



Determinants of Tuberculosis Treatment Outcomes in Asia and Africa



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Abstract

Tuberculosis (TB) is a disease that is both infectious and deadly. Although it can be prevented and treated, the increasing number of TB patients is a nationwide and global challenge, and thus it requires efforts to control the disease appropriately leading to good treatment outcomes. Identifying the determinants of treatment outcomes is necessary to improve control strategies and programs for TB. Scientific evidence on this issue is still limited. This systematic review aims to describe the potential determinants of TB treatment outcomes regarding the patient's internal and external factors. The review was carried out using the procedures specified in the PRISMA guidelines. Five databases were used to identify studies related to the determinants of treatment outcomes obtained. 829 articles were meeting the screening criteria, 23 met the criteria for full article review and 21 for analysis. Most scientific evidence reports the age, sex, HIV status, and location of TB as determinants of treatment outcomes. Sorting and selecting data consistently is necessary for reporting the results of TB treatment which then becomes the foundation for formulating appropriate, targeted, effective, and most needed policies or interventions in improving treatment outcomes and reducing the incidence of TB.

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1 Introduction

Infectious diseases are a major cause of morbidity and mortality in poor and developing nations (Muluye et al., 2018). TB is an infectious disease, and it is the leading cause of death as an infectious agent (WHO, 2020). The global commitment to dealing with TB is embodied in the sustainable development goals (SDGs) and the implementation of the 'End TB Strategy' with the reduction of TB incidence and mortality as the established target. In 2019, the number of TB incidents in the world was 7.1 million cases, an increase from the previous year, with 1.2 million deaths, and there were 177,099 cases of TB which are resistant to various drugs or Rifampicin (WHO, 2020). Geographically, countries with high TB caseloads are low- and middle-income countries in Southeast Asia, Africa, and the Western Pacific (WHO, 2020). In poor and developing countries, populations are living in disadvantaged conditions, characterized by low education, inadequate housing, deficient nutrition, and low economic levels. TB generally occurs in poor and developing countries (Umeokonkwo et al., 2020). These conditions ultimately lead to further transmission of TB and poor treatment outcomes.

TB disease can be prevented and treated. Through a minimum of six months of treatment, about 85% of TB patients are successfully cured (WHO, 2020). A long period of treatment can cause patients to feel bored and not comply with treatment rules. Treatment has benefits as an effort to cure, prevent a recurrence, prevent death, prevent resistance of bacteria to Antituberculosis Drugs (ATD), and reduce further transmission of infections (WHO, 2020). Correct TB treatment is very important to improve treatment outcomes. The treatment success rate is the percentage of all cases of tuberculosis that have recovered and received complete treatment among all the cases of tuberculosis that are treated and reported (Kementerian Kesehatan RI, 2020). The success rate of TB treatment globally in 2018 was 85%, but this is still behind the WHO (World Health Organization) target of 90% (WHO, 2020).

Adverse treatment outcomes, especially mortality and dropouts, have made control of TB difficult, and these outcomes increase the risk of transmission and drug resistance, and they are correlated with an increased incidence of TB. Globally, in 2019 there were half a million people who developed Rifampicin-resistant TB, and 78% of that number had Multidrug-Resistant TB (WHO, 2020). Drug-resistant bacilli types pose a greater risk to human health, require longer treatment time with more complex drugs, and have poorer treatment outcomes. For this reason, WHO recommends that treatment outcomes be evaluated annually. The monitoring of treatment outcomes provides evidence to assess the effectiveness of TB control programs (Ahmad et al., 2020).

TB treatment outcomes are influenced by internal and external factors of the patient. However, previous studies that separately identify internal and external determinants (the terms *factor* and *determinant* are used interchangeably in this manuscript) of TB treatment outcomes have not been found (Freundlich et al., 2010). The Ethiopian study examined general determinants, and it cited age, the distance to health care facilities, and HIV (Human Immunodeficiency Virus) status as predictors for successful TB treatment outcomes, with an overall successful treatment outcome of 80.8% (Tesema et al., 2020; Yeh et al., 2005). The study in India also identified factors of TB treatment outcomes in general, including gender and distance to health care facilities, with a successful treatment outcome of 51.5% (Sahyog et al., 2018; Widana et al., 2021). Research related to the factors and outcomes of TB treatment is also mostly conducted in limited populations, so it is not generalizable to a region (Son et al., 2021) and has not been optimal in providing additional information for national and global TB programs for the implementation of targeted interventions to achieve TB elimination by 2030. This is especially true for countries with a high TB incidence. This is supported by a study in India on factors of treatment outcomes in TB patients, and it was only conducted in one district in central India (Mundra et al., 2019). The study in Ethiopia regarding TB treatment outcomes and their factors was also conducted in a limited area of three health facilities in the City of East Wollega (Muluye et al., 2018). Similarly, a study in South Korea on factors of TB treatment outcomes was conducted only to evaluate cases in the

country (Son et al., 2021; Fattakhov et al., 2021; Tilyakov et al., 2021). Thus, it is important to understand the patient's internal and external factors of treatment outcomes in countries with high TB caseloads, so appropriate corrective actions can be planned to lead to prioritizing the improvement of treatment outcomes in reducing TB incidence and mortality. Therefore, this study aims to conduct a systematic review of the determinants and outcomes of TB treatment in Asia and Africa as regions with high TB burden, so it can serve as evidence for policymakers in making decisions.

2 Materials and Methods

This systematic review used the procedures specified in the PRISMA guidelines as a guide for reporting systematic reviews and meta-analyses (Page et al., 2021). Inclusion criteria are studies that reported the determinants and outcomes of TB treatment, have access to a full text, are in English, and are published in the last ten years, considering that the increase in TB has occurred in several countries in Asia and Africa since 2013 (WHO, 2020), which is in line with the results of the study that an increase in TB diagnoses in Nigeria has occurred since 2010, and an increase in TB incidence in Ethiopia has occurred since 2012 (Muluje et al., 2018; Oladimeji et al., 2021). Articles will be excluded if the study location is not in the Asian and African continents, the study design is a systematic review, or the study population is MDR TB patients or TB with comorbidities. The research questions were based on PICO (patient, intervention, comparative, outcome), P: TB patients in Asia and Africa, I: determinants, C: none, O: TB treatment outcomes. Thus the research question is: what factors determine the outcome of TB treatment?.

Systematically, the literature search used five databases, namely ProQuest, EBSCOhost, Sage, SpringerLink, and ScienceDirect to retrieve articles published between 2011 and 2021. The keywords were based on independent terms with the following boolean operator tuberculosis AND treatment outcomes AND determinant. The literature search results are stored in a RIS format and entered into Mendeley, and the duplicates are deleted. The titles and abstracts acquired were thoroughly assessed to exclude publications that did not meet the inclusion criteria. Extraction of information on eligible studies includes the author, year of publication, study period, country, study design, sample size, eligibility criteria, determinants and treatment outcomes determined based on WHO criteria, and 95% confidence interval (CI) reported by the authors.

3 Results and Discussions

3.1 Results

Selection of studies

Screening of five databases with the preset search terms identified 875 articles. There were 46 duplicate articles, 806 articles not following the research objectives, and 2 articles with unclear results. In the end, 21 articles met the review criteria. The study selection process is shown in the PRISMA flowchart in Figure 1.

Description of selected studies

In the final analysis, there were 21 studies from 13 countries grouped into two continents, namely 10 studies from countries on the African continent including Ethiopia (3 studies), Nigeria (3 studies), Uganda (1 study), Mozambique (1 study), Zimbabwe (1 study), Ghana (1 study), and 11 studies from the Asian continent including the following regions: India (4 studies), Malaysia (1 study), South Korea (1 study), Pakistan (1 study), China (1 study), Turkey (1 study), Iran (2 studies). Based on these studies, 17 studies reported on the determinants and outcomes of TB treatment in pediatric and adult patients, and 4 studies reported only on pediatric TB patients aged 1 to 15 years. There were 8 cross-sectional studies, 12 retrospective cohort studies, and one retrospective observational study that identified the determinants and outcomes of TB treatment. The study findings can be seen in Table 1. The determinants were identified as either internal or external to the patient or both. TB treatment outcomes were reviewed based on WHO criteria. TB treatment outcome is the result acquired after starting TB treatment. The results of successful treatment are the number of patients

cured and a complete course of treatment (Kementerian Kesehatan RI, 2020). The outcome of unsuccessful treatment is the number of dropouts, treatment failure, and mortality (Kementerian Kesehatan RI, 2020).

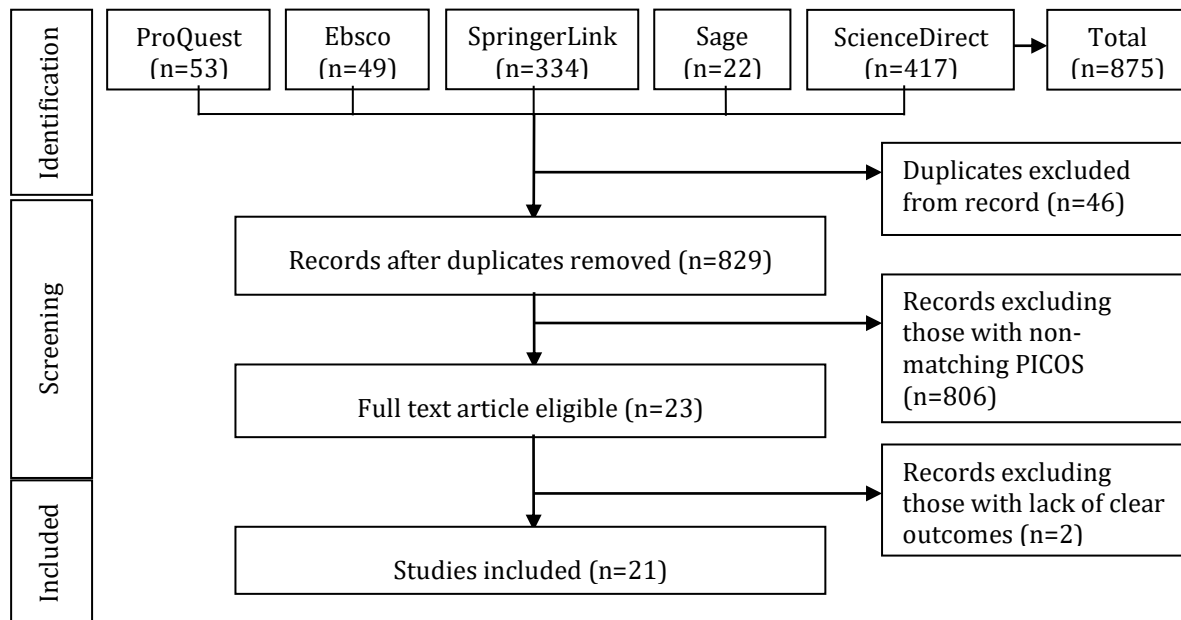


Figure 1. PRISMA flowchart of the study selection and inclusion process

TB treatment outcomes

Regarding treatment outcomes, there was variability in TB treatment outcomes among the studies. In general, the general outcome of successful treatment is satisfactory, though four studies reported very low treatment outcomes. Three of the 11 studies in Asia and two of the 10 studies in Africa succeeded in achieving treatment outcomes following the WHO target of 90% (WHO, 2020). Overall, the highest successful TB treatment outcomes were in Asia, namely at 95.0%, and the lowest was 51.5%, while in Africa it was 92.2% and 56.5%, respectively.

Table 1
Study characteristics and treatment outcomes

Reference	Author	Year	Country	Method	Number of TB patients	Treatment outcome		Determinant
						Successful outcome	Unsuccessful outcome	
Studies from Asia								
(Ahmad et al., 2020)	Ahmad et al.	2020	Pakistan	Cohort retrospective	515	86.2 %	13.8 %	Internal, external
(Sahyog et al., 2018)	Sahyog et al.	2018	India	Cohort retrospective	4,979	51.5 %	48.5 %	Internal, external
(Son et al., 2021)	Son et al.	2021	South Korea	Cohort retrospective	137,901	81.6 %	18.4 %	Internal
(Mundra et al., 2019)	Mundra et al.	2019	India	Cohort	510	81.9 %	18.1 %	Internal
(Banerjee, Bandyopadhyay, Taraphdar, & Dasgupta, 2020)	Banerjee S, Bandyopadhyay K, Taraphdar P, Dasgupta A	2020	India	Cross-sectional	140	79.3 %	20.7 %	Internal, external

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Reference	Author	Year	Country	Method	Number of TB patients	Treatment outcome		Determinant
						Successful outcome	Unsuccessful outcome	
(Atif et al., 2014)	Atif et al.	2014	Malaysia	Cross sectional	336	67.3 %	32.7 %	Internal
(Wen et al., 2018)	Wen et al.	2018	China	Cohort retrospective	22,998	95.0 %	5.0 %	Internal
(Babalik, Kiziltas, Gencer, & Kilicaslan, 2014)	Babalik, Kiziltas, Gencer, Kilicaslan.	2014	Turkey	Cohort retrospective	23,845	94.0 %	6.0 %	Internal
(Khazaei et al., 2016)	Khazaei et al.	2016	Iran	Cross sectional retrospective	510	83.1%	16.9 %	Internal
(Sadana, Verma, & Nagpal, 2020)	Sadana, Verma, Nagpal.	2020	India	Cross sectional	62	93.6 %	6.4 %	Internal, external
(Mohammadzadeh, Ghayoomi, & Maghsoudloo, 2016)	Mohammadzadeh, Ghayoomi, Maghsoudloo.	2016	Iran	Cohort retrospective	167	85.6 %	14.4 %	Internal
Studies from Africa								
(Muluye et al., 2018)	Muluye et al.	2018	Ethiopia	Cross sectional	995	91.9 %	8.1 %	Internal, external
(Umeokonkwo et al., 2020)	Umeokonkwo et al.	2020	Nigeria	Cohort retrospective	1,070	56.5 %	43.5 %	Internal
(Tesema et al., 2020)	Tesema et al.	2020	Ethiopia	Cross sectional	328	80.8 %	19.2 %	Internal, external
(Oladimeji et al., 2021)	Oladimeji et al.	2021	Nigeria	Cohort retrospective	1,337	78.1 %	21.9 %	Internal, external
(Habte et al., 2020)	Habte et al.	2020	Ethiopia	Cohort retrospective	2,557	92.2 %	7.8 %	Internal, external
(DesJardin, Chirenda, Ye, Mujuru, & Yang, 2020)	DesJardin, Chirenda, Ye, Mujuru, & Yang.	2020	Zimbabwe	Cross sectional	853	56.9 %	43.1 %	Internal, external
(Ogbudebe et al., 2018)	Ogbudebe et al.	2018	Nigeria	Cohort retrospective	724	83.0 %	7.0 %	Internal, external
(Mulogo, Nahabwe, Bagenda, & Batwala, 2017)	Mulogo, Nahabwe, Bagenda, Batwala.	2017	Uganda	Cross sectional	128	89.8 %	10.2 %	Internal, external
(García-Basteiro et al., 2016)	García, Basteiro et al.	2016	Mozambique	Observational retrospective	1,957	71.2 %	28.8 %	Internal
(Tetteh, Agyarko, Otchere, Bimi, & Ayi, 2018)	Tetteh, Agyarko, Otchere, Bimi, Ayi.	2018	Ghana	Cohort retrospective	213	89.2 %	10.8 %	Internal

Internal factors

Internal factors are determinants that come from within the TB patient, which can be in the form of demographic characteristics, behavior, and other determinants. Based on the articles reviewed, internal factors as determinants of TB treatment outcomes were included in all articles. Internal factors consist of 11 determinants from within the TB patient, namely age, gender, education, HIV status, TB location, treatment category, alcohol consumption, drug use, smoking, type of ARB (Acid Resistant Bacteria), and comorbidities (Ahmad et al., 2020; Atif et al., 2014; Babalik et al., 2014; Banerjee et al., 2020; DesJardin et al., 2020; García-Basteiro et al., 2016; Habte et al., 2020; Khazaei et al., 2016; Mohammadzadeh et al., 2016; Mulogo et al., 2017; Muluye et al., 2018; Mundra et al., 2019; Ogbudebe et al., 2018; Oladimeji et al., 2021; Sadana et al., 2020; Sahyog et al., 2018; Son et al., 2021; Tesema et al., 2020; Tetteh et al., 2018; Umeokonkwo et al., 2020; Wen et al., 2018). 13 articles described age as an internal factor for TB treatment outcomes (Ahmad et al., 2020; Atif et al., 2014; Babalik et al., 2014; Habte et al., 2020; Mundra et al., 2019; Ogbudebe et al., 2018; Oladimeji et al., 2021; Sadana et al., 2020; Son et al., 2021; Tesema et al., 2020; Tetteh et al., 2018; Umeokonkwo et al., 2020; Wen et al., 2018). The likelihood of a successful treatment outcome was higher among patients aged 15-24 years, compared to patients younger than 14 years (Tesema et al., 2020), and over 61 years (Ahmad et al., 2020; Habte et al., 2020). The determinants of TB treatment outcomes can be seen in Table 2.

Gender is the next internal factor, and it was reviewed by 11 articles. The treatment failure rate in men was higher than that in women (Atif et al., 2014; Babalik et al., 2014; Banerjee et al., 2020; García-Basteiro et al., 2016; Khazaei et al., 2016; Mohammadzadeh et al., 2016; Muluye et al., 2018; Mundra et al., 2019; Oladimeji et al., 2021; Sahyog et al., 2018; Son et al., 2021). Women are known to show better treatment outcomes as well as lower dropout rates and mortality. Seven other studies identified HIV status as a determinant of treatment outcomes (García-Basteiro et al., 2016; Habte et al., 2020; Khazaei et al., 2016; Ogbudebe et al., 2018; Oladimeji et al., 2021; Tesema et al., 2020; Umeokonkwo et al., 2020). Negative HIV status increases the likelihood of a successful treatment outcome.

The location of TB as a determinant of treatment outcome was identified by eight studies. One study reported a higher probability of successful treatment outcomes in smear-positive PTB patients than in extrapulmonary TB patients (Ahmad et al., 2020). However, seven studies argue otherwise (Atif et al., 2014; Mundra et al., 2019; Oladimeji et al., 2021; Sadana et al., 2020; Son et al., 2021; Tetteh et al., 2018; Wen et al., 2018). Three articles cited the medication category as a cause of unfavorable TB treatment outcomes (Ahmad et al., 2020; Banerjee et al., 2020; Mundra et al., 2019). Patients with category one TB treatment had a higher successful treatment outcome than those with category two. The results of the sputum examination were stated to affect TB treatment outcomes by two articles (Atif et al., 2014; DesJardin et al., 2020). Positive sputum smear results increase the chance of poor treatment outcomes and risk of death.

Education was also identified as a determinant of TB treatment outcomes by one article (Atif et al., 2014). TB patients who received education have a higher chance of recovering than those who never attended a school (Reis-Santos et al., 2019). Furthermore, one article each identified narcotic use (Mohammadzadeh et al., 2016), alcohol consumption, comorbid diabetes, and smoking (Atif et al., 2014) as independent determinants of the longer treatment duration, higher mortality rate, and lower cure rate.

External factors

External factors are determinants that originate from outside or from the TB patient's environment. Based on a review of all articles, eight external factors were found to be determinants of TB treatment outcomes, including the location of health care facilities, DOTS (Directly Observed Treatment Shortcourse) program, diagnosis method, contact history, year of diagnosis, discrimination, counseling, and attitude of medical staff (Ahmad et al., 2020; Banerjee et al., 2020; DesJardin et al., 2020; Habte et al., 2020; Mulogo et al., 2017; Muluye et al., 2018; Ogbudebe et al., 2018; Oladimeji et al., 2021; Sadana et al., 2020; Sahyog et al., 2018; Tesema et al., 2020). External factors were identified by 11 articles.

Table 2
Determinants of Tuberculosis Treatment Outcomes

Determinant	Number of studies	Reference
Internal Factor		
Age	13	(Ahmad et al., 2020; Atif et al., 2014; Babalik et al., 2014; Habte et al., 2020; Mundra et al., 2019; Ogbudebe et al., 2018; Oladimeji et al., 2021; Sadana et al., 2020; Son et al., 2021; Tesema et al., 2020; Tetteh et al., 2018; Umeokonkwo et al., 2020; Wen et al., 2018)
Sex	11	(Atif et al., 2014; Babalik et al., 2014; Banerjee et al., 2020; García-Basteiro et al., 2016; Khazaei et al., 2016; Mohammadzadeh et al., 2016; Muluye et al., 2018; Mundra et al., 2019; Oladimeji et al., 2021; Sahyog et al., 2018; Son et al., 2021)
TB location	8	(Ahmad et al., 2020; Atif et al., 2014; Mundra et al., 2019; Oladimeji et al., 2021; Sadana et al., 2020; Son et al., 2021; Tetteh et al., 2018; Wen et al., 2018)
HIV status	7	(García-Basteiro et al., 2016; Habte et al., 2020; Khazaei et al., 2016; Ogbudebe et al., 2018; Oladimeji et al., 2021; Tesema et al., 2020; Umeokonkwo et al., 2020)
Treatment category	3	(Ahmad et al., 2020; Banerjee et al., 2020; Mundra et al., 2019)

Determinant	Number of studies	Reference
ARB type	2	(Atif et al., 2014; DesJardin et al., 2020)
Education	1	(Atif et al., 2014)
Drug use	1	(Mohammadzadeh et al., 2016)
Alcohol consumption	1	(Atif et al., 2014)
Smoking habits	1	(Atif et al., 2014)
Diabetes as comorbidity	1	(Atif et al., 2014)
External Factor		
Location of healthcare facilities	3	(DesJardin et al., 2020; Sahyog et al., 2018; Tesema et al., 2020)
Diagnostic method		
Year of TB diagnosis	3	(Ogbudebe et al., 2018; Oladimeji et al., 2021; Sadana et al., 2020)
DOTS Program	2	(Ahmad et al., 2020; Oladimeji et al., 2021)
Discrimination	1	(Habte et al., 2020)
Counseling	1	(Banerjee et al., 2020)
Attitude of medical staff	1	(Sadana et al., 2020)
Contact history	1	(Mulogo et al., 2017)
	1	(Mulogo et al., 2017)

Three articles identified health facility location as a determinant of treatment outcomes (DesJardin et al., 2020; Sahyog et al., 2018; Tesema et al., 2020). Patients who are close to a health facility, namely located less than five kilometers away, have better treatment outcomes than those who are far from the treatment location (Tesema et al., 2020). The method of diagnosis as a determinant of the TB treatment outcome was observed in three articles (Ogbudebe et al., 2018; Oladimeji et al., 2021; Sadana et al., 2020). Patients diagnosed through gen expert examination tend to have poorer treatment outcomes than diagnosis through bacteriological examination (Oladimeji et al., 2021). Two articles mention that the year of diagnosis affects the outcome of TB treatment (Ahmad et al., 2020; Oladimeji et al., 2021). TB patients treated before 2013/2014 have a higher chance to achieve better treatment outcomes. Furthermore, the DOTS program as a factor influencing treatment outcomes was identified by two articles (Habte et al., 2020). The DOTS program has contributed to improving good treatment outcomes. TB patients enrolled in a DOTS program had a higher chance of recovery than TB patients who were not enrolled in DOTS (Reis-Santos et al., 2019).

Furthermore, each article mentions the history of contact with a TB patient (Sadana et al., 2020), discrimination (Banerjee et al., 2020), counseling, and attitude of the medical staff as factors influencing treatment outcomes (Mulogo et al., 2017). History of contact with TB patients in pediatric TB patients was identified as a determinant of the treatment outcome (Sadana et al., 2020). Child TB patients who have no history of contact with other TB patients have better treatment outcomes than those who have a history of contact (Sadana et al., 2020). Counseling in TB patients has been shown to improve treatment completion (Mulogo et al., 2017). Meanwhile, the poor attitude of health workers made patients feel uncomfortable causing some to stop their treatment (Mulogo et al., 2017).

3.2 Discussions

TB treatment outcomes

At present, efforts to cure TB are challenged by increasing drug resistance worldwide. Based on all the articles reviewed, there are differences and variability in TB treatment outcomes that could be due to study time, sample size, and geographic variations (Tesema et al., 2020). Among the Asian and African countries studied, one in three studies in India reported the lowest treatment outcome (Sahyog et al., 2018), and one study in China reported the highest treatment outcome (Wen et al., 2018). The differences in the characteristics and determinants of individual health involved in each study mean that direct comparisons between countries are to be treated with caution (Rose, 2000). Based on the review, unsuccessful TB treatment outcomes were largely due to high dropout rates, failure, and mortality rates. That is an alarming situation that requires further action (Sahyog et al., 2018).

A dropout is defined as a TB patient who does not take ATD for two consecutive months or more while the treatment process is still ongoing (WHO, 2020). Dropping out of TB therapy is dangerous for patients, their families, and their environment. Consumption of ATDs that stop before the end of treatment duration results

in drug resistance and makes TB more difficult to treat, and it also increases the risk of transmission and requires more complex drugs (WHO, 2020). The complexity and long duration of the currently available treatment regimens for TB can make patients feel bored and discontinue treatment due to a lack of knowledge about the disease and its treatment. A person's knowledge about TB treatment and cure has been shown to increase adherence, so good treatment results can be achieved (Haq, Nasim, & Kakar, 2020). Low adherence increases the risk of poor treatment outcomes, including treatment failure, recurrence, and development or strengthening of drug resistance (Alipanah et al., 2018). The treatment program must be adhered to properly so that TB can be cured.

Deaths that occur in the intensive phase are a reflection of delayed TB treatment (Sahyog et al., 2018), so increasing efforts to find cases, checks, and early treatment should be the focus, especially in four countries in Asia and Africa, namely India, Indonesia, the Philippines, and South Africa as these four countries are the largest contributors of global TB cases (WHO, 2020). Intensive efforts are needed to increase access to diagnosis and treatment. Finding and overcoming barriers at the system and patient-level in seeking treatment could be the solution (Sullivan, Esmaili, & Cunningham, 2017). Contact investigation for TB case findings can be done through the active participation of health cadres in the community. Early diagnosis and initiation of TB treatment should be conducted through the WHO diagnostics and treatment algorithm (WHO, 2020).

In general, the high achievement of successful treatment outcomes in some of the countries reviewed in this study is evidence of the good performance of TB control (Wen et al., 2018). This is in line with the results of other studies that reported an increase in good TB treatment outcomes in recent years, which is related to an increase in the quality of services and TB control (Habte et al., 2020). Quality of care and TB control is achieved through policies and the social welfare of the people in a country, and this can explain better treatment outcomes (Chemtob & Ogum, 2020). Monitoring of TB treatment outcomes is essential to assess the effectiveness and improvement of interventions and identify potential barriers to their control. The development of digital health technology, adherence interventions, and psychological interventions are also known to have led to better treatment outcomes (Whitelaw et al., 2020).

The commitment to ending TB requires collaboration and coherence to effectively address its multiple determinants. This study provides input to health care facilities that age, gender, location of TB, HIV status, and other determinants are relevant indicators that must be considered for better TB diagnosis and treatment outcomes, and they must be displayed separately as determinants that cause inequalities in improving TB treatment outcomes (Nguyen et al., 2020). Thus, consistently sorting and examining data is necessary for reporting treatment outcomes for TB patients.

Internal factors

The systematic review identified internal factors as determinants with the highest impact on TB treatment outcomes. It has been described previously that age is associated with TB treatment outcomes (Kurtieva et al., 2021). Age influences the possibility of the younger population (15 to 24 years old) to have the ability to reach the location of health care facilities, enthusiasm to adhere to treatment advice, and a better immune system than that of children and older individuals (Tesema et al., 2020). However, at an older age, there are a physiological decline and comorbidities thus achieving a worse treatment outcome. Another study reported a similar account that new TB cases of patients aged over 45 years had an increased risk of TB treatment failure (Wen et al., 2018). Old age is a major risk factor for death in TB patients (Son et al., 2021). TB treatment outcomes are also influenced by gender. The difference in roles and lifestyles between men and women is a determining factor for treatment outcomes (Velázquez et al., 2021). The mobility and complexity of men's activities as breadwinners can affect the irregular consumption of ATD resulting in treatment failure and poorer treatment outcomes. Men's health-seeking behavior is known to be lower than that of women, and they often seek medical treatment after suffering from the disease at an advanced stage (Tetteh et al., 2018). In addition, several studies have reported that risk behaviors such as alcohol consumption, smoking, and drugs for men may lead to poor treatment outcomes (Atif et al., 2014; Son et al., 2021).

Immunity status in HIV coinfecting patients further explains the possible poor treatment outcomes (Umeokonkwo et al., 2020). Treatment of coinfecting TB/HIV presents a greater challenge for patients (Umeokonkwo et al., 2020). Adverse drug interactions and concomitant toxicity of taking ARVs

(Antiretrovirals) and daily antituberculosis drugs for long periods are likely to lead to non-adherence and treatment failure (Adamu et al., 2018). This is in line with a study in Vietnam that stated that TB/HIV patients were associated with poorer treatment outcomes and higher dropout rates (Vo et al., 2020). A study in Mozambique showed that during TB treatment, HIV-infected patients were also 2.3 times more likely to die than TB patients who were not infected with HIV (García-Basteiro et al., 2016). HIV-positive people have higher immunosuppression, lower CD4 cell counts, and are often paucibacillary, so they are less likely to have a smear-positive result, which in turn causes delays in diagnostics and contributes to poor treatment outcomes (García-Basteiro et al., 2016).

The location of TB as a determinant of treatment outcome has two different explanations (Ahmad et al., 2020; Atif et al., 2014; Mundra et al., 2019; Oladimeji et al., 2021; Sadana et al., 2020; Son et al., 2021; Tetteh et al., 2018; Wen et al., 2018). The first explanation is related to better treatment outcomes in pulmonary TB patients compared to extrapulmonary TB patients. Evaluation of the results of AFB and chest X-rays in pulmonary TB patients carried out at the end of the intensive phase and the continuation phase can become the best information in determining the next course of treatment, thereby improving treatment outcomes. The second explanation is related to better treatment outcomes in extrapulmonary TB patients than pulmonary TB patients, which is supported by studies that state that after treatment initiation, the survival of extrapulmonary TB patients is longer than that of pulmonary TB patients (García-Basteiro et al., 2016). Pulmonary TB patients with cavitation have less chance of achieving successful treatment outcomes (Wen et al., 2018). However, a study in Vietnam is not in line with the results of the two studies above. This study reported the same success rate in both cases and stated that smear-negative pulmonary TB and extrapulmonary TB patients showed better treatment outcomes than other TB cases (Vo et al., 2020). The outcome of treatment in cases of pulmonary TB can be affected by the presence of extensive lesions in the lungs that can increase mortality (Atif et al., 2014). Thus, there are other conditions related to the location of TB that also affect the outcome of treatment.

TB treatment is provided based on WHO recommendations, including through two types of categories. Category one treatment is given to new TB patients, while category two is given to TB patients with a relapse and treatment failure, and it is also for patients who dropped out. The treatment category was reported as a factor influencing treatment outcome (Ahmad et al., 2020; Banerjee et al., 2020; Mundra et al., 2019). Unfavorable treatment outcomes were reported to be higher in category two than in category one (Banerjee et al., 2020). The type of TB patients treated in category two is likely to lead to an increase in poor outcomes. Education is an internal factor that influences the outcome of TB treatment. Low education can be an obstacle in increasing patient knowledge about TB, thus making it a barrier in completing treatment. Lack of knowledge related to the treatment process can cause TB patients to stop taking ATD, and they are confirmed by a clinician to be cured (Atif et al., 2014).

Sputum microscopic examination of ARB (Acid-Resistant Bacteria) is a bacteriological TB diagnostic test that is efficient, precise, and reliable, and it aims to find TB germs and works as an evaluation for the treatment given (Tetteh et al., 2018). Sputum examination of ARB is a WHO guideline for diagnosing TB cases and treatment. Symptom screening with chest X-ray examination and AFB sputum will improve the detection of TB cases and provide information on a positive and progressive response to treatment, so there is a possibility of better treatment outcomes (Aung et al., 2013). The presence of smear-positive at the time of diagnosis is known to increase the unfavorable outcome of treatment compared to smear-negative (Desjardin et al., 2020). Positive sputum smears contain germs with a higher rate of transmission and require sputum conversion time, thus increasing the risk of treatment failure and death (Wen et al., 2018). Once treatment starts, smear-positive pulmonary TB patients continue to excrete viable bacilli for varying lengths of time (Tetteh et al., 2018). A study in Ghana reported 8.4% of smear-positive pulmonary TB patients still had AFB after 2-3 months of treatment, and at the end of 5-8 months of treatment 1.9% of patients still did not experience a conversion, continuing to excrete live bacilli (Tetteh et al., 2018). This is a condition that can lead to treatment failure.

Drug use is associated with low cure rates (Reis-Santos et al., 2019). A prospective cohort study in Brazil determined that drug use was independently associated with dropout rates (Silva et al., 2017). Efforts to reduce drop out and improve recovery rates can be done by diagnosing and treating drug dependence along with TB treatment, so health professionals must have the ability to identify symptoms of drug abuse for early treatment (Silva et al., 2017). TB patients who consume alcohol have a higher chance of dying than those who

do not consume alcohol (Atif et al., 2014). Organ damage from prolonged alcohol consumption is likely to be the cause of poor TB treatment outcomes (Myers et al., 2018). A meta-analysis found that smoking significantly increases the likelihood of poor TB treatment outcomes (Burusie et al., 2020). In humans, smoking weakens defensive immunity by affecting cellular immunity, which can lead to unchanged sputum yield or delayed conversion and potentially cause TB treatment failure (Atif et al., 2014). The risk of treatment failure and death in TB patients with diabetes was reported to be higher than in TB patients without diabetes (Atif et al., 2014; Gautam et al., 2021). Diabetes is also known to weaken the immune system by affecting cellular immunity (Atif et al., 2014; Gautam et al., 2021). The weak immune system results in delayed sputum conversion resulting in extended treatment duration.

External factors

The distance between the patient's residence and the location of health services is related to the failure of TB treatment (Desjardin et al., 2020; Sahyog et al., 2018; Tesema et al., 2020). Improving access to health services is linked to lower dropout rates (Son et al., 2021). Thus, improving good treatment outcomes can be achieved by setting the location of health services or where the community can access the nearest health facilities (Tesema et al., 2020). In addition to setting the location, the number of adequate health service facilities must also be considered. The limited number of health services makes the facilities available be focused in one place. This has increased the number of patients and long waiting times, thus becoming a barrier for patients seeking treatment, and this has been shown to cause patient dropout (Adamu et al., 2018).

The DOTS program is a comprehensive, patient-oriented approach to preventing treatment nonadherence (Silva et al., 2017), and it has been accepted as a strategy for treating TB globally (Tetteh et al., 2018). Patients receiving TB treatment who are directly under DOTS observation will be well monitored (Habte et al., 2020; Reis-Santos et al., 2019). Through DOTS, TB sufferers are supervised in taking ATD, given a control schedule, provided education related to the disease and the treatment process, given motivation, and provided other interventions that can improve good treatment outcomes. DOTS medical staff also play a role in conducting contact investigations for case findings, tracing dropped outpatients, and recording and reporting treatment results periodically. The existence of DOTS in conjunction with the support from professional health workers has been shown to contribute to better TB treatment outcomes (Reis-Santos et al., 2019).

The method of diagnosis in TB is related to the outcome of treatment, but this needs to be investigated further (Ogbudebe et al., 2018; Oladimeji et al., 2021; Sadana et al., 2020). The use of the gen expert diagnostic method which is limited to TB/HIV recurrence or co-infection leads to poorer treatment outcomes (Oladimeji et al., 2021). Meanwhile, the method of diagnosis through bacteriological examination is generally performed on new TB patients. The differences in the characteristics of TB patients in the two diagnostic methods may cause the diagnostic method to be a determinant of treatment outcomes. Thus, it is important to conduct research using the same type of diagnostic examination in different TB cases, so its true effect is known.

A history of contact with TB patients in pediatric patients is known to be significantly associated with treatment outcomes. A study reported that treatment failure was found in pediatric TB patients who had a history of contact with TB patients (Sadana et al., 2020). TB cases in children are an indication of the occurrence of TB transmission in the community, so household contact investigations must be carried out systematically (Ogbudebe et al., 2018; Sadana et al., 2020). Close contact with untreated TB patients increases the risk of transmission especially in children as a vulnerable population. TB in children causes more severe symptoms and less successful treatment outcomes than TB in adults, so breaking the chain of transmission by treating the source is very important (Desjardin et al., 2020; Tesema et al., 2020).

The year of TB diagnosis is a determining factor for the outcome of subsequent TB treatment (Ahmad et al., 2020; Oladimeji et al., 2021). The increase in the number of TB patients from year to year can reduce the quality of health services affecting the stability of treatment outcomes (Oladimeji et al., 2021). The increasing prevalence of MDR TB, XDR (Extensively Drug-Resistant) TB, and HIV TB coinfection also contributes to the low outcome of successful treatment. The clinical conditions related to these cases are evidence of a higher risk of death compared to TB cases alone. As an infectious disease, TB often makes sufferers receive discrimination in the form of rejection and exclusion from their family or environment (Banerjee et al., 2020). Discrimination can be a barrier in seeking treatment because it makes TB sufferers prefer to hide their

disease. An even worse impact of discrimination is stopping TB treatment before the specified time. Community-based support can be appropriate and is a much-needed response to this.

The implementation of counseling through good communication will be able to provide information and improve understanding of TB patients, thereby increasing treatment adherence and producing better treatment outcomes (Mulogo et al., 2017). Thus, healthcare workers are expected to improve their verbal and non-verbal skills in communicating. A good assessment of health services can be given if the patient can feel satisfaction from various aspects, including the attitude and approach of the staff when providing services. The unfriendly attitude of medical staff in providing health services has been proven to cause patients to stop treatment (Tetteh et al., 2018). However, the patients can move to find other health services and become recorded as a dropout at the initial treatment place. For this reason, it is important to develop a professional attitude for healthcare workers.

4 Conclusion

The main conclusions of the study may be presented in a short Conclusions section, which may stand alone or form a subsection of a Discussion or Results and Discussion section. Provide a statement that what is expected, as stated in the "Introduction" chapter can ultimately result in the "Results and Discussions" section, so there is compatibility. Moreover, it can also be added the prospect of the development of research results and TB treatment outcome is influenced by determinants that originate from internal and external factors of the patients. Internal factors are the most dominant determinants that affect treatment outcomes. This study demonstrates the need to optimize TB patient-focused interventions to achieve better treatment outcomes. To our knowledge, this study is the first systematic review to identify determinants of TB treatment outcomes from internal and external factors in countries with a high TB disease burden, thus providing theoretical implications for filling a research gap yet to be explored. The practical implication is to provide input for health care facilities that age, gender, location of TB, HIV status, and other determinants are related indicators that must be considered for better TB diagnosis and treatment outcomes. However, further research is required with wider demographic coverage, and it should focus on TB patients with comorbidities, TB/HIV co-infected patients, MDR TB, and XDR TB- who are those with a greater risk for poorer treatment outcomes. Although we conducted a systematic literature search, we may have missed some articles that do meet the inclusion criteria. The results of this review may not provide a complete or uniform picture of the determinants and outcomes of TB treatment among countries in Asia and Africa due to the time difference of the studies reviewed.

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