



Determinants of Medication Adherence in Pulmonary Tuberculosis: A Systematic Review

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Abstract

Adherence to therapy is an essential component of successful pulmonary tuberculosis treatment, affecting patient recovery, prevention of drug resistance, and public health outcomes. Understanding compliance factors can guide interventions to improve treatment success rates. This systematic review explored the factors influencing adherence to therapy among tuberculosis patients, synthesizing evidence from various studies to understand the problem comprehensively. A systematic literature search followed PRISMA guidelines, including primary databases and screening for relevant studies. Twenty-four studies that met the inclusion criteria were analyzed. Data extraction and quality assessment were carried out to ensure the robustness of the findings. There were 2,729 articles identified according to the criteria, and 24 articles were obtained that analyzed several factors affecting patient with tuberculosis (PTB) therapy adherence, which were classified into individual, socioeconomic, and healthcare system domains. Key individual factors include patient knowledge about TB, stigma, mental health challenges, and substance use. Socioeconomic barriers, such as financial constraints and limited social support, are particularly prominent. Health system factors, including accessibility, quality of provider-patient communication, and ease of care facilities, also significantly affect compliance. Addressing adherence to TB therapy requires a multi-faceted approach that combines patient education, socioeconomic support, and healthcare system improvement. Targeted interventions based on these findings are critical to improving treatment outcomes and reducing TB-related health disparities.

Keywords: Healthcare System, Patient Behavior, Pulmonary Tuberculosis, Systematic Review, Therapy Adherence.

INTRODUCTION

An essential strategy for managing and eradicating tuberculosis is an effective treatment, with medication adherence being a significant factor influencing the success of treatment (Mok et al., 2018). Although various approaches have been implemented, including directly observed therapy, cases of nonadherence to tuberculosis treatment still occur, and most patients fail to comply with the prescribed rules of treatment (Tola et al., 2017)). Experts in the treatment of tuberculosis have assessed the range of nonadherence to treatment between 20% and 100% (Munro et al., 2007).

Nonadherence to treatment for tuberculosis significantly reduces the chances of successful treatment and recovery (van den Boogaard et al., 2011). Furthermore, it contributes to treatment failures, extended hospital stays, and delays in completing treatment regimens (Tola et al., 2016). The protracted nature of the treatment process not only increases healthcare costs but also leads to psychological complications, a higher likelihood of disease relapse, an increased risk of drug resistance, and increased mortality associated with the disease



(SCHAAF et al., 2010). Each suffering from active tuberculosis has the potential to transmit the disease to 5 to 15 people in a year. As a result, failure and delay in treatment can increase the risk of spreading tuberculosis in the community, thereby exacerbating the overall burden of the disease (Adane et al., 2013).

Our study showed that noncompliance, noncompliance, and discontinuation of treatment are prevalent among elderly tuberculosis patients (Oshi et al., 2014). Previous research has reported the rate of noncompliance in tuberculosis treatment is ranging from 38,1-56,4% (Swarjana et al., 2024). This phenomenon is significant enough that specific scientific evidence suggests that challenges in eradicating tuberculosis can be attributed to treatment failure in this age group (Kiros et al., 2014).

The prevalence of tuberculosis among older people is three times higher, and the associated mortality rate is six times greater compared to younger individuals (Oshi et al., 2014). With the anticipated demographic shift and the growing elderly population, an increase in tuberculosis cases in this age group is expected. As a result, effective management of tuberculosis in older adults can significantly impact prevention and control initiatives in all countries (Li et al., 2017; Velayutham et al., 2014).

Given the critical role of medication adherence in the treatment of tuberculosis, particularly among older patients, it is vital to identify and examine the factors influencing adherence to improve strategies aimed at eradicating tuberculosis (Bhattacharya et al., 2018). This paper aimed at recognizing these factors and implementing appropriate interventions can lead to improved compliance, thereby facilitating more effective management of tuberculosis and assisting policymakers, healthcare professionals, the community, and patients in addressing tuberculosis-related challenges (Culqui et al., 2012; Gugssa Boru et al., 2017).

METHODS

Search Strategy

This systematic review was conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 criteria. We used PubMed, Google Scholar, Cochrane Library, and ScienceDirect to scour the literature. At the identification stage, 2,729 articles were found from the entire database and filtered according to the criteria that had been determined. The predefined keyword "(("treatment adherence and compliance"[MeSH Terms] OR ("treatment"[All Fields] AND "adherence"[All Fields] AND "compliance"[All Fields]) OR "treatment adherence and compliance"[All Fields] OR ("treatment"[All Fields] AND "adherence"[All Fields]) OR "treatment adherence"[All Fields] OR ("adherence"[All Fields] OR "adhere"[All Fields] OR "adhered"[All Fields] OR "adherence"[All Fields] OR "adherences"[All Fields] OR "adherent"[All Fields] OR "adherents"[All Fields] OR "adherer"[All Fields] OR "adherers"[All Fields] OR "adheres"[All Fields] OR "adhering"[All Fields]) AND ("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "therapies"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "therapy s"[All Fields] OR "therapys"[All Fields])) OR ("compliances"[All Fields] OR "patient compliance"[MeSH Terms] OR ("patient"[All Fields] AND "compliance"[All Fields]) OR "patient compliance"[All Fields] OR "compliance"[All Fields] OR "compliance"[MeSH Terms]) OR ("medication adherence"[MeSH Terms] OR ("medication"[All Fields] AND "adherence"[All Fields]) OR "medication adherence"[All Fields]) OR ("medication adherence"[MeSH Terms] OR ("medication"[All Fields] AND "adherence"[All Fields]) OR "medication adherence"[All Fields] OR ("medication"[All Fields] AND "compliance"[All Fields]) OR "medication compliance"[All Fields])) AND ("factor"[All Fields] OR "factor s"[All Fields] OR "factors"[All Fields]) AND ("tuberculosi"[All Fields] OR "tuberculosis"[MeSH Terms] OR "tuberculosis"[All Fields] OR "tuberculoses"[All Fields] OR "tuberculosis s"[All Fields]))" is used throughout the literature search. Articles with relevant titles and abstracts are included for further qualitative examination and full-text observation. These findings will be covered in English-language papers published between 2005 and 2024 and have full-text accessibility. This criterion finally sorted out 2,693 articles with the main reason of excluded studies do not comply to our research question (specific PICO-based question), and then the researcher conducted further screening by excluding duplicate articles. At this stage, the article was separated into 31 articles. After reading and screening articles that did not comply to our determined participants and study design, 24 articles were included for final review. Figure 1 shows the requirements of the study search strategy.



Inclusion and Exclusion Criteria

One of the main objectives of the study selection criteria is to find a study that offers comprehensive information on the variables that affect the level of availability of maintenance documentation. We use a PICO-based research question for determining whether or not the identified study is able to be included with a population of tuberculosis patients, exposure of noncompliance patients and comparing them to the compliant one, and a specific outcome of factors affecting the noncompliance of the patients. Only papers that meet these requirements are considered for inclusion to ensure a thorough analysis. To guarantee the validity and authenticity of the results, the following essential factors are considered: 1) a study that omits critical information and 2) articles that are not available in their entirety.

Data Extraction and Assessment of Study Quality

The following data were extracted: author name, year of publication, study design, participant characteristics, and study results related to factors influencing the level of adherence of patients with advanced pulmonary tuberculosis to take the drug. Next, we extract data from selected articles. Articles are also assessed in terms of quality using the JBI critical appraisal checklist, which is used for each inclusion study type. Quality assessments are carried out collaboratively by all reviewers until a consensus is reached.

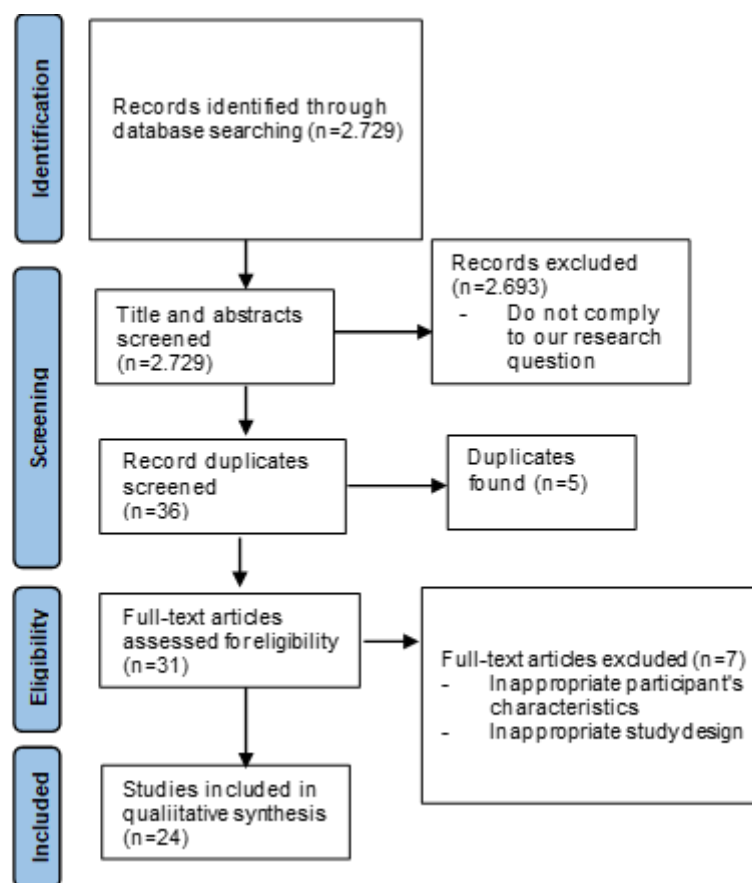


Figure 1. Flowchart of the Literature Search Strategy for This Systematic Review

Table 1. Study Characteristics and Study Results

No	Author, year/Country	Method	Measuring instruments used	Study Results and Discussion
1	Dewi Hapsari Wulandari, 2015/ Indonesia	Mixed-method	Interview	Factors that have a relationship with TB patient compliance to take medication are: Perception of TB disease (p 0.00), perception of distance to RS (p 0.00), perception of attitude officer (p 0.02), Drug Swallowing Supervisor (PMO) (p 0.00), Side effects (p-value 0.0007)
2	Okmina Tri Kusmiyani, Hermanto, Kristin Rosela, 2024/ Indonesia	Data primer Cross-sectional	Questionnaire	Based on the Chi-Square test results, the occupational factor's P-value was 0.698. The education factor was 0.471, the distance factor was 0.277 > 0.05, and then H1, H2, and H3 were rejected, so there was no relationship with medication compliance. At the PMO factor of 0.000 and the motivation factor of 0.000 < 0.05, so that H4 and H5 are accepted, a relationship exists between PMO and motivation with medication adherence.
3	Zaruhi Grigoryan, McPherson Robert, Hutunyan Tsovinar, Nun Truzyan, Serin Sahakyan, 2022 / Armenia	Qualitative	Interview	Former patients' awareness of TB and its treatment, beliefs about TB, trust in TB healthcare providers, and a sense of responsibility are the most common factors that make them more likely to complete treatment. The support received from service providers, family, and friends, the desire to avoid TB-related stigma, and a good tolerance of TB treatment were the main reinforcing factors.
4	Frezghi Hidray Gebreweld, Meron Mehari Kifle, Fitum Eyob Gebremicheal, Leban Lebahati Simel, Meron Mebrahtu Gezae, Shewit Sibhatu Ghebreyesus, Yordanos Tesfamariam Mengsteab, Nebiat Ghirmay Wahd, 2018 / Eritrea	Qualitative	Interview	The most common reason for stopping treatment is that the patient "feels cured". Nearly half of the respondents were unaware of the duration of standard therapy and the consequences they faced if they stopped treatment. Patients reported losing their jobs when their diagnosis was known, being too sick to continue working or being unable to find a day job due to time-consuming medication arrangements. With a few exceptions, most patients report that the proximity to the clinic encourages them to attend regular follow-up treatments.
5	Upik Rahmi, 2020/ Indonesia	Quantitative	Questionnaire	The most dominant factor is Gender, with P value (0.014) and P value work (0.025) where $p < 0.05$ while factors that are not related to age, knowledge, education, and family income, $p > 0.05$.
6	Somayeh Hassani, Farahnaz Mohammadi Shahboulagi, Mahshid Foroughan, Seyed Alireza Nadjji, Payam Tabarsi, and	Qualitative	Interview	Treatment adherence in elderly tuberculosis patients is not limited to physical and biological factors. Still, it is a multidimensional phenomenon influenced by various individual factors, interpersonal factors, factors related to

7	Gholamreza Ghaedamini Harouni, 2023/ Iran Ikhwanuliman Putera, Trevino A Pakasi, Elvina Karyadi, 2015/ Indonesia	Qualitative	Interview	health care centres, and extra-organizational factors. In the univariate analysis, no sociodemographic factors were associated with treatment failure, but lack of knowledge and misperception of prior TB therapy (OR 2.49 1.30-4.79 95% CI, $p = 0.006$; OR 5.40 2.64-11.04 95% CI, $p < 0.001$). In multivariate analyses, only misperceptions of TB showed a significant association with treatment failure (OR 4.75 2.30-9.86 95% CI).
8	Rohith Motappa, Tuba Fathima, Himani Kotian, 2022/ India	Studi cross-sectional	Medical card and medical record	Results: It was found that patients who were positive for human immunodeficiency virus (HIV) were more likely to become non-compliant, and this was statistically significant. Among the participants, 66 (33%) were diabetics, and 28.8% of them were found to be non-compliant. The proportion of noncompliance was 27 times higher in those who had a bad relationship with the patient's provider. Patients who reported experiencing side effects of TB treatment were 5.23 times more likely to become non-compliant. Conclusion: Advice regarding regular consultation with healthcare facilities, adherence to treatment regimens, and education about its benefits should be the main focus of providing health education to all TB patients, both at the individual and community levels.
9	Yuvaraj Krishnamurthy, Selvaraja c, Dhanajayan Govindan, 2024/ India	Quantitative secondary data	Medical records	The Marginal Total Effect (MTE) showed that women were likelier to have positive phlegm than men (OR: 6.77; $p = 0.003$). The immediate effect of being female increases the likelihood of positive phlegm at the end of the intensive phase (OR: 3.42; $p = 0.03$). The indirect effect of being female through medication adherence significantly increases the likelihood of positive phlegm at the end of the intensive phase (OR: 1.98; $p = 0.03$).
10	Zulfa Rindy Al Fitry, Erlina Puspitaloka mahadewi, Ade Heryana, Ira Marti, 2021/ Indonesia	Quantitative	Interview	The results of the univariate analysis in this study show that the proportion of respondents with higher education is the highest at 65%, namely respondents with higher education 65% do not work, 65% have good knowledge of the availability of health facilities, and Respondents' facilities that stated complete 65%, access to health services 68%. Respondents stated that it was not difficult, 86.5% of family support was good, 68% were healthy Good worker support. This study also found the results of a bivariate analysis that there are relationship of educational status (p



				= 0.039; PR = 2.46; CI 95% = 1,089-5,563), medication adherence (p = 0.039; QR = 2.46; CI 95% = 1.09-5.56), availability of health services facilities and facilities (p = 0.039; QR = 2.46; 95% CI = 1.09 - 5.56), access to health care (p = 0.006; QR = 3.32; 95% CI = 1.46-7.85), family support (p = 0.039; QR = 2.46; 95% CI = 1.09 - 5.56), and health worker support (p = 0.027; QR = 2.78; CI 95% = 1.24 - 6.21) with adherence to taking medication.
11	Samanta Madeira de Oliveira, Stephan Altmayer, Matheus Zanon, Luzielio Alves Sidney-Filho, Ana Luiza Schneider Moreira, Paulo de Tarso Dalcin, Anderson Garcez, Bruno Hochegger, José da Silva Moreira, Guilherme Watte, 2018/ Brazil	Quantitative secondary data	Medical records	The factors of nonadherence after adjustment in the overall population were, in order of magnitude, living in low-income areas (OR = 4.35, 95%CI: 2.50-7.58), drug abuse (OR = 2.73, 95%CI: 1.47-5.09), nonadherence to previous treatment regimens (OR = 2.1, 95%CI: 1.28-3.45), and smoking history (OR = 1.72, 95%CI: 1.00-3.00). Age, race, gender, education level, HIV infection or diabetic status were not associated with a higher risk of non-compliance. In the subgroup of retreatment cases, poverty (OR = 2.65; 95%CI = 1.06-6.66), smoking history (OR = 2.94; 95%CI = 1.09-7.92), male sex (OR = 3.25; 95%CI = 1.32-8.0), and younger age (OR = 4.3; 95%CI = 1.15-16.07) were also associated with a higher risk of dropping out.
12	Yun Wang, Sisi Jian, Zhongfeng Huang, Huijuan Chen, Yuanxia Hu, Shilin Fang, 2024/ China	Qualitative	Interview	Patients with higher scores in domain 2 (practical difficulty) [OR adj = 1.19; 95% CI (1.11-1.28)] and domain 4 (burden of side effects of prescribed medications) [OR adj = 1.16; 95% CI (1.06-1.27)] were more likely to develop noncompliance. However, patients with higher scores in domain 8 (control/autonomy of drug use) [OR adj = 0.70; 95% CI (0.61, 0.81)] were more likely to develop adherence. Patients with higher education levels [OR adj = 0.29; 95% CI (0.08, 0.92)] had a lower risk of non-compliance, but those with living expenses from a retirement salary [OR adj = 2.55; 95% CI (1.16, 5.71)] had an increased risk of non-compliance.
13	Peter Michael Marin, Musso Munyeme, Clovice Kankya, Ambrose Samuel Jubara, Enock Matovu, Peter Waiswa, Javier Sanchez Romano, Francis Mutebi, David Onafro, Estella Kitale, Owori Benard, Kayla J Buhler, Morten Tryland, 2024/ South Sudan	Mixed-method	Urine isoniazid metabolite testing (IsoScreen®) dan kuisioner	Nonadherence was significantly associated with reduced symptoms (APR 1.93, 95% CI 1.12 - 3.34, p = 0.018), alcohol use (APR 2.12, 95% CI 1.33 - 3.96, p = 0.019) and wait time to receive medication (APR 1.77, 95% CI 1.11 - 2.83, p = 0.017).



14	Addisu Alemayehu Gube, Megbaru Debalkie, Kalid Seid, Kiberalem Bisete, Asfaw Mengesha, Abubeker Zeynu, Freselam Shimelis, Feleke Gebremeskel, 2018/ Ethiopia	Quantitative	Morisky Medication Adherence Scale-8 (MMAS-8)	Noncompliance is high when patients experience adverse events (AOR = 13,332; 95% CI = 2,282-77,905), are far from health facilities (AOR = 21,830; 95% CI = 0.054-77,500), and experience long waiting times to receive health care (AOR = 14,260; 95% CI = 2,135-95,241).
15	Lyar Lemma Tirore, Tadele Ercido, Tilahun Beyen Handiso, Aubriham Shiferao Areba, 2024/ Ethiopia	Qualitative	Interview	Being in the advanced phase (AOR = 3.09, 95% CI: 1.16, 8.23), not attending formal education (AOR = 2.47, 95% CI: 1.12, 5.42), not disclosing TB status to family (AOR = 2.36, 95% CI: 0.11, 5.04) and having poor knowledge about TB (AOR = 3.09, 95% CI: 1.48, 6.48) were significantly associated with nonadherence to TB treatment.
16	Nour srianah, Suradi Efendi, Halmina Ilyas, Nadira, 2022/ Indonesia	Analytical study with a cross-sectional study approach	Questionnaire	20 respondents (57.1%) had knowledge in the good category, and 19 people (54.3%) had a positive attitude, and there was a relationship between knowledge (p = 0.021) and attitude (p = 0.009) with family support as a supervisor of taking medication in patients with pulmonary tuberculosis at the Bonton Health Center, Maros Regency.
17	Castelnuovo B, 2010/ Africa	Medline (http://www.ncbi.nlm.nih.gov/mesh?itool=sidebar)	article	Identified four published manuscripts and included 1 study from the infectious diseases institute. The proportion of absent patients varies from 11.3% (8) to 29.6%. Risk factors for missing treatment are a distance from the hospital, not undergoing first-stage TB treatment, not doing repeated smear checks, changing units after the intensive phase, experiencing drug side effects, not having family support, poor knowledge of TB treatment, being over 25 years old and using public transportation.
18	Sandra Albino, Joseph, Karen M, David Requana, Miguel Egoavill, maria F, Peneros-leano, R. Zunt, patricia J, Garcy, 2014/ Peru	Qualitative	interview	Three main themes of the data: limited literacy and health information pose challenges to the success of TB treatment adherence, treatment motivation sometimes facilitates adherence to TB treatment, and SMS recipients include a positive perception of SMS to improve TB adherence. Patient prevalence shares considerations on how to effectively and confidentially manage SMS interventions with participants who are TB-positive.
19	Nithin Ranawaka, Sumal Nandasena, Sunil De Alwis, 2021/ Sri Lanka	Cross-sectional	Questionnaire	Results: Data were collected from 252 patients [male = 160 (63.5%) and female = 92 (36.5%)]. The percentage of noncompliance was 18.3% (n = 46) among newly diagnosed TB patients.



				Only 13.5% (n = 34) of TB patients visit a Directly Observed Treatment, Short-Course (DOTS) provider daily. The majority (61.9%, n = 156) of DOTS service providers do not make observations on drug intake. Factors that were significantly associated with TB treatment nonadherence were (1) not observed by DOTS service providers, (2) drug side effects, (3) education level, (4) living environment, and (5) absence of drug ingestion supervisors.
20	Asriwati, Ernie Yeti, Niakurniawati, Andi Nilawati Usman, 2021/ Indonesia	Cross-Sectional	using a tabulation and statistical system using the SPSS program with odds ratio and logistic regression tests.	Results: It was found that there was an influence on the role of health workers OR=8.933 (95% CI: 1.085-73.525), side effects of drugs with OR=6.873 (95% CI; 2.435-19.398), feeling healthy OR=4.643 (95% CI; 1.247-17.287), and OR=2.700 (95% CI; 1.083-6.731).
21	Made, Made, Made, and Made, 2021/ Indonesia	Qualitative	interview	Logistic regression analysis shows that the Health Belief Model (HBM) based on motivational interviews (MI) and knowledge are the most appropriate variables affecting improving treatment adherence and success. Treatment adherence was 4.5 times greater (APR = 4.51, p=0.018), and treatment success was 3.8 times greater (APR=3.81, p<0.038) in the intervention group compared to the control group. At the same time, secondary outcomes from knowledge of other factors influenced treatment adherence and success.
22	K O Ajao, Q A Ogundun, O T Afolabi, t o oJO. B p Atiba, d o oguntunase, 2014/ Nigeria	Cross-sectional descriptive	Questionnaire	Results: TB patients who had no formal education ($x^2 = 12.941$, $p < 0.05$), who smoked during treatment ($x^2 = 13.194$, $p < 0.001$), who consumed alcohol during TB treatment ($x^2 = 6.371$, $p < 0.05$), and who were HIV positive ($x^2 = 23.039$, $p < 0.001$) were more likely to not comply with TB treatment. TB patients who waited for an hour or more at a healthcare facility ($x^2 = 21.761$, $p < 0.001$), who reported that TB treatment should be stopped before six months ($x^2 = 9.804$, $p < 0.05$) or when the patient felt better ($x^2 = 35.185$, $p < 0.001$) and who travelled 10 km or more ($x^2 = 13.610$, $p < 0.001$) significantly did not comply with TB treatment.
23	Liang Du, Xu Chen, Xue Xue Zhu, Yu Zhang, Ruiheng Wu, Jia Xu, Hao Qiang Ji, Ling Zhou, Xiwei Lu, 2020/ China	survey	Using Thiongkok's version of the Morisky compliance scale	Of the 564 eligible participants, 236 (41.84%) and 183 (32.45%) showed high and moderate medication adherence, but 145 (25.71%) showed low medication adherence. Ordinal logistic regression showed that the older patient (QR: 1.02, $p=0.013$) was working. (QR: 1.61, $p=0.011$) had better knowledge of tuberculosis (QR: 1.34, $p<0.001$) and did not consume alcohol (QR: 1.84, $p=0.032$), showed

				higher medication adherence. However, patients who did not follow the doctor's recommendation to consume adjuvant drugs (QR: 0.44, p=0.001), had a history of TB treatment (QR: 1.76, p=0.009), experienced unexpected drug reactions (QR: 0.65, p=0.017), experienced stigma (QR: 0.67, p=0.032) and required supervised treatment (QR: 0.66, p=0.012) showed a level of compliance.
24	Arkshad M. Shinde, 2023/ India	Quantitative	Interview-based questionnaire	Of the 181 patients, 110 (60.8%) were found to be compliant, while 71 (39.2%) were found to be non-compliant. Among those who did not comply, 64 (90.9%) had treatment interruptions (doses missed at regular intervals), and 7 (9.9%) indicated discontinuation of treatment. Most patients reported personal obligations and began to feel better as an excuse for noncompliance (p<0.0001). Sociodemographic factors that had a significant impact on the level of adherence were the patient's age (p=0.013), education level (p=0.035), number of families (p=0.018), family history of TB (p=0.0001) and current smoking habits (p=0.025).

Table 2. Assessment of the quality of qualitative studies

Qualitative research	Wulandari, 2015	Grigoryan, 2022	Breweld, 2018	Hassani, 2023	Prince, 2015	Al Fotri, 2021	Wang, 2024	Tirote, 2024	Albino, 2014	Parrot, 2021
Is there a fit between the stated philosophical perspective and the research methodology?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Is there a fit between the research methodology and the question or purpose of the research?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Is there a compatibility between the research methodology and the methods used to collect the data?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Is there a compatibility between research methodologies	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes



and data representation and analysis?											
Is there a compatibility between the research methodology and the interpretation of the results?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Are there any statements that place the researcher culturally or theoretically?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Is the influence of researchers on research, and vice versa, discussed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Are participants and their voices adequately represented?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Is the study ethical according to current criteria or, for the current study, and is there evidence of ethical approval by the appropriate body?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Do the conclusions drawn in the study report flow from the analysis or interpretation of the data?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Table 3. Quality assessment of cross-sectional studies

Qualitative study	Kusmiyani, 2024	Rahmi, 2020	Motappa, 2022	Krishnamurthy, 2024	de Oliveira, 2018	Marín, 2024	Gube, 2018	Srianah, 2022	Ranawaka, 2021	Asriwatu, 2021	Ajao, 2014	Du, 2020	Shinde, 2023
Are the criteria for inclusion in the sample clearly defined?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Are the study subjects and their settings	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

describe d in detail?													
Is exposure measure d validly and reliably?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Are objective standard criteria used to measure the condition ?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Have strategie s for dealing with disruptiv e factors been mention ed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Are the results measure d validly and reliably?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Is the statistica l analysis used accuratel y?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Are the criteria for inclusion in the sample clearly defined?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the study subjects and the setting describe d in detail?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

RESULTS AND DISCUSSION

Our systematic review highlighted several factors affecting patient's compliance in taking tuberculosis medications which broadly classified into several group, which are: (1) knowledge and perception of the patients regarding the disease, (2) sociodemographic and behavioral factors, and lastly (3) economic factors. The

knowledge and perception seemed to be the most influential factors across all included studies. Almost all studies reported a prevalent patient's misperception and lack of understanding regarding tuberculosis as the main factors affecting their compliance to tuberculosis treatment. Furthermore, educational status was also played a significant role both directly to the compliance and indirectly by affecting the ability of the patients to comprehend the disease. Sociodemographic and behavioral factor was the second most influential factor especially in low-middle income region which still stigmatized tuberculosis patients which enforced them to not take their medications which eventually leads to noncompliance. Furthermore, especially in low-middle income region, health-related behavior was either not adequately disseminated or hindered to be implemented.

Based on the results of the journal analysis, researchers found 24 supporting journals to strengthen this literature review, from the 24 journals found, they were analyzed according to their characteristics and components, it was found that 8 journals used qualitative methods, 4 journals used quantitative research methods, 2 journals used secondary data quantitative methods, 2 journals used mix-methods, and 6 journals used cross-sectional methods, survey methods and medline methods. For example, research that is in accordance with the characteristics of the literature review regarding Factors Related to the Compliance of Advanced Pulmonary Tuberculosis Patients to Take Medication, research using the mixed method by Dewi Hapsari Wulandari in 2015 said that Factors that have a relationship with the compliance of Pulmonary TB patients taking medication are Perception of TB disease, perception of distance to the hospital, perception of the attitude of officers, Drug Swallowing Supervisors (PMO), and Side effects (Wulandari, 2015).

Other supporting journals are 8 journals with qualitative methods by researchers Zaruhi Grigoryan, et al. 2022 with the title Factors Influencing Treatment Adherence Among Drug-Sensitive Tuberculosis (DS-TB) Patients in Armenia: A Qualitative Study (Grigoryan et al., 2022), research by Frezghi Hidray Gebreweld, et al. 2018 with the title Factors influencing adherence to tuberculosis treatment in Asmara, Eritrea: a qualitative study (Gebreweld et al., 2018), research by Somayeh Hassani, et al. 2023 with the title Factors Associated with Medication Adherence in Elderly Individuals with Tuberculosis: A Qualitative Study (Hassani et al., 2023), research by Ikhwanuliman Putera, et al. 2015 with the title Knowledge and perception of tuberculosis and the risk to become treatment default among newly diagnosed pulmonary tuberculosis patients treated in primary health care, East Nusa Tenggara: a retrospective study (Putera et al., 2015), research by Yun Wang, et al. 2024 with the title Medication-related burden and its association with medication adherence among elderly tuberculosis patients in Guizhou, China: a cross-sectional study (Wang et al., 2024), research by Lire Lemma Tiore, et al 2024 with the title Non-adherence to anti-tuberculosis treatment and associated factors among TB patients in public health facilities of Hossana town, Southern Ethiopia (Lemma Tiore et al., 2024), research by Sandra Albino, et al 2014 with the title Perception and Acceptability of Short message service technology to improve treatment adherence among tuberculosis patients in Peru: A focus group study (Albino et al., 2014), research by Ni made Parwati, et al 2021 with the title A health belief model-based motivational inter-viewing for medication adherence and treatment success in pulmonary tuberculosis patients (Parwati et al., 2021).

Other supporting journals are 4 journals with quantitative methods by researcher Upik Rahmi 2020 with the title Factor Analysis Of Adherence To Treatment For Pulmonary Tuberculosis sufferers in Bandung (Rahmi, 2020), research by Zulfa Rindy Al Fitry, et al. 2021 with the title Medication Compliance analysis in Pulmonary Tuberculosis Patients At Bekasi Jaya Health Center Indonesia (Rindy Al Fitry et al., 2022), research by Addisu Alemayehu Gube, et al. 2018 with the title Assessment of Anti-TB Drug Nonadherence and Associated Factors among TB Patients Attending TB Clinics in Arba Minch Governmental Health Institutions, Southern Ethiopia (Gube et al., 2018), research by Arkshad M. Shinde with the title Sociodemographic factors and compliance of newly diagnosed pulmonary tuberculosis patients with a newly introduced daily regimen: a follow-up study based on a hospital survey (Shinde, 2024).

Five journals with cross-sectional methods by researchers Rohith Motappa, et al. 2022 with the title Appraisal on patient compliance and factors influencing the daily regimen of anti-tubercular drugs in Mangalore city: A Cross-Sectional study (Motappa et al., 2022), research by Nour srianah, et al. 2022 with the title Relationship between knowledge, attitudes and family support as supervisors of medication compliance in pulmonary tuberculosis patients (Sriyanah et al., 2022), research by Nithin Ranawaka, et al. 2021 with the title Noncompliance of treatment among tuberculosis patients in intensive phase at Kalutara District of Sri Lanka (Ranawaka et al., 2021), research by Asriwati, et al. 2021 with the title Risk factors analysis of noncompliance of tuberculosis (TB) patients taking medicine in puskesmas polonia medan 2021 (Asriwati et al., 2021), research

by KO Ajao, et al. 2014 with the title Treatment compliance and challenges among tuberculosis patients across selected health facilities in osun state Nigeria (Ajao et al., 2014).

Other supporting journals are 4 journals with quantitative research methods by researcher Upik Rahmi in 2020 entitled Factor Analysis Of Adherence To Treatment For Pulmonary Tuberculosis sufferers in Bandung (Rahmi, 2020), research by Zulfa Rindy Al Fotri et al in 2021 entitled Medication Compliance analysis in Pulmonary Tuberculosis Patients At Bekasi Jaya Health Center Indonesia (Rindy Al Fitry et al., 2022), research by Addisu Alemayehu Shinde et al in 2018 entitled Assessment of Anti-TB Drug Nonadherence and Associated Factors among TB Patients Attending TB Clinics in Arba Minch Governmental Health Institutions, Southern Ethiopia, and research by Arkshad M. Shinde in 2023 entitled Sociodemographic factors and compliance of newly diagnosed pulmonary tuberculosis patients with a newly introduced daily regimen: a follow-up study based on a hospital survey (Shinde, 2024).

For quantitative research, secondary data has 2 supporting journals, research by Yuvaraj Krishnamoorthy, et al. in 2024 entitled Sex-based differences in TB treatment compliance: A mediating factor for sputum conversion among newly diagnosed pulmonary TB patients in Chennai, South India (Krishnamoorthy et al., 2024) and research by Samanta Madeira de Oliveira, et al. in 2018 entitled Predictors of noncompliance to pulmonary tuberculosis treatment: An insight from South America (Madeira de Oliveira et al., 2018). In addition, there is 1 study with a cross-sectional primary data method by Okmina Tri Kusmiyani, in 2024 entitled Analysis of Factors Related to Compliance with Taking Anti-Tuberculosis Drugs in Pulmonary TB Patients at Samuda and Bapinang Health Centers East Kotawaringin (Kusmiyani et al., 2024).

Research on adherence to anti-TB treatment and factors predicting poor adherence in Sub - Saharan Africa over the past 10 years has shown that the proportion of patients lost to follow-up varies from 11.3% to 29.6%. Risk factors for loss to treatment include distance from hospital, not undergoing the first phase of TB treatment, not undergoing repeat smear examination, moving units after the intensive phase, experiencing drug side effects, not having family support, poor knowledge of TB treatment, being over 25 years of age and using public transportation.

The results of the literature review found that several factors contribute to patient non-adherence to taking medication, starting from the lack of information in these patients, including the absence of a family history of tuberculosis and their failure to read or attend public education about the disease (Muture et al., 2011). Several characteristics, including alcoholism, relatively high costs and time to visit a health facility, having a family member with tuberculosis, age and marital status, and low monthly income, were found to be significantly associated with patient non-adherence in other studies (Burman et al., 1997; Muture et al., 2011; Tachfouti et al., 2012).

The level of medication compliance among outpatients with pulmonary tuberculosis is very important to note. Compliance with taking medication during the treatment process during pulmonary TB is very important for controlling tuberculosis. There is one supporting journal that says that patients who do not follow the doctor's advice to take adjuvant drugs, have a history of TB treatment, experience unexpected drug reactions by researchers (Chen et al., 2020)

According to a study by Gebreweld et al., some patients expressed dissatisfaction with the high cost of transportation to the clinic (Gebreweld et al., 2018). According to the participants, poverty and sporadic financial assistance from family or relatives were the main reasons why these difficulties made it difficult for them to access TB treatment easily. According to a related study, many TB patients are too weak to go to medical facilities; therefore, they often lack money for transportation. Thus, further decentralization of clinics providing DOTS Care is urgently needed. Furthermore, a study by Gebreweld et al. also shows that the long-term impact of poverty on the individual's financial goals is jeopardized (Gebreweld et al., 2018). Financial dependence was caused by most study participants who reported losing their source of income (M. J. van der Werf et al., 2009; T. S. Van Der Werf et al., 1990). Economic tensions can be a barrier, according to a similar study conducted in China, which found that patients and their families are experiencing severe financial hardship due to job losses, rising food prices, and transportation costs (Zou et al., 2012). According to a study by Gebreweld et al., even when free TB treatment is available, treatment adherence may still be hampered by financial issues such as transportation costs. Incentives to improve treatment adherence are included in the WHO TB treatment

guidelines (Gebreweld et al., 2018). However, respondents claimed they were not given any incentives and that any assistance would help.

Patient compliance is greatly influenced by aspects related to the patient. Another study found that a lack of awareness about tuberculosis and ignorance about treatment adherence caused treatment failures studies (Putera et al., 2015). Several factors contribute to the lack of information on these patients, including the absence of a family history of tuberculosis and their inability to read or attend public education regarding the disease (Muture et al., 2011). Several characteristics, including alcoholism, relatively high costs and times to visit health facilities, having a family member with tuberculosis, age and marital status, and low monthly income, were found to be significantly associated with non-compliant patients in (Burman et al., 1997; Muture et al., 2011; Tachfouti et al., 2012).

The main categories of individual factors and their subcategories, which include biological factors, affective-emotional factors, behavioral factors, cognitive factors, factors related to tuberculosis, and economic factors, were found to have the most effective effects on medication adherence based on the results of a study by Hassani et al. in 2023 (Hassani et al., 2023). According to the study's findings, there may be a relationship between medication adherence and the age of elderly TB patients. As a result, elderly patients are less likely to take medication as prescribed (Hassani et al., 2023). The study's findings also showed that comorbidities decreased the adherence of elderly TB patients to their treatment (Rodgers et al., 2018; SCHAAF et al., 2010). Comorbidities, more complicated treatment and drug plans, and drug interactions due to polypharmacy are also associated with ageing (Di Gennaro et al., 2020). Therefore, the continuation of antituberculosis therapy can also be affected by the occurrence of comorbidities. Older people are more likely to experience treatment failure for TB, according to a study conducted in Iran by Kalhori. One of the leading causes of treatment failure for TB is nonadherence to treatment. As a result, in countries like Iran, it is crucial to give extra attention to elderly TB patients (Tola et al., 2017).

Adherence to therapy is proven to be significantly facilitated by patients' perceptions of the severity of their disease and their belief in the efficacy of their treatment (Gebremariam et al., 2010). In the same vein, Gebremariam et al. found that among TB patients who were also HIV-positive, attitudes towards disease severity and cure were favorable variables for adherence to TB therapy. According to another study, adherence was positively influenced by confidence in the effectiveness of the treatment. Former patients who participated in our study interviews reported that knowing that untreated TB could cause them difficulties, It is easier to stay on their medication (Munro et al., 2007; Shargie & Lindtjorn, 2007).

CONCLUSION

According to this synthesis, patients often undergo TB treatment under challenging conditions and face several obstacles, many of which are beyond their control. Long-term use of medications is not always easy and frequently requires difficult choices, which often incur significant social and personal costs for patients. Compliance phenomena are dynamic and varied; Various interrelated factors affect treatment behavior, and patient behavior can change during treatment. To improve treatment adherence and lower the global burden of disease associated with tuberculosis, more patient-centered treatment and more focus on structural constraints are needed. Our systematic review serves as the foundation for future policymaker to tackle the identified factors associated with tuberculosis treatment noncompliance to improve the medication adherence and reduce the risk of failed or unfinished tuberculosis therapy.

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