' AND 'adherence' OR 'compliance' OR 'treatment dropout' OR 'lost to follow-up' and tuberculosis OR TB OR TBC. Inclusion criteria for the study were limited to articles written in Indonesian or English, open access, full text availability, and research conducted in Indonesia. Exclusion criteria were applied to articles containing keywords related to other diseases or drug-resistant TB cases. As depicted in Figure 1, the selection flowchart illustrates the process of article selection.

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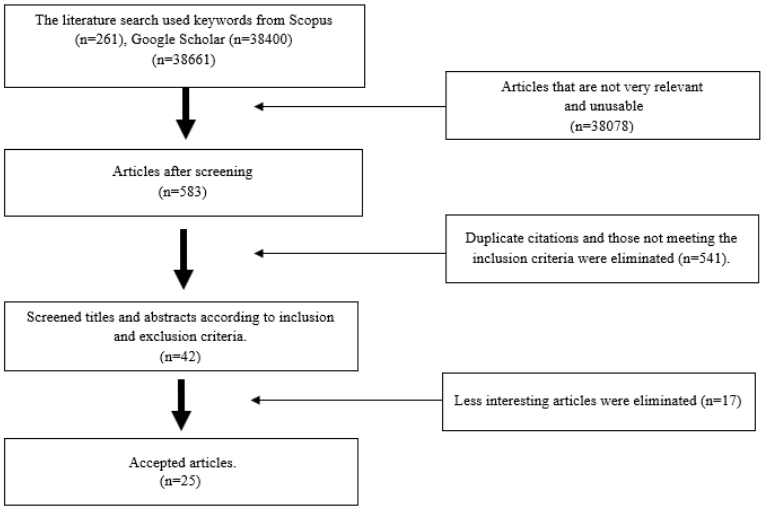

Figure 1. The flow of the article review

3. RESULTS

Based on the search results, 25 articles meeting both inclusion and exclusion criteria were determined as sources for conducting the literature review. A summary of the literature used in the literature review is shown in table 1.

Table 1. Summary of articles used (n=25)

Author	Design	Purpose	Location	Statistic analysis	Result
[41]	Case-control study	Identification of factors associated with non-adherence to TB treatment among patients at a health center in Jayapura, Papua.	Jayapura	Chi-square / Fisher	Access to health services (distance/cost of travel and history of moving within the past year), lack of knowledge, treatment experience, and form of medication given are associated with treatment adherence.
[12]	Cross-sectional	to analyse the determinants of patient medication adherence	Padang	Chi-square & linear logistic regression	The dominant factor influencing drug adherence of pulmonary TB patients was knowledge (p=0.000, OR 29.169), followed by attitude (0.000), education (0.000), employment (0.001), and family support (0.000).
[56]	Case control	to analysed determine the factors associated with adherence to pulmonary tuberculosis treatment.	Subang	Chi-square and multivariate analysis of multiple logistic regression	Factors associated with pulmonary TB treatment adherence were family support (p=0.003; OR=2.956), gender (p=0.045; OR=1.961), education (p=0.045; OR=1.962), occupation (p=0. 043; OR=1.989), knowledge (p=0.005; OR=2.529), drug side effects (p=0.045; OR=1.961), medication supervisor (p=0.000; OR=3.500), health facility distance (p=0.044; OR=1.967), staff attitude (p=0.020; OR=2.172).

[27]	Cross-sectional	To identify relationship between the level of knowledge and motivation of patients with pulmonary tuberculosis with adherence to taking medication.	Menado	Chi-square	There is a relationship between knowledge and motivation of pulmonary tuberculosis patients with adherence to taking medication, the higher the level of knowledge of motivation, the cure can be obtained.
[15]	Cross-sectional	To investigate the determinants of adhering to treatment for TB patients.	Bengkulu	Chi-square & linear regression	Factors such as age, gender, education, income, knowledge, drug availability, and family support positively influenced adherence to anti-tuberculosis treatment, while side effects, distance to health services, and tenure had a negative impact. Income, knowledge, and the role of treatment supervisors indirectly affected adherence.
[42]	Cross-sectional	To determine the education, knowledge and attitude factors associated with adherence to anti-TB drugs in patients with pulmonary TB at the community health center.	Indramayu	Chi-square	There was no relationship between education and OAT consistency (p=0.082); there was a relationship between knowledge (p =0.012) and attitude (p=0.040) with drug consistencies.
[35]	Cross-sectional	To analyse the effect of family factors (family stress levels and family resilience) on medication adherence	Surabaya	Pearson correlation	Family stress levels were mostly in the normal category (86.6%), family resilience was mostly in the good category (79.9%), and moderate TB medication adherence (39.8%). The results of the Pearson correlation test obtained family stress levels (p = 0.004) and family resistance (p = 0.001) with medication adherence.
[3]	Cross-sectional	To analyze Fixed Dose Combination treatment adherence factors in patients	Tangerang	Chi-square	Respondents of productive age as many as 46 (97.9%), while based on bivariate analysis it was found that there was a relationship with knowledge, AOT side effects, distance of residence, PMO role, and health role with a p value< 0.05.

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[36]	Cross sectional	To determine the relationship between the side effects of anti-tuberculosis drug and the role of the medication monitoring officer (PMO) with medication adherence.	Palembang	Chi-square	The frequency distribution of pulmonary TB respondents who adhered to treatment was 37 respondents (72.5%), respondents who experienced low anti-tuberculosis drug side effects as many as 39 respondents (76.5%), respondents the role of good PMO as many as 34 respondents (66.7%). Chi-squared test results showed that there was an association between OAT side effects (p = 0.011) and the role of PMO (p = 0.007) with adherence.
[40]	Cross sectional	To analyze relationships age, gender, education, side effects of treatment, knowledge, attitudes of health workers with medication adherence	Banjarmasin	Fisher exact	The knowledge variable (p = 0.019) was associated with medication adherence. The higher the patient's knowledge, the higher the level of treatment adherence.
[7]	Cross-sectional	To know the determinants of medication adherence	Palembang	Chi-Square & multiple logistic regression	Achieved treatment adherence of 42.8% in tuberculosis patients. There was a significant relationship between perceived benefits (p=0.000; OR=3.556), family support (p=0.000; OR=3.512), health worker support (p=0.001; OR=2.712), knowledge (p=0.018; OR=2.027) and adherence.
[25]	Cross sectional	To find out the relationship between knowledge and attitudes of pulmonary TB patients with medication adherence.	Demak	Chi-Square	There is a relationship between the knowledge and attitude of TB sufferers with medication adherence (p = 0.000)
[57]	Cross sectional	To analyze the factors that related to medication adherence.	Kendari	Chi-Square & logisric regression	Factors that were significantly associated were knowledge (OR 14,909), motivation (OR 6,783), home distance (OR 5,591), family support (OR 4,071), and the role of health workers (OR 11,500) with medication adherence. The knowledge and role of health workers correlate significantly (p=0.001; p=0.003), with a contribution to complianc by 53%.

[26]	Cross-sectional	To determine the influencing factors medication adherence.	Sukabumi	Chi-Square & simple linear regression	Factors associated with medication adherence are age, education level, length of treatment, medication side effects, and family support.
[52]	Case-control	To analysed factors associated with patient withdrawal in community health centers	Gowa-Sulawesi Selatan	Chi-square	There is a relationship between patient knowledge, PMO support, family motivation, side effects. medication, and health worker support with drug withdrawal.
[5]	Cross sectional	To analyze factors related to medication adherence	Surakarta	Chi-square	Most patients were adherent to treatment (79%). Factors associated with medication adherence were the role of health workers (p = 0.045) and PMO (p = 0.035).
[51]	Case-control	To determine the risk factors for non-adherence to treatment.	Mamuju-Sulawesi Barat	Chi-square	Knowledge factors (OR=2.472; 95%CI=1.047-1.058), motivation (OR=4.392; 95%CI=1.795-10.742), PMO (family support) (OR=2.781; 95%CI=1.229-6.291) support (OR=1.28; 95%CI=0.349-3.644) and access to health facilities (OR=1.609); 95%CI=0.670-3.864) are risk factors for non-adherence.
[18]	Cross-sectional	To analyze the factors of Acceptance and Commitment Therapy (ACT)	Medan	Chi-square	There was an association between age (p = 0.004), length of time suffering from TB (p = 0.001), age (p = 0.001) and ACT. There was no relationship between gender with ACT.
[1]	Cross-sectional	To determine the level of treatment adherence	Jambi	Chi-square	A total of 26 respondents (76.47%). The Chi-square test obtained results have a significant relationship with the level of compliance.
[47]	Case control	To analyze the factors that associated with the incidence of drug withdrawal.	Nabire-Papua	Spearman correlation	Family support factors of 0.000, health worker support of 0.003, difficulty in seeing health facilities of 0.002 are related to drug withdrawal.
[49]	Cross-sectional	To know the relationship between the level of knowledge about and adherence to taking medication in tuberculosis patients	Wonogiri	Kendall's Tau correlation	Respondents with a moderate level of knowledge were as much as 55.30% The adherence rate of drinking OAT was high in 44.70% of respondents. Analysis of the relationship between knowledge level and medication adherence level was obtained (p = 0.000; r = 0.489).

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[20]	Cross-sectional	To analysed association factors that are thought to influence the unsuccessful treatment of pulmonary TB patients.	Surakarta	Multivariate logistic analysis	The belief in drug hazards subscale (p = 0.001; OR = 8.167), drug overuse subscale (p = 0.038; OR = 3.504) and experience of drug side effects (p = 0.022; OR = 4.222) were predicted factors influencing non-adherence to anti-tuberculosis drugs.
[13]	Cross-sectional	To identify relationships between self-efficacy and adherence to treatment on pulmonary tuberculosis patients	Depok	Chi-square	Respondents who had a poor self-effectiveness of 53.3%, were correlated with the level of drug compliance on drug intake in lung tuberculosis patients (p=0.004), with OR (1,417).
[45]	Cross-sectional	To analysed relationship knowledge with medication adherence in pulmonary tuberculosis patients in Community Health Centre.	Nias Selatan	Spearman Rho Correlation	There is a knowledge relationship with medication adherence in pulmonary tuberculosis patients (p = 0.008, r = 0.466)
[29]	Cross-sectional	To analysed determinants the level of compliance and whatever factors influence TB patients in treatment during pandemics.	Surabaya	SEM	Factors influencing adherence are age, education, employment status, marital status, residence, and income. The multiple logistic regression analysis shows that the dominant factor with the greatest influence on adherence is the level of education. Higher educated respondents tend to have a good adherence rate of 22.07 compared to lower educated respondents.

4. DISCUSSION

Medication adherence refers to the extent to which an individual's behaviour in taking medication aligns with changes in their diet or lifestyle, as evaluated by their compliance with recommended and agreed-upon guidelines. Factors associated with medication/therapy adherence were categorized into five WHO adherence dimensions, the first being the socioeconomic dimension (environmental/social factors such as interactions, social context, stigma, norms, external support, and environment; lifestyle factors such as alcohol, drugs; economic factors such as income, education, employment, living conditions, and insurance). The second dimension of the health system includes characteristics of medical personnel such as relationships, communication, understanding trust, treatment practices, and patient education; and factors related to the health care system such as access, regulatory processes, quality of health services, information support, and insurance. The third dimension of the therapy dimension includes treatment regimen factors such as complexity, dose, type, capsule load, clarity of label instructions, and familiarity with the regimen;

treatment impact factors such as side effects, effectiveness, safety, treatment experience; treatment element factors such as cost, physical elements, and prescribing [59], [33].

The fourth dimension of the patient dimension includes psychological and cognitive related factors such as perception, beliefs, and doubts; behavioral factors such as organization, planning, and lifestyle; priority factors such as quality of life, and other competitive needs; non-modifiable characteristics such as demographics, experience, physical factors; family characteristic factors such as doubts, support, and relationships. The fifth dimension, the condition dimension, includes disease control factors such as symptoms, complications, severity, impairment, and influence on lifestyle; disease characteristic factors such as cognitive decline, impairment of symptoms, and consequences, patient-specific factors such as health decline, comorbidities, time since diagnosis [33], [59].

4.1 Socioeconomics

Knowledge is the factor most commonly found to be associated with adherence to taking medication [3], [12], [15], [27], [30], [42], [45], [49], [51], [52], [56]. Knowledge about the disease, how the disease is transmitted, recovery treatment can improve patient compliance with taking medication. This knowledge is sometimes associated with education level. A person with a high level of education is more likely to understand the information presented to increase knowledge related to TB disease. The level of education in several studies was concluded to be associated with adherence to taking medication [15], [26], [29], [56]. In higher education groups it is easier to access information and health facilities, education is closely related to understanding the disease, the risks if not treated. TB patients with a high level of education have a better compliance rate of 22.077 times compared to patients with lower education levels [29].

In addition, information on other diseases associated with TB also affects the success of therapy, one of the comorbidities often found in patients with TB is diabetes mellitus, so sugar control and treatment of comorbidities determine the success of TB therapy [44]. Outdoor work and environmental factors increase the risk of TB infection. Based on gender, the dropout rate in men is higher because they are busy working, so they have less time to visit health facilities, while women are more concerned with health and usually undergo treatment regularly [12], [29]. The patient's economic status and income are also factors related to compliance. Living conditions, costs for treatment, and nutritional status are directly related to income [1], [15], [29]. Nutritional needs, especially protein, are needed for successful treatment, nutrition will have an impact on immune status indirectly [24], [14].

4.2 Health System

Health facilities that are easily accessible from residential locations, health workers, diagnostic support facilities, availability of pharmacy installations, as well as information media facilities, and modern technology facilities are associated with adherence to therapy. Support from health workers is needed, and promotive health efforts such as counseling and education to prevent TB transmission need to be carried out actively. In addition, information about the symptoms of the disease, the drugs to be given, and the length of treatment has an impact on adherence to taking medication [7], [15], [17], [31], [38], [41], [47], [51], [54], [56]. A range of interventions, both cognitive and behavioural, need to be implemented by health professionals and patients' families to increase the level of knowledge and awareness of patients [58], [6].

The development of technology utilisation in the health system to monitor patient compliance and complaints during treatment has a positive impact on patients and health workers in doing their work [23], [48]. Hospital infrastructure development and supporting facilities are needed, as well as facilities, infrastructure, and supporting examination facilities to support the successful treatment of TB patients [32].

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4.3 Drug Therapy

TB is divided into several categories, namely drug-sensitive tuberculosis, drug resistance, multidrug-resistant tuberculosis, and XDR tuberculosis. Depending on these categories, the type and duration of therapy will vary. In the case of drug-sensitive TB, 4 types of drugs are given in the form of a combination fix in the first 2 months and continued with 2 types of drugs for 4 months, so that the minimum therapy period is 6 months [21], [39]. The availability of complete drugs, as well as clear information to patients about drug use, and possible side effects that will arise can increase patient compliance with taking medication [3], [15], [17], [26], [36], [56]. Information about the course of the disease, complications of the disease if not treated and the consequences of drug withdrawal need to be conveyed to patients and become the knowledge of TB patients. Monitoring complaints that arise during drug use is very important, this is part of pharmacovigilance, all complaints submitted need to be recorded and analyzed further. The implementation of pharmacovigilance by health workers provides benefits for patient safety [55], [37]. Information about side effects needs to be conveyed to medical staff and needs to be responded well so that patients do not become afraid of drugs, drug supervisors play an important role in completing treatment, information related to drug side effects and need to be conveyed to health workers need to be informed to drug supervisors [2], [28]. The side effects of drugs that are felt have an impact on daily activities so that patients will stop self-medication [11], [26], [35], [52]. Long treatment periods increase the risk of drug withdrawal, drug administration in the intensive phase in the first 2 months patients will feel the benefits of therapy or better conditions and will stop self-medication. Regarding the length of treatment, patients who undergo ≥2 months of therapy will have a 2.7 times risk of being irregular in taking medication [10].

4.4 Patient

Patients with pulmonary TB are more commonly found in the male gender, and at productive age [15], [17], [29], [56]. Patients with TB more in men are associated with a history of smoking habits and daily activities outside the home and breadwinners for the family. Age shows a relationship with acceptance and commitment to undergo therapy so that it will increase adherence to taking medication [18]. Family support factors are concluded to be associated with adherence to TB patient therapy [7], [12], [15], [16], [17], [26], [47], [56]. Family support in the form of family acceptance and acceptance of the patient's disease condition will provide added value for patients while undergoing acceptance. The family is the closest person who understands the patient's disease complaints, the patient's therapy process. The family can be a drug supervisor, so it is necessary to conduct training for drug supervisors so that they can understand their functions and duties properly [5], [50].

TB patients with married status show better compliance, support from spouses or children in undergoing long-term TB therapy. Widow/widower status is more likely to drop out compared to married or unmarried groups [29]. Lifestyle is associated with attitude. Attitudes will shape behavior in accordance with the beliefs and beliefs of the patient. An increase in attitude will increase compliance with taking medication [25]. Attitude is a reaction to a person's interval which is influenced by personal experience, environment, and people around, religion, emotional factors. Attitudes will shape behavior to prevent transmission, maintain hygiene and healthy living behaviors to support the success of therapy in addition to adherence to taking medication [3], [7], [12], [41], [42].

4.5 Condition

Among the various concomitant diseases associated with TB, diabetes mellitus and depression are two of the most common non-communicable diseases among TB patients worldwide. It is important to carefully consider these conditions when providing medical care, as TB patients with diabetes mellitus (TB-DM) or depression are at a higher risk of death, relapse, and recurrence. When a patient is diagnosed with both TB

and DM, it can lead to a compounding negative impact on their health. TB-DM patients with high blood glucose levels may experience decreased effectiveness of anti-tuberculosis drugs. However, it is possible that higher doses of anti-TB drugs could help to reduce the incidence of DM drug effects [14], [4].

TB treatment usually lasts for a minimum of 6 months, which may result in a high rate of lost to follow up (LTFU) among patients, especially during the first 3 months of treatment. It has been observed that patients with a history of hospitalization due to TB are comparatively less likely to experience LTFU than other patients. Furthermore, it is worth noting that patients who arrive at the hospital with urgent symptoms, such as high fever, chest pain, coughing up blood, and shortness of breath, may be less likely to experience loss to follow-up. This information may serve as an incentive for patients to seek medical attention, consult with experienced physicians for guidance and treatment, manage their condition, and avoid the progression of more serious complications [19].

There are several other factors associated with therapy adherence based on the literature search, including distance to health facilities, transportation costs, location of residence, distance of tenure. The limitation of this literature search is that there is a risk of research bias, and this literature review attempts to synthesize findings from multiple studies, the risk of misinterpretation and synthesis of data remains, especially as the included studies may vary in methodology, sample size, and the context of the crisis studied.

5. CONCLUSION

Socioeconomic and health system dimensions dominate TB patient treatment adherence. Adherence is key to successful treatment. TB treatment management is complex, with many factors involved. This makes it possible to develop multidisciplinary and integrated policies in an effort to achieve TB elimination in Indonesia.

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AUTHORS' CONTRIBUTIONS

Conceptualization: M, AB Data curation: M, Y, EM, LTM, A. Formal analysis: PM, AB. Methodology: M, AB, Pr. Writing of original draft: M. Writing of review and editing: LTM, A, Pr.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest in this study.

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Exploring the Determinants of Adherence to Pulmonary Tuberculosis Treatment During 2018-2023 in Indonesia: A Literature Review

Meiyanti[1,2*], Adang Bachtiar[3], Yohana[4], Eveline Margo[5], Lie Tanu Merijanti[6], Alvina[7], Pusparini[7]

Doctoral Student at the Faculty of Public Health, Universitas Indonesia, Depok, Jawa Barat, Indonesia[1]
Department of Pharmacology and Pharmacy, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia[2]
Department of Administration and Policy, Faculty of Public Health, Universitas Indonesia, Depok, Jawa Barat, Indonesia[3]
Departement of Biochemistry, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia[4]
Departement of Physiology, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia[5]
Department of Occupational Medicine, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia[6]
Clinical Pathology Department, Faculty of Medicine, Universitas Trisakti, Jakarta, Indonesia[7]

Corresponding author: 1,2*

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Dimension, Infection, Resistance, Transmission.

ABSTRACT

Indonesia's tuberculosis treatment success rate currently stands at 86.5%. Medication adherence is an important key to achieving treatment success. This literature review aims to provide an overview of factors contributing to medication adherence. Articles were obtained from the Scopus database, and a manual review was conducted using Google Scholar for accredited national journals in Indonesia in 2018-2023. A literature review was conducted on quantitative studies to identify factors associated with tuberculosis treatment adherence. The keywords used for the search were "determinants" AND "adherence" OR "compliance" OR "treatment dropout" OR "lost to follow-up" and tuberculosis OR TB OR TBC. A total of 25 articles were obtained for the literature review of treatment adherence factors extracted and synthesized into the five World Health Organization adherence dimensions. The main dimension contributing to TB treatment adherence in Indonesia was socio-economic. Other factors associated with treatment adherence were distance to health facilities, transportation costs, residence location, and residence distance. Successful treatment of this disease is a complex and multi-dimensional problem with many factors involved. It requires integrated treatment from health services, access to health facilities, socioeconomic support, and family and neighborhood support to achieve successful treatment outcomes.

1. Introduction

Tuberculosis (TB) is a health problem that is still faced by various countries in the world including

Indonesia. Based on data from the Global Tuberculosis Report in 2022, the number of TB cases in Indonesia was 969,000 cases (354 per 100,000 population), currently, Indonesia is the second largest TB burden after India [60]. This is a challenge for Indonesia and requires attention from various parties, TB infectious disease cases currently provide a high burden of morbidity and mortality. The Indonesian government is currently committed to achieving TB elimination by 2030. In line with the sustainable development goals (SDGs) target for TB in 2030 is a 90% reduction in the number of deaths from TB and an 80% reduction in TB incidence [8].

Data from the World Health Organization (WHO) shows that TB is the 2nd cause of death from infectious diseases in the world, after the Covid-19 pandemic. In 2020, it is estimated that the number of people infected with TB will reach 10 million in the world. Even in developed countries, the morbidity and mortality rates due to TB are in line with the increase in cases of HIV/AIDS infection [61]. The high number of TB cases has an impact on the economic burden on the state, Global Fund data reports that global economic losses due to tuberculosis amount to 12 billion USD every year for the cost of treating cases of drug-sensitive TB and drug-resistant TB, this is due to unproductivity due to TB treatment and due to the development of TB disease. These costs are exacerbated in economically disadvantaged groups as patients who are the breadwinners lose their jobs due to a history of therapy or long-term TB treatment [53].

Adherence to TB medication is critical to achieving a cure. TB treatment is carried out using a combination of several drugs and given over a while, so patient compliance with taking medication is required. The success rate of TB treatment in Indonesia based on the annual report of the Ministry of Health's TB program in 2022 only reached 86.5%, still below the expected target of more than 90%. Based on these data, the estimated number of TB patient dropouts in Indonesia is still high at more than 10% [8]. Various reasons for patient dropouts such as drug side effects, economic conditions, lack of psychosocial support, and others have an impact on increasing cases of drug-resistant TB with the consequence that sufferers must undergo TB treatment for a longer time, more drug combinations, higher costs and an increased risk of morbidity and mortality due to TB disease [22], [46], [9], [34], [43].

Incomplete TB treatment puts patients at risk of recurrence, increases the severity of the disease, and results in hospitalization due to deterioration in health and complications of the disease. Previous studies conducted in Indonesia and other countries have concluded that many factors play a role in TB patient adherence. The importance of conducting a literature review on factors influencing pulmonary tuberculosis treatment adherence in Indonesia between 2018-2023 is that it will help formulate more effective control strategies to address the burden of disease, understand the impact of social and economic contexts on adherence, identify barriers and opportunities in treatment practices, and provide a basis for developing locally of each region in Indonesia appropriate interventions. The purpose of this literature review is to identify literature related to causal factors associated with medication adherence among TB patients in Indonesia.

2. METHOD

This study used a literature review approach to provide information on treatment adherence among TB patients and the determinants that contribute to it. The literature search was limited to the period between 2018 and 2023. The Scopus and Google Scholar databases were used for the literature search using the following keywords: 'determinants' AND 'adherence' OR 'compliance' OR 'treatment dropout' OR 'lost to follow-up' and tuberculosis OR TB OR TBC. Inclusion criteria for the study were limited to articles written in Indonesian or English, open access, full text availability, and research conducted in Indonesia. Exclusion criteria were applied to articles containing keywords related to other diseases or drug-resistant TB cases. As depicted in Figure 1, the selection flowchart illustrates the process of article selection.

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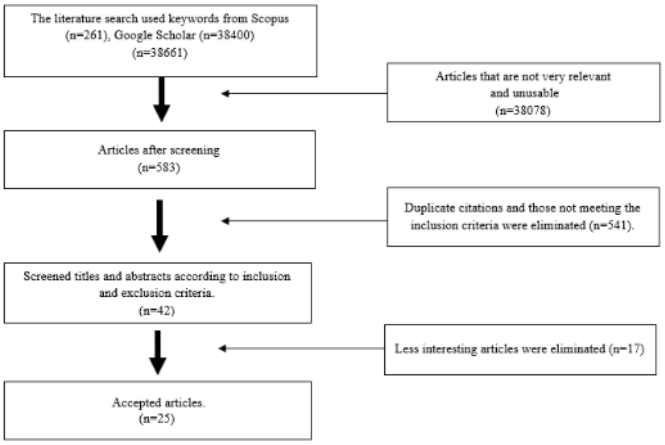

Figure 1. The flow of the article review

3. RESULTS

Based on the search results, 25 articles meeting both inclusion and exclusion criteria were determined as sources for conducting the literature review. A summary of the literature used in the literature review is shown in table 1.

Table 1. Summary of articles used (n=25)

Author	Design	Purpose	Location	Statistic analysis	Result
[41]	Case-control study	Identification of factors associated with non-adherence to TB treatment among patients at a health center in Jayapura, Papua.	Jayapura	Chi-square / Fisher	Access to health services (distance/cost of travel and history of moving within the past year), lack of knowledge, treatment experience, and form of medication given are associated with treatment adherence.
[12]	Cross-sectional	to analyse the determinants of patient medication adherence	Padang	Chi-square & linear logistic regression	The dominant factor influencing drug adherence of pulmonary TB patients was knowledge (p=0.000, OR 29.169), followed by attitude (0.000), education (0.000), employment (0.001), and family support (0.000).
[56]	Case control	to analysed determine the factors associated with adherence to pulmonary tuberculosis treatment.	Subang	Chi-square and multivariate analysis of multiple logistic regression	Factors associated with pulmonary TB treatment adherence were family support (p=0.003; OR=2.956), gender (p=0.045; OR=1.961), education (p=0.045; OR=1.962), occupation (p=0. 043; OR=1.989), knowledge (p=0.005; OR=2.529), drug side effects (p=0.045; OR=1.961), medication supervisor (p=0.000; OR=3.500), health facility distance (p=0.044; OR=1.967), staff attitude (p=0.020; OR=2.172).

[27]	Cross-sectional	To identify relationship between the level of knowledge and motivation of patients with pulmonary tuberculosis with adherence to taking medication.	Menado	Chi-square	There is a relationship between knowledge and motivation of pulmonary tuberculosis patients with adherence to taking medication, the higher the level of knowledge of motivation, the cure can be obtained.
[15]	Cross-sectional	To investigate the determinants of adhering to treatment for TB patients.	Bengkulu	Chi-square & linear regression	Factors such as age, gender, education, income, knowledge, drug availability, and family support positively influenced adherence to anti-tuberculosis treatment, while side effects, distance to health services, and tenure had a negative impact. Income, knowledge, and the role of treatment supervisors indirectly affected adherence.
[42]	Cross-sectional	To determine the education, knowledge and attitude factors associated with adherence to anti-TB drugs in patients with pulmonary TB at the community health center.	Indramayu	Chi-square	There was no relationship between education and OAT consistency (p=0.082); there was a relationship between knowledge (p =0.012) and attitude (p=0.040) with drug consistencies.
[35]	Cross-sectional	To analyse the effect of family factors (family stress levels and family resilience) on medication adherence	Surabaya	Pearson correlation	Family stress levels were mostly in the normal category (86.6%), family resilience was mostly in the good category (79.9%), and moderate TB medication adherence (39.8%). The results of the Pearson correlation test obtained family stress levels (p = 0.004) and family resistance (p = 0.001) with medication adherence.
[3]	Cross-sectional	To analyze Fixed Dose Combination treatment adherence factors in patients	Tangerang	Chi-square	Respondents of productive age as many as 46 (97.9%), while based on bivariate analysis it was found that there was a relationship with knowledge, AOT side effects, distance of residence, PMO role, and health role with a p value< 0.05.

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[36]	Cross sectional	To determine the relationship between the side effects of anti-tuberculosis drug and the role of the medication monitoring officer (PMO) with medication adherence.	Palembang	Chi-square	The frequency distribution of pulmonary TB respondents who adhered to treatment was 37 respondents (72.5%), respondents who experienced low anti-tuberculosis drug side effects as many as 39 respondents (76.5%), respondents the role of good PMO as many as 34 respondents (66.7%). Chi-squared test results showed that there was an association between OAT side effects (p = 0.011) and the role of PMO (p = 0.007) with adherence.
[40]	Cross sectional	To analyze relationships age, gender, education, side effects of treatment, knowledge, attitudes of health workers with medication adherence	Banjarmasin	Fisher exact	The knowledge variable (p = 0.019) was associated with medication adherence. The higher the patient's knowledge, the higher the level of treatment adherence.
[7]	Cross-sectional	To know the determinants of medication adherence	Palembang	Chi-Square & multiple logistic regression	Achieved treatment adherence of 42.8% in tuberculosis patients. There was a significant relationship between perceived benefits (p=0.000; OR=3.556), family support (p=0.000; OR=3.512), health worker support (p=0.001; OR=2.712), knowledge (p=0.018; OR=2.027) and adherence.
[25]	Cross sectional	To find out the relationship between knowledge and attitudes of pulmonary TB patients with medication adherence.	Demak	Chi-Square	There is a relationship between the knowledge and attitude of TB sufferers with medication adherence (p = 0.000)
[57]	Cross sectional	To analyze the factors that related to medication adherence.	Kendari	Chi-Square & logisric regression	Factors that were significantly associated were knowledge (OR 14,909), motivation (OR 6,783), home distance (OR 5,591), family support (OR 4,071), and the role of health workers (OR 11,500) with medication adherence. The knowledge and role of health workers correlate significantly (p=0.001; p=0.003), with a contribution to complianc by 53%.

[26]	Cross-sectional	To determine the influencing factors medication adherence.	Sukabumi	Chi-Square & simple linear regression	Factors associated with medication adherence are age, education level, length of treatment, medication side effects, and family support.
[52]	Case-control	To analysed factors associated with patient withdrawal in community health centers	Gowa-Sulawesi Selatan	Chi-square	There is a relationship between patient knowledge, PMO support, family motivation, side effects. medication, and health worker support with drug withdrawal.
[5]	Cross sectional	To analyze factors related to medication adherence	Surakarta	Chi-square	Most patients were adherent to treatment (79%). Factors associated with medication adherence were the role of health workers (p = 0.045) and PMO (p = 0.035).
[51]	Case-control	To determine the risk factors for non-adherence to treatment.	Mamuju-Sulawesi Barat	Chi-square	Knowledge factors (OR=2.472; 95%CI=1.047-1.058), motivation (OR=4.392; 95%CI=1.795-10.742), PMO (family support) (OR=2.781; 95%CI=1.229-6.291) support (OR=1.28; 95%CI=0.349-3.644) and access to health facilities (OR=1.609); 95%CI=0.670-3.864) are risk factors for non-adherence.
[18]	Cross-sectional	To analyze the factors of Acceptance and Commitment Therapy (ACT)	Medan	Chi-square	There was an association between age (p = 0.004), length of time suffering from TB (p = 0.001), age (p = 0.001) and ACT. There was no relationship between gender with ACT.
[1]	Cross-sectional	To determine the level of treatment adherence	Jambi	Chi-square	A total of 26 respondents (76.47%). The Chi-square test obtained results have a significant relationship with the level of compliance.
[47]	Case control	To analyze the factors that associated with the incidence of drug withdrawal.	Nabire-Papua	Spearman correlation	Family support factors of 0.000, health worker support of 0.003, difficulty in seeing health facilities of 0.002 are related to drug withdrawal.
[49]	Cross-sectional	To know the relationship between the level of knowledge about and adherence to taking medication in tuberculosis patients	Wonogiri	Kendall's Tau correlation	Respondents with a moderate level of knowledge were as much as 55.30% The adherence rate of drinking OAT was high in 44.70% of respondents. Analysis of the relationship between knowledge level and medication adherence level was obtained (p = 0.000; r = 0.489).

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[20]	Cross-sectional	To analysed association factors that are thought to influence the unsuccessful treatment of pulmonary TB patients.	Surakarta	Multivariate logistic analysis	The belief in drug hazards subscale ($p = 0.001$; OR = 8.167), drug overuse subscale ($p = 0.038$; OR = 3.504) and experience of drug side effects ($p = 0.022$; OR = 4.222) were predicted factors influencing non-adherence to anti-tuberculosis drugs.
[13]	Cross-sectional	To identify relationships between self-efficacy and adherence to treatment on pulmonary tuberculosis patients	Depok	Chi-square	Respondents who had a poor self-effectiveness of 53.3%, were correlated with the level of drug compliance on drug intake in lung tuberculosis patients (p=0.004), with OR (1,417).
[45]	Cross-sectional	To analysed relationship knowledge with medication adherence in pulmonary tuberculosis patients in Community Health Centre.	Nias Selatan	Spearman Rho Correlation	There is a knowledge relationship with medication adherence in pulmonary tuberculosis patients ($p = 0.008$, $r = 0.466$)
[29]	Cross-sectional	To analysed determinants the level of compliance and whatever factors influence TB patients in treatment during pandemics.	Surabaya	SEM	Factors influencing adherence are age, education, employment status, marital status, residence, and income. The multiple logistic regression analysis shows that the dominant factor with the greatest influence on adherence is the level of education. Higher educated respondents tend to have a good adherence rate of 22.07 compared to lower educated respondents.

4. DISCUSSION

Medication adherence refers to the extent to which an individual's behaviour in taking medication aligns with changes in their diet or lifestyle, as evaluated by their compliance with recommended and agreed-upon guidelines. Factors associated with medication/therapy adherence were categorized into five WHO adherence dimensions, the first being the socioeconomic dimension (environmental/social factors such as interactions, social context, stigma, norms, external support, and environment; lifestyle factors such as alcohol, drugs; economic factors such as income, education, employment, living conditions, and insurance). The second dimension of the health system includes characteristics of medical personnel such as relationships, communication, understanding trust, treatment practices, and patient education; and factors related to the health care system such as access, regulatory processes, quality of health services, information support, and insurance. The third dimension of the therapy dimension includes treatment regimen factors such as complexity, dose, type, capsule load, clarity of label instructions, and familiarity with the regimen;

treatment impact factors such as side effects, effectiveness, safety, treatment experience; treatment element factors such as cost, physical elements, and prescribing [59], [33].

The fourth dimension of the patient dimension includes psychological and cognitive related factors such as perception, beliefs, and doubts; behavioral factors such as organization, planning, and lifestyle; priority factors such as quality of life, and other competitive needs; non-modifiable characteristics such as demographics, experience, physical factors; family characteristic factors such as doubts, support, and relationships. The fifth dimension, the condition dimension, includes disease control factors such as symptoms, complications, severity, impairment, and influence on lifestyle; disease characteristic factors such as cognitive decline, impairment of symptoms, and consequences, patient-specific factors such as health decline, comorbidities, time since diagnosis [33], [59].

4.1 Socioeconomics

Knowledge is the factor most commonly found to be associated with adherence to taking medication [3], [12], [15], [27], [30], [42], [45], [49], [51], [52], [56]. Knowledge about the disease, how the disease is transmitted, recovery treatment can improve patient compliance with taking medication. This knowledge is sometimes associated with education level. A person with a high level of education is more likely to understand the information presented to increase knowledge related to TB disease. The level of education in several studies was concluded to be associated with adherence to taking medication [15], [26], [29], [56]. In higher education groups it is easier to access information and health facilities, education is closely related to understanding the disease, the risks if not treated. TB patients with a high level of education have a better compliance rate of 22.077 times compared to patients with lower education levels [29].

In addition, information on other diseases associated with TB also affects the success of therapy, one of the comorbidities often found in patients with TB is diabetes mellitus, so sugar control and treatment of comorbidities determine the success of TB therapy [44]. Outdoor work and environmental factors increase the risk of TB infection. Based on gender, the dropout rate in men is higher because they are busy working, so they have less time to visit health facilities, while women are more concerned with health and usually undergo treatment regularly [12], [29]. The patient's economic status and income are also factors related to compliance. Living conditions, costs for treatment, and nutritional status are directly related to income [1], [15], [29]. Nutritional needs, especially protein, are needed for successful treatment, nutrition will have an impact on immune status indirectly [24], [14].

4.2 Health System

Health facilities that are easily accessible from residential locations, health workers, diagnostic support facilities, availability of pharmacy installations, as well as information media facilities, and modern technology facilities are associated with adherence to therapy. Support from health workers is needed, and promotive health efforts such as counseling and education to prevent TB transmission need to be carried out actively. In addition, information about the symptoms of the disease, the drugs to be given, and the length of treatment has an impact on adherence to taking medication [7], [15], [17], [31], [38], [41], [47], [51], [54], [56]. A range of interventions, both cognitive and behavioural, need to be implemented by health professionals and patients' families to increase the level of knowledge and awareness of patients [58], [6].

The development of technology utilisation in the health system to monitor patient compliance and complaints during treatment has a positive impact on patients and health workers in doing their work [23], [48]. Hospital infrastructure development and supporting facilities are needed, as well as facilities, infrastructure, and supporting examination facilities to support the successful treatment of TB patients [32].

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4.3 Drug Therapy

TB is divided into several categories, namely drug-sensitive tuberculosis, drug resistance, multidrug-resistant tuberculosis, and XDR tuberculosis. Depending on these categories, the type and duration of therapy will vary. In the case of drug-sensitive TB, 4 types of drugs are given in the form of a combination fix in the first 2 months and continued with 2 types of drugs for 4 months, so that the minimum therapy period is 6 months [21], [39]. The availability of complete drugs, as well as clear information to patients about drug use, and possible side effects that will arise can increase patient compliance with taking medication [3], [15], [17], [26], [36], [56]. Information about the course of the disease, complications of the disease if not treated and the consequences of drug withdrawal need to be conveyed to patients and become the knowledge of TB patients. Monitoring complaints that arise during drug use is very important, this is part of pharmacovigilance, all complaints submitted need to be recorded and analyzed further. The implementation of pharmacovigilance by health workers provides benefits for patient safety [55], [37]. Information about side effects needs to be conveyed to medical staff and needs to be responded well so that patients do not become afraid of drugs, drug supervisors play an important role in completing treatment, information related to drug side effects and need to be conveyed to health workers need to be informed to drug supervisors [2], [28]. The side effects of drugs that are felt have an impact on daily activities so that patients will stop self-medication [11], [26], [35], [52]. Long treatment periods increase the risk of drug withdrawal, drug administration in the intensive phase in the first 2 months patients will feel the benefits of therapy or better conditions and will stop self-medication. Regarding the length of treatment, patients who undergo ≥2 months of therapy will have a 2.7 times risk of being irregular in taking medication [10].

4.4 Patient

Patients with pulmonary TB are more commonly found in the male gender, and at productive age [15], [17], [29], [56]. Patients with TB more in men are associated with a history of smoking habits and daily activities outside the home and breadwinners for the family. Age shows a relationship with acceptance and commitment to undergo therapy so that it will increase adherence to taking medication [18]. Family support factors are concluded to be associated with adherence to TB patient therapy [7], [12], [15], [16], [17], [26], [47], [56]. Family support in the form of family acceptance and acceptance of the patient's disease condition will provide added value for patients while undergoing acceptance. The family is the closest person who understands the patient's disease complaints, the patient's therapy process. The family can be a drug supervisor, so it is necessary to conduct training for drug supervisors so that they can understand their functions and duties properly [5], [50].

TB patients with married status show better compliance, support from spouses or children in undergoing long-term TB therapy. Widow/widower status is more likely to drop out compared to married or unmarried groups [29]. Lifestyle is associated with attitude. Attitudes will shape behavior in accordance with the beliefs and beliefs of the patient. An increase in attitude will increase compliance with taking medication [25]. Attitude is a reaction to a person's interval which is influenced by personal experience, environment, and people around, religion, emotional factors. Attitudes will shape behavior to prevent transmission, maintain hygiene and healthy living behaviors to support the success of therapy in addition to adherence to taking medication [3], [7], [12], [41], [42].

4.5 Condition

Among the various concomitant diseases associated with TB, diabetes mellitus and depression are two of the most common non-communicable diseases among TB patients worldwide. It is important to carefully consider these conditions when providing medical care, as TB patients with diabetes mellitus (TB-DM) or depression are at a higher risk of death, relapse, and recurrence. When a patient is diagnosed with both TB

and DM, it can lead to a compounding negative impact on their health. TB-DM patients with high blood glucose levels may experience decreased effectiveness of anti-tuberculosis drugs. However, it is possible that higher doses of anti-TB drugs could help to reduce the incidence of DM drug effects [14], [4].

TB treatment usually lasts for a minimum of 6 months, which may result in a high rate of lost to follow up (LTFU) among patients, especially during the first 3 months of treatment. It has been observed that patients with a history of hospitalization due to TB are comparatively less likely to experience LTFU than other patients. Furthermore, it is worth noting that patients who arrive at the hospital with urgent symptoms, such as high fever, chest pain, coughing up blood, and shortness of breath, may be less likely to experience loss to follow-up. This information may serve as an incentive for patients to seek medical attention, consult with experienced physicians for guidance and treatment, manage their condition, and avoid the progression of more serious complications [19].

There are several other factors associated with therapy adherence based on the literature search, including distance to health facilities, transportation costs, location of residence, distance of tenure. The limitation of this literature search is that there is a risk of research bias, and this literature review attempts to synthesize findings from multiple studies, the risk of misinterpretation and synthesis of data remains, especially as the included studies may vary in methodology, sample size, and the context of the crisis studied.

5. CONCLUSION

Socioeconomic and health system dimensions dominate TB patient treatment adherence. Adherence is key to successful treatment. TB treatment management is complex, with many factors involved. This makes it possible to develop multidisciplinary and integrated policies in an effort to achieve TB elimination in Indonesia.

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AUTHORS' CONTRIBUTIONS

Conceptualization: M, AB Data curation: M, Y, EM, LTM, A. Formal analysis: PM, AB. Methodology: M, AB, Pr. Writing of original draft: M. Writing of review and editing: LTM, A, Pr.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest in this study.

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