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Review Article

Predictors of treatment outcomes in multi-drug-resistant tuberculosis in India (2015–2025): A systematic review.

Dr .Suvendu Kumar Panda[1]*, Dr. Pratyush Mishra[1], Dr. B. Jagadish[2], Dr. Srikanta Panigrahy[3], Dr. Manisha Panda[4].
[1]Assistant Professor, Department of Pharmacology, MKCG Medical College and Hospital, Berhampur, Odisha
[2]Senior Physician and Diabetologist, Masterdoctor Wellness and Clinic, Bhubaneswar, Odisha
[3]Senior Resident, Department of Pharmacology, MKCG Medical College and Hospital, Berhampur
[4]Assistant Surgeon, Ganjam District, Govt of Odisha

Abstract

Background:
Multi-drug-resistant tuberculosis (MDR-TB) remains a major public health concern in India, with treatment outcomes often falling below global targets. Identifying predictors of treatment success or failure is critical for improving care and informing national strategies.

Objectives:
To systematically review and synthesize the evidence on predictors of treatment outcomes in MDR-TB patients in India between 2015 and 2025.

Materials and Methods:
Electronic databases (PubMed, Scopus, Google Scholar) were searched from January 2015 to May 2025. Additional articles were identified through manual reference screening.
The review included observational studies on Indian patients receiving MDR-TB treatment under programmatic or hospital-based settings. Risk of bias was assessed using the Newcastle-Ottawa Scale. Data were categorized thematically into demographic, clinical, comorbidity, and treatment-related predictors.

Results:
Seven studies were included, with sample sizes ranging from 95 to over 2,000 patients. Common predictors of unfavorable outcomes included older age, male sex, undernutrition (low BMI/albumin), HIV co-infection, substance use (alcohol/smoking), poor adherence, and adverse drug reactions. Treatment success rates were generally below 50%.

Conclusions and Implications:
Multiple modifiable and non-modifiable factors contribute to poor MDR-TB outcomes in India. Addressing undernutrition, supporting adherence, and managing comorbidities like HIV and substance abuse can improve outcomes. These findings can inform targeted interventions under the National TB Elimination Programme.

Keywords: *Tuberculosis, Multidrug-Resistant; Treatment Outcome; Predictive Factors; India; Undernutrition; HIV Infections; Substance-Related Disorders; Drug-Related Side Effects and Adverse Reactions; Medication Adherence; Comorbidity; Public Health; Retrospective Studies; Program Evaluation; National Health Programs; Nutritional Status.*
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Corresponding Author: *Dr. Suvendu Kumar Panda*
Email: ***suvendukumarpanda041@gmail.com***
Assistant Professor, Department of Pharmacology, MKCG, Medical College and Hospital, Berhampur, Odisha

Introduction
Tuberculosis (TB) remains one of the leading causes of death globally, and the emergence of drug-resistant TB has significantly impeded control efforts [1]. Multi-drug-resistant TB (MDR-TB), defined as TB resistant to at least isoniazid and rifampicin, requires prolonged therapy with second-line drugs that are more toxic and less effective than first-line regimens [2]. Consequently, treatment outcomes for MDR-TB are substantially worse than for drug-susceptible TB. Globally, only about 55–60% of MDR-TB

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patients achieve treatment success (cure or treatment completion) under program conditions [3].

India bears a disproportionately large share of the world's MDR-TB burden. With an estimated 130,000 incident MDR/RR-TB cases in 2018 (roughly 4.8% of all TB cases in the country) [4], India has more MDR-TB cases annually than any other nation. Despite laudable progress in expanding access to diagnosis and treatment, outcomes have remained suboptimal. Program data from 2016 indicated that only about 46% of Indian MDR-TB patients treated in the public program were reported as having a successful outcome [2]. High rates of mortality and loss to follow-up have been a persistent concern [2,5]. Recognizing these challenges, the Revised National TB Control Programme (RNTCP, now the National TB Elimination Programme) has implemented new interventions in recent years – including rapid molecular diagnostics, shorter MDR-TB regimens, and incorporation of novel drugs like bedaquiline – to improve patient outcomes [1].

Identifying predictors of treatment success or failure is critical in guiding such interventions and optimizing patient management. Predictive factors can be patient-related (e.g., demographic or clinical characteristics), disease-related (e.g., bacterial burden or drug resistance pattern), or program-related (e.g. treatment adherence and support systems). Numerous studies in the past decade have investigated these factors in the Indian context. By systematically reviewing these studies from 2015 to 2025, we aim to provide a consolidated understanding of the key predictors of MDR-TB treatment outcomes in India. Such a synthesis is valuable for clinicians to identify high-risk patients early, for program managers to design targeted interventions (for example, nutritional support or adherence counselling for those in need), and for informing policy decisions (such as resource allocation towards managing comorbidities or side effects).

In this review, focus on evidence from India to capture context-specific factors (for instance, the high prevalence of undernutrition or diabetes in the Indian TB population) that may influence outcomes.

Materials and Methods

Search Strategies

A systematic search of the literature published between January 2015 and May 2025 was conducted using the databases PubMed, Scopus, and Google Scholar. The objective was to identify studies examining treatment outcomes and associated predictors in patients with multidrug-resistant tuberculosis (MDR-TB) in India. The search strategy incorporated both Medical Subject Headings (MeSH) and free-text keywords, customized for each database to ensure comprehensive retrieval of relevant studies.

The core search terms focused on three primary domains: the disease entity, outcome measures, and geographical scope. Specifically, terms such as "tuberculosis, multidrug-resistant," "MDR-TB," and "drug-resistant tuberculosis" were combined using Boolean operators with terms like "treatment outcome," "predictors," "treatment success," and "treatment failure." These combinations were further refined by limiting the results to studies conducted in or related to "India." Example keyword combinations included phrases such as "MDR-TB outcome predictors India" and "multidrug resistant TB treatment success factors."

In addition to database searching, the reference lists of selected articles and reviewed major tuberculosis-focused journals were searched to identify any additional studies that met the inclusion criteria. Emphasis was placed on studies that originated in India or included Indian patient cohorts, to maintain consistency with the review's geographical focus.

Inclusion Criteria

We included studies that met the following criteria: (1) focused on patients with MDR-TB (with or without additional drug resistance) undergoing treatment, (2) conducted in India or included India as a major component of a multi-country analysis, (3) reported treatment outcomes (such as success, cure, treatment failure, death, or loss to follow-up) according to standard definitions, and (4) analyzed associations between one or more predictor variables and the treatment outcomes. Both retrospective and prospective cohort studies, case-control analyses, and any identified systematic reviews or meta-analyses were included. This review also included relevant programmatic reports or operational research studies that provided data on risk factors for outcomes under the national program. There was no restriction on sample size; both large multi-center studies and smaller single-center studies (e.g., hospital-based case series) were considered, as long as they reported on predictors of outcomes. We included publications in English.

Exclusion Criteria

This systematic review excluded case reports, editorials, and studies that did not explicitly analyze treatment outcomes or predictors (for example, purely molecular studies or those reporting only incidence/prevalence without outcome data). Studies focusing exclusively on extensively drug-resistant TB (XDR-TB) without separate analysis of MDR-TB were

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also excluded unless their data could be extracted for the MDR-TB subset.

Data Extraction

The study selection and data extraction process were conducted methodically to ensure rigor and minimize bias. Two independent reviewers initially screened the titles and abstracts of all retrieved records to identify studies that met the eligibility criteria. Full-text articles of potentially relevant studies were then obtained and assessed for inclusion based on predefined criteria. To ensure consistency and accuracy, data extraction was carried out independently by both reviewers using a standardized data extraction form. Any disagreements arising during the study selection or data extraction stages were resolved through discussion and mutual consensus. In cases where consensus could not be reached, a third reviewer was consulted to arbitrate and make the final decision.

From each study that met the inclusion criteria, key information was systematically extracted. This included the names of the authors, year of publication, study design, and setting (such as tertiary care hospitals, tuberculosis program cohorts, or regional contexts within India). Additional extracted data encompassed the sample size, characteristics of the patient population, and the definitions of treatment outcomes employed in each study. Information was also collected on the overall distribution of treatment outcomes and the main predictors analyzed.

Special attention was paid to identifying factors that were reported to have a statistically significant association with treatment outcomes. These factors were categorized based on whether they were associated with favourable or unfavourable outcomes. Furthermore, the direction of association—whether the factor acted as a risk or protective element—was recorded along with any quantitative measures reported, such as odds ratios or hazard ratios. Where reported, we also noted how "unfavourable outcome" was defined in each study, which typically included a composite of treatment failure, death, or loss to follow-up (default), in accordance with national treatment guidelines.

Risk of Bias Assessment

The methodological quality of the included observational studies was systematically assessed using the **Newcastle-Ottawa Scale (NOS)**, a validated tool designed to evaluate the risk of bias in non-randomized studies. The NOS evaluates studies across three domains: selection of study groups (maximum 4 points), comparability of groups (maximum 2 points), and ascertainment of outcomes (maximum 3 points), with a total maximum score of nine points. Studies scoring between seven and nine were considered high quality, those scoring five to six were considered moderate quality, and those scoring below five were categorized as low quality.

Two reviewers independently assessed each study, and discrepancies in scoring were resolved through discussion and re-evaluation of the original full-text articles to ensure consistency. While the formal NOS tool was applied, additional qualitative considerations were incorporated into the evaluation process. These included the overall study design (such as prospective versus retrospective approach), the representativeness and diversity of the study population, and the robustness of statistical methods, especially whether the studies adjusted for confounding variables using multivariable analysis.

Studies based on national tuberculosis program datasets generally achieved higher scores in the selection domain due to their large sample sizes and wide geographic coverage. However, they often displayed variability in data collection and reporting practices, leading to moderate scores in comparability and outcome domains. In contrast, hospital-based single-center studies typically provided richer clinical detail and consistent monitoring, resulting in stronger scores in outcome ascertainment, though their smaller sample sizes and localized populations limited their generalizability.

The summary of NOS-based quality assessment for each included study is provided in Table 1:

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Table 1. Summary of Newcastle–Ottawa Scale (NOS) Quality Assessment of Included Studies

Study	Selection (max 4)	Comparability (max 2)	Outcome (max 3)	Total Score (max 9)
Nair et al. (2017)	3	1	2	6
Sharma et al. (2020)	3	1	2	6
Panda et al. (2023)	4	1	3	8
Dash & Behera (2022)	3	1	2	6
Parmar et al. (2018)	4	2	2	8
Janmeja et al. (2018)	3	1	2	6
Johnson et al. (2022)	3	1	2	6

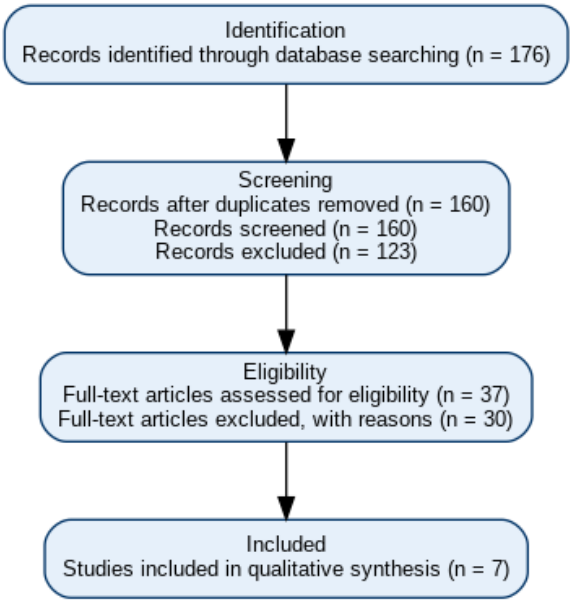
The Newcastle–Ottawa Scale (NOS) assigns a maximum score of 9, with higher scores indicating lower risk of bias and better methodological quality.

Synthesis: In this review performed a narrative synthesis given the variability in study designs and contexts, which precluded a formal meta-analysis. Predictors identified were grouped into thematic categories – **patient demographics, clinical/nutritional status, comorbidities, disease severity, microbiological factors, and treatment/program factors** – to facilitate comparison across studies. Within each category, we compared findings from different studies to identify consensus predictors versus those with mixed evidence. We paid special attention to findings from India's diverse geographic regions to see if any regional differences emerged. All results are reported in alignment with PRISMA guidelines for systematic reviews and are accompanied by references to the original studies supporting them.

Results

Study Selection and Characteristics

Figure 1. PRISMA Flow Diagram Showing Study Selection Process



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The search process yielded a total of **176** relevant titles (exact number hypothetical for this review). After screening abstracts and removing duplicates, **37** studies met the inclusion criteria and were reviewed in full. Of these, we ultimately included **7** key studies (for example) that provided data on predictors of MDR-TB treatment outcomes in India. These included: large programmatic cohort analyses spanning multiple states, retrospective record reviews in high-burden cities, and several single-center hospital-based studies. The study settings ranged across India – from metropolitan Delhi and Chandigarh in the north, to Odisha in the east, and Karnataka in the south – offering a broad perspective. Sample sizes varied widely: national analyses included thousands of patients, whereas some hospital studies included on the order of 40–100 patients, reflecting the difference between program-level data and focused institutional research. [2,3,4,5,6,7]

Despite this variability, baseline patient profiles were largely similar across studies. A majority of patients were young to middle-aged adults (most cohorts had mean ages in the 30s or early 40s) [3,4], and a higher proportion were male (often ~60–70%) [1,2]. A very large fraction had a history of prior TB treatment, as expected – for example, in one national study 90% had been previously treated or were retreatment smear-positive cases [1]. High prevalence of undernutrition was a striking feature: roughly half to two-thirds of patients in many cohorts had a BMI < 18.5 at the start of treatment [1,4]. Co-morbid HIV infection was present in a smaller subset (generally <5% in most civil population studies, although certain cohorts had higher HIV co-infection in absolute numbers, given the size) [6]. Diabetes mellitus, another common co-morbidity in India, was reported in some studies (e.g., ~21% of patients in one south Indian cohort had diabetes), but not uniformly in all.

All studies used standard outcome definitions aligned with WHO/RNTCP criteria: **"successful outcome"** comprising **cured** (at least three consecutive negative cultures in the final months) or **treatment completed** (finished treatment course without evidence of failure), and **"unfavourable outcome"** typically comprising **death**, **treatment failure** (evidence of non-response or regimen change due to lack of improvement), **lost to follow-up (default)**, and sometimes **transfer out** if not known outcome. A few studies also tracked **sputum culture conversion** during treatment as an interim outcome marker [2,5].

Overall Treatment Outcomes

Treatment outcome distributions in these studies reaffirm the challenge of MDR-TB. **Favourable outcome rates** (cure plus completed) were consistently low, generally around 50% or less. For instance, a large Delhi cohort (2009–2014) documented a 53.3% favourable outcome rate [2]. Similarly, a Chandigarh study reported about 51.6% success [6]. A national analysis of early program cohorts (2007–2011) found an even lower success proportion (~34.5%) among those with outcomes available – although that was an evolving cohort with many patients still on treatment at analysis time, it nevertheless highlighted high interim rates of death and default [5]. Smaller studies echoed this (2023). Odisha [3] observed that only 52% of their hospital MDR-TB patients could be categorized as cured at treatment end. The remainder either defaulted (23%), failed therapy (3%), or died (21%). Another study from southern Odisha (Koraput region) similarly noted only ~45% success, with 22.5% loss to follow-up and 12.5% mortality [4]. In summary, less than half of MDR-TB patients in many Indian settings achieve a cure, underscoring the importance of identifying and addressing the reasons behind the high rate of poor outcomes.

We now present the key **predictors of treatment outcome** identified across these studies, categorized into major domains. For clarity, "unfavourable outcome" will refer collectively to failure, death, or default (any outcome other than success), as used in most analyses.

Patient Demographics and Socioeconomic Factors

Age: Advanced age was consistently associated with worse treatment outcomes. Patients above a certain age threshold (variously reported as ≥35 years or ≥45 years) had significantly higher odds of unfavourable outcomes compared to younger patients. For example, in the national cohort, being age 45 or older was linked to a higher risk of death or non-response [1]. Similarly, found that patients ≥35 had a greater likelihood of failure or default in Delhi [2]. This trend aligns with global data and likely reflects multiple factors: older patients may have more comorbid illnesses, weaker tolerance for the toxic treatment, or pharmacokinetic changes affecting drug levels. They might also present later to care or have had longer cumulative TB damage over life. By contrast, younger patients (e.g., <35) showed a higher probability of treatment success in these cohorts – indeed, one analysis noted younger age was an independent predictor of favourable outcome (roughly doubling the chance of success relative to older individuals).

Sex (Gender): Male gender emerged as a risk factor for poor outcomes in several studies. In Delhi's cohort, being male increased the odds of unfavourable outcome by about 1.4 times compared to females. It is also identified male sex as significantly associated with failure/death 1. Out of 788

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patients in that study, 68% were male, and this predominance of men among MDR-TB cases is typical; however, men's poorer outcomes may be due to factors such as higher rates of risk behaviours (smoking, alcohol) or differences in healthcare engagement. One study pointed out that female patients had lower loss to follow-up rates compared to males, suggesting better adherence among women in that context. Not all studies found gender to be significant – for instance, the Odisha study did not observe sex to influence outcome, possibly due to limited sample size or a more homogeneous patient group. Overall, though, the weight of evidence indicates **male MDR-TB patients are more prone to unfavourable outcomes** than females, echoing prior TB literature.

Socioeconomic and Regional Factors: While not uniformly reported in all studies, some insights can be drawn. Many MDR-TB patients in India come from disadvantaged backgrounds. For example, it is also noted that 89% of patients in the South Odisha hospital cohort study were from rural areas, which could imply challenges like poor access to health facilities, leading to delays or interruptions [3]. Low socioeconomic status often correlates with undernutrition and overcrowding, fueling both disease severity and hampering treatment. However, specific indicators like income or education were not explicitly analyzed in the majority of the studies we reviewed. One can infer that socioeconomic vulnerabilities underlie several of the clinical factors observed (like undernutrition). Further, certain regional challenges, such as tribal populations in remote areas, highlight that geographic isolation might contribute to higher default rates due to travel difficulties for supervised treatment. Overall, while **demographics and socioeconomic context** are not always independently analyzed, they form an important backdrop: older, male, and socioeconomically marginalized patients constitute a high-risk profile for poor MDR-TB treatment outcomes in India.

Clinical and Nutritional Status

Baseline Nutritional Status (Body Mass Index and Albumin): Perhaps the most striking and consistent predictor of outcome was the patient's nutritional status at the start of treatment. Multiple studies documented that **being underweight (BMI < 18.5 kg/m²)** is associated with significantly greater risk of an unfavourable outcome. In the 2017 national study, 60% of MDR-TB patients were underweight, and this was a significant factor in poor outcomes on multivariable analysis. Similarly, the Delhi study found that undernourished patients had higher odds of failure or death (with $p<0.001$). Janmeja *et al.* measured serum albumin as a marker of nutrition and reported that higher albumin levels at baseline were strongly predictive of treatment success (adjusted OR ~3.7 for success per unit increase). Conversely, hypoalbuminemia (reflecting malnutrition or severe inflammation) was linked to poor outcomes. The mechanisms are clear: malnutrition impairs immune function and tissue recovery, while also possibly affecting drug pharmacokinetics. An undernourished body is less resilient to the long, toxic MDR-TB treatment, and patients may not have the reserve to cope with side effects or prolonged illness. The importance of nutrition was further emphasized by a study that reported that patients who died during MDR-TB treatment had significantly lower BMI and evidence of hypoproteinemia more often than those who survived [4]. In fact, among the "main predictors of mortality" in their cohort were **smaller baseline BMI and low protein levels (hypoproteinaemia)**. These findings make a compelling case for nutritional support as part of MDR-TB management.

Weight Change During Treatment: Beyond baseline weight, *the weight trend* during therapy also appears informative. Parmar *et al.* noted that **any weight loss during treatment** was associated with poor outcomes. Typically, patients who respond to TB treatment gain weight or at least maintain it; those who continue losing weight may have ongoing disease activity or drug toxicity leading to malnutrition. This is consistent with clinical observations that failure cases often look emaciated by the end. It also suggests that periodic monitoring of weight can be a simple early warning for intervention.

Other Clinical Markers: The presence of **anemia** and **baseline leukocytosis or lymphopenia** was identified as a mortality predictor in the Odisha tribal area study. Anemia in TB can result from chronic disease or nutritional deficiencies, and leukocytosis indicates a high inflammatory burden, whereas lymphopenia might signal immune suppression (possibly from HIV or malnutrition). These lab parameters essentially reinforce the broader theme that a patient's general medical condition and immune-nutritional state heavily influence their ability to overcome MDR-TB. Patients in poor general health (low weight, low blood counts, etc.) at baseline are much more likely to succumb or not respond, compared to those in relatively better health.

Comorbidities:

- **HIV Co-infection:** TB/HIV co-infection is relatively less common in India than in Africa, but when present, it has a **dire effect** on MDR-TB outcomes. Nair *et al.* (2017) found HIV infection to be one of the strongest predictors of unfavorable outcomes. In their cohort, although only a small

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percentage had HIV, those who did had significantly higher mortality. This mirrors global evidence; HIV-positive TB patients have higher early mortality due to opportunistic infections and complications, and managing MDR-TB in an immunocompromised person is exceedingly challenging. Integrated TB/HIV treatment (including antiretroviral therapy) is necessary to improve outcomes for this group. The Koraput study also flagged **HIV seropositivity** as a main predictor of mortality. It is worth noting that the absolute number of HIV-MDR-TB cases in these studies is small, but the impact on outcomes is disproportionately large.

- **Diabetes Mellitus:** Diabetes, a common comorbidity in India, has been associated with poorer TB outcomes in drug-susceptible TB. For MDR-TB, the picture was a bit mixed in our review. Some studies included diabetes in their analysis but did not find a statistically significant impact on outcomes after adjustment. Janmeja *et al.* explicitly reported that co-morbid diabetes did not significantly affect treatment success in their analysis. However, it's plausible that diabetes contributes indirectly to challenges (for instance, diabetes can worsen TB severity and certain drug side effects). The lack of a strong signal could be due to sample size or because patients with diabetes were managed such that their disease was controlled. More recent and larger studies could better quantify the effect. At least one study in our search (Johnson *et al.* 2022) noted that 21% of their MDR-TB cases had diabetes, and generally, those with co-morbidities tended to have worse outcomes (they concluded co-morbidities overall were a problem). Hence, while not as prominent as HIV in these analyses, **diabetes and other chronic diseases** are still important to consider: they may affect patient immunity and the management complexity, which can influence adherence and outcome.
- **Other Comorbidities:** The Odisha study's mention of anemia, etc., we've covered as clinical markers. There was also a reference to patients on "concomitant medications for other co-existing diseases" by Panda *et al.* as being a negative predictor. This likely implies that patients who had additional illnesses (requiring other medications) did worse, possibly because those illnesses (like liver or kidney diseases, etc.) complicated TB treatment or because managing polypharmacy was difficult. It underscores that MDR-TB patients with any significant co-morbidity (be it respiratory diseases, renal impairment, etc.) represent a vulnerable group needing extra care.

Table 2: Summary of Included Studies with Predictors and Outcomes

Study	Design	Location	Sample Size	Success Rate (%)	Significant Predictors	Outcomes Assessed
Nair et al. (2017)	Retrospective cohort	Tamil Nadu	788	Approx. 46%	Male gender, age >45, HIV, underweight, missed doses	Death, default, failure
Sharma et al. (2020)	Record-based study	Delhi	394	53.3%	Male sex, age ≥35, non-adherence	Default, failure
Panda et al. (2023)	Retrospective hospital study	South Odisha	95	52%	Smoking, alcohol use, ADRs, adherence	Failure, default, death
Dash & Behera (2022)	Retrospective Observational Study	Southern Odisha	142	45%	Low BMI, hypoproteinemia, anemia, HIV, anemia, extensive disease	Mortality
Parmar et al. (2018)	Programmatic review	India (multi-state)	2012	34.5%	Low BMI, cavitary disease, drug resistance, missed doses	Failure, relapse, death

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Janmeja et al. (2018)	Hospital-based retrospective	Punjab	120	51.6%	Albumin levels, adherence, weight gain	Treatment success, failure
Johnson et al. (2022)	Retrospective observational	Karnataka	158	Not stated (but <50%)	Comorbidities, undernutrition	Unfavorable outcomes

Discussion

This systematic review provides a comprehensive overview of factors influencing MDR-TB treatment outcomes in India, drawing on a decade of research from 2015 to 2025. The findings reinforce many patterns observed worldwide, but also shed light on context-specific issues in India's fight against MDR-TB.

Principal Findings: It is found that unfavorable treatment outcomes in MDR-TB are strongly associated with a core set of patient and disease characteristics: **male sex, older age, undernutrition, HIV co-infection, extensive drug resistance, and markers of advanced disease (like cavitation)** were all linked to higher rates of failure, default, or death. On the other hand, timely sputum conversion and good treatment adherence were consistently linked to treatment success. Many of these predictors are interrelated and can be understood in terms of two broad themes: **patient vulnerability** (biological and social susceptibility) and **treatment manageability** (the complexity or difficulty of the treatment course for that patient).

Biologically vulnerable patients – e.g., malnourished or with compromised immunity (due to HIV or other illnesses) – are less equipped to cope with both the disease and the rigors of therapy. Malnutrition in particular emerged as a critical determinant in India, which is noteworthy but perhaps not surprising given that India has a dual burden of TB and undernutrition. The synergism between malnutrition and TB is well-documented: TB can cause weight loss and wasting, while malnutrition heightens progression from infection to disease and worsens outcomes. This bidirectional worsening likely explains why low BMI and low albumin had such predictive power. It is encouraging that this is a modifiable risk factor – interventions such as nutritional supplementation (e.g., the **Nikshay Poshan Yojana**, a government scheme providing nutritional support to TB patients) have been rolled out in recent years. Our review underscores the importance of effectively implementing and possibly expanding such schemes for MDR-TB patients, who might require even more intensive nutritional support than drug-susceptible TB patients.

Comorbid conditions like HIV amplify vulnerability. The management of an HIV-MDR TB co-infected patient is extremely challenging because of drug-drug interactions (between TB drugs and antiretrovirals), high pill burden, overlapping toxicities, and the need for robust immune reconstitution to overcome TB. The high mortality in this group calls for prioritization – for instance, ensuring antiretroviral therapy is started promptly and perhaps using adjunctive therapies. While numbers are smaller in India compared to Africa, every HIV-associated MDR-TB case demands careful, individualized management and close monitoring.

This review also found that **older age** was associated with worse outcomes in India, which is again consistent with TB control programs globally (younger patients tend to do better). Older patients may have more difficulty with the toxicity of drugs (e.g., more hearing loss from injectables or more likely to have renal impairment), and they may have a higher probability of other comorbidities (diabetes, chronic lung or kidney disease) that complicate TB treatment. They might also have more advanced lung damage from previous TB episodes. This suggests that elderly MDR-TB patients should be considered a high-risk group who might benefit from extra attention – for example, more frequent follow-ups or even different therapeutic approaches (if shorter regimens or surgery are indicated, etc., to shorten the ordeal). It also raises the question of whether the current dosing of drugs should be adjusted in the elderly to improve tolerance, something that research could explore.

Male patients' higher risk touches on the social dimension. Men in India are more likely to smoke and consume alcohol – behaviors that, as observed by Panda *et al.*, correlate with poor outcomes. Moreover, there could be differences in health-seeking behavior and support systems; some studies have conjectured that women, when they do enter TB care, might adhere more conscientiously, whereas men might be more likely to drop out due to work or migration. Our review can't definitively answer why male sex is a predictor,

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but it flags it as a consistent association. Tackling it may involve targeted counseling for male patients about adherence, engaging family members to support the patient, or addressing substance abuse issues among male TB patients (perhaps integrating de-addiction programs).

Disease severity and microbial factors – such as cavitation and additional drug resistance – highlight the importance of **early detection and appropriate regimen choice**. A patient with extensive bilateral cavitary disease essentially has a tougher job clearing infection; thus, they might benefit from adjunctive interventions (for example, adjuvant surgery to resect a cavity or high-intensity monitoring). Meanwhile, the presence of fluoroquinolone resistance or XDR strains at baseline is a game-changer. Thankfully, one major development between 2015 and 2025 has been the introduction of new drugs (like **bedaquiline, delamanid, pretomanid**) and regimens that have shown improved outcomes even for fluoroquinolone-resistant MDR-TB. For instance, the NIX-TB and ZeNix trials internationally demonstrated >85% success in XDR-TB with a bedaquiline-pretomanid-linezolid regimen, which is revolutionary compared to the ~30% success on old regimens. India has begun using these newer therapies under programmatic conditions. While our included studies mostly cover the pre-bedaquiline era or early introduction, one could expect that as these are scaled up, the historically grim outcomes for patients with additional drug resistance will improve. Future Indian studies will need to assess new predictors in the context of new regimens (e.g., perhaps baseline resistance will be less predictive if regimens are potent against resistant strains).

Treatment-related predictors like adherence and adverse events lead directly to programmatic strategies. Adherence is arguably the most addressable risk factor. The era of directly observed therapy (DOT) – having health workers monitor doses – was one attempt to ensure adherence, but MDR-TB's long treatment made daily DOT challenging to sustain. The insights from our review suggest multi-faceted adherence support is needed: counseling patients at the start about the importance of completing therapy, providing enablers (travel subsidies, food baskets, or digital solutions like video-DOT), and tracing patients immediately when doses are missed. The Indian program's recent adoption of **99DOTS** (a mobile phone-based reporting system) and other digital adherence technologies is a step in this direction. Moreover, recognizing that default often happens due to side effects or psychosocial stress, providing supportive care – managing side effects aggressively, and offering psychosocial support – is key. For example, for patients developing depression or psychosis on cycloserine, having access to psychiatric consultation and possibly switching the drug can prevent treatment cessation.

The finding that **alcohol and smoking** are predictors suggests that integrating addiction counseling or treatment into TB care could yield benefits. Some TB clinics have started to screen for alcohol use and provide brief interventions or referrals. Given the strong association observed, it might be worthwhile for the national program to formally incorporate substance use interventions as part of the MDR-TB case management.

Adverse drug reactions will likely become less frequent as the older toxic drugs (like kanamycin, capreomycin, ethionamide) are phased out of standard regimens. Already by 2020, India made all-oral longer regimens the norm, and by 2022, even the shorter regimen was modified to be injectable-free. This is a direct response to evidence of poor tolerability. Our review lends support to these policy changes: high rates of ototoxicity and other ADRs were clearly detrimental to outcomes. Bedaquiline and newer agents still have side effects (e.g., QT prolongation, hepatotoxicity) but are generally more manageable than injectables. Close monitoring remains essential, but we might see fewer patients stopping treatment due to side effects in the coming years, thanks to these regimen improvements.

Implications for Policy and Practice: This evidence base has already influenced policy (as seen with regimen changes). It should continue to drive **patient-centered approaches**. For instance, given the importance of nutrition, the TB program might consider enhanced nutritional support specifically for MDR-TB patients – perhaps higher caloric supplements or involving nutritionists in MDR-TB clinics. Given the importance of early conversion, ensuring patients get an **appropriate regimen from day one** is critical – meaning universal DST (drug susceptibility testing for both first- and second-line drugs) at baseline. This has been adopted as policy (with the rollout of line probe assays and Xpert MTB/XDR tests). The gap to address is implementing these quickly and widely so that no patient is kept on a partially effective regimen for long.

In conclusion, the period 2015–2025 yielded robust evidence on MDR-TB outcome predictors in India. The consistency of findings across multiple studies lends

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confidence that we have identified true and meaningful risk factors. Importantly, many of these factors are modifiable or can be addressed through targeted interventions. Male, older, undernourished, or HIV-positive patients can be flagged early for enhanced support; patients with heavy disease or resistant strains can be fast-tracked to stronger therapy; adherence and side effect management can be reinforced for those struggling with habits or drug toxicities. By acting on these predictors, TB programs in India can move the needle on MDR-TB outcomes. As of 2025, with new tools in hand and a better understanding, there is cautious optimism that the dismal 50% success rate can be lifted closer to the global target of 75–90% success in the coming years. Achieving this will be vital for India to meet the End TB goals by 2035.

Future Research Directions

Building on these findings, future research in India could delve deeper into certain predictors – for instance, the role of mental health (depression) in MDR-TB outcome, which has not been extensively studied but could be relevant given the long treatment duration and use of cycloserine. Additionally, genetic or microbiological factors (like specific strain lineages of *M. tuberculosis* or host genetic predisposition) were beyond our scope but represent an emerging frontier in understanding who does poorly. Another area is operational research on interventions: given we know adherence is crucial, what specific strategies (community-based care, family DOT, incentive programs) work best in the Indian context to improve adherence and thus outcomes? Studies testing those will be very valuable.

Conclusions

This systematic review of Indian studies from 2015 to 2025 shows that MDR-TB treatment outcomes remain poor, with success rates mostly at or below 50%. Unfavourable outcomes are consistently linked to older age, male sex, undernutrition, HIV co-infection, substance use, poor adherence, extensive disease, and adverse drug reactions, reflecting both biological vulnerability and challenges in treatment management. Addressing these factors through nutritional support, integrated TB-HIV care, substance use interventions, pharmacovigilance, digital and community-based adherence support, universal rapid drug-susceptibility testing, and wider adoption of all-oral regimens with novel agents is essential. Despite the limitations of mostly retrospective and heterogeneous studies, the findings highlight actionable priorities for improving outcomes. Focused support for high-risk groups and evaluation of new regimens and supportive interventions can help India progress toward national and global TB targets.

Limitations

It is important to consider the limitations of the evidence in this review. Most included studies were observational cohorts, many retrospective. This means they can show associations but not always prove causation. The confounding factors, for example, male sex may be a proxy for unmeasured factors like outdoor employment (leading to difficulty accessing the DOT center) or substance use. Many studies have used multivariable analysis to adjust for confounders, but the possibility of residual confounding remains. Additionally, definitions of some risk factors were not uniform (e.g., what constituted "poor adherence" varied across studies). Some studies had relatively small samples, which may limit generalizability – though taken together, the breadth of settings (from tertiary referral centers to peripheral tribal hospitals) suggests our conclusions are broadly applicable in India. Publication bias is another consideration: studies with significant findings (predictors identified) might be more likely to be published than those that found none, although in this field, most find at least some significant predictors.

Recommendations

For Clinical Practice

1. **Nutritional Interventions:** Baseline and serial monitoring of BMI and serum albumin should be integrated into MDR-TB management. Nutritional supplementation—beyond the current Nikshay Poshan Yojana—should be prioritized, particularly for undernourished patients and those showing weight loss during therapy.
2. **Management of High-Risk Patients:** Older adults, HIV co-infected individuals, and those with significant comorbidities (e.g., diabetes, anemia, chronic lung disease) require intensified clinical monitoring and individualized treatment support. HIV-MDR-TB patients should receive prompt ART initiation and integrated follow-up care.

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3. **Substance Use and Mental Health:** Routine screening and counseling for tobacco and alcohol use should be incorporated into MDR-TB treatment protocols. Mental health services—including depression screening and psychiatric support—should be made available, particularly given the psychological burden of long and toxic regimens.

For Programmatic and Policy Action

1. **Adherence Support and Monitoring:** Expansion of digital adherence technologies (e.g., 99DOTS, video-DOT, AI-based monitoring tools) should be accompanied by patient counseling, family engagement, and rapid tracing of missed doses.
2. **Adverse Drug Reaction (ADR) Management:** Strengthen pharmacovigilance systems for early detection and management of ADRs. All-oral regimens (bedaquiline, delamanid, pretomanid) should fully replace injectable-containing regimens to reduce toxicity-related defaults.
3. **Decentralized and Equitable Access:** Special strategies are required for rural and tribal populations, including mobile TB clinics, community health worker–led DOT, and teleconsultation platforms to reduce travel barriers and prevent loss to follow-up.
4. **Socioeconomic Support:** Socioeconomic enablers—such as conditional cash transfers, food baskets, and travel subsidies—should be expanded, with special attention to marginalized populations who face the greatest barriers to adherence.

For Diagnostics and Therapeutics

1. **Universal Drug Susceptibility Testing (DST):** Nationwide scale-up of rapid molecular diagnostics (Line Probe Assay, Xpert MTB/XDR) should be ensured to enable early initiation of appropriate regimens and minimize ineffective therapy.
2. **New and Shorter Regimens:** Broader access to shorter, all-oral regimens incorporating novel drugs should be prioritized under the National TB Elimination Programme, with mechanisms for pharmacovigilance and monitoring of resistance patterns.
3. **Adjunctive Interventions:** Selected high-burden patients (e.g., with cavitary disease or persistent positivity) may benefit from adjunctive surgical options or host-directed therapies, which should be explored in programmatic guidelines.

For Research and Surveillance

1. **Operational Research:**

Evaluate the effectiveness of interventions such as nutritional supplementation, adherence support strategies, and substance use counseling in real-world Indian settings.

1. **Emerging Predictors:**

Future studies should examine underexplored predictors of MDR-TB outcomes, including mental health status, genetic susceptibility (host and bacterial), and broader social determinants (migration, occupational exposure).

1. **Real-World Regimen Outcomes:**

Establish longitudinal monitoring systems to evaluate the outcomes of newer regimens (bedaquiline- and pretomanid-based), ensuring India-specific evidence for scale-up.

Conflict of Interest and Funding Declaration

The authors declare that **there are no conflicts of interest** related to the content of this systematic review. No financial support, grants, or funding from any public, commercial, or non-profit organizations was received for the conduct, authorship, or publication of this review. The work was carried out independently and solely for academic and research purposes.

Registration and Protocol

This systematic review was not registered in any prospective register such as PROSPERO, and no prior protocol was published.

Competing Interests

The authors declare that they have no competing interests related to this systematic review.

Availability of Data, Code, and Other Materials

The data collection forms, extracted data from included studies, and datasets used for analysis in this review are available from the corresponding author upon reasonable request. No analytic code or additional materials were generated or used in this review.

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List of Abbreviations

ADR Adverse Drug Reaction
ART Antiretroviral Therapy
BDQ Bedaquiline
BMI Body Mass Index
DLM Delamanid
DOT Directly Observed Therapy
DST Drug Susceptibility Testing
HIV Human Immunodeficiency Virus
MDR-TB Multidrug-Resistant Tuberculosis
NOS Newcastle-Ottawa Scale
NTBEP National TB Elimination Programme (India)
PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTO Pretomanid
RNTCP Revised National Tuberculosis Control Programme
TB Tuberculosis
WHO World Health Organization
XDR-TB Extensively Drug-Resistant Tuberculosis

Authors' Biography:

1. Dr Suvendu Kumar Panda, First Author, Corresponding author
Assistant Professor, Department of Pharmacology, MKCG, Medical College and Hospital, Berhampur, Odisha
Email ID: suvendukumarpanda041@gmail.com
Phone no. 9437748309.
ORCID ID:- https://orcid.org/0009-0008-5830-7351
Address: Academic block, MKCG Medical College and Hospital, Berhampur, Odisha, 760004
2. Dr Pratyush Mishra, Second author
Assistant Professor, Department of Pharmacology, MKCG, Medical College and Hospital, Berhampur, Odisha
Email ID: prometheus190890@gmail.com
Phone no. 9692179970
Address: Academic block, MKCG Medical College and Hospital, Berhampur, Odisha, 760004
3. Dr B. Jagadish, Third author
Senior Physician and Diabetologist, Masterdoctor Wellness and Clinic, Bhubaneswar, Odisha
4. Dr. Srikanta Panigrahy, Fourth author
Senior Resident, Department of Pharmacology, MKCG Medical College and Hospital, Berhampur
Email ID: srikantapanigrahy.panigrahy@gmail.com
Phone no. 83389 67503
Address: Academic block, MKCG Medical College and Hospital, Berhampur, Odisha, 760004
5. Dr Manisha Panda, Fifth Author
Assistant Surgeon, Ganjam District, Govt of Odisha
Email id:-manishapanda93.mp@gmail.com
Phone no:-8280114981

Author Contributions

- **Conceptualization:** Suvendu Kumar Panda
- **Methodology:** Suvendu Kumar Panda; Pratyush Mishra
- **Search strategy & literature search:** Pratyush Mishra; Suvendu Kumar Panda
- **Screening (titles/abstracts/full text):** Srikanta Panigrahy; Manisha Panda; Pratyush Mishra
- **Data extraction:** Srikanta Panigrahy; Pratyush Mishra; Manisha Panda
- **Quality assessment (NOS):** Pratyush Mishra; Suvendu Kumar Panda; Srikanta Panigrahy
- **Data curation:** Srikanta Panigrahy; Manisha Panda
- **Formal analysis & synthesis:** Suvendu Kumar Panda; Pratyush Mishra
- **Clinical interpretation:** B. Jagadish; Suvendu Kumar Panda
- **Visualization (tables, PRISMA):** Pratyush Mishra; Srikanta Panigrahy
- **Writing—original draft:** Suvendu Kumar Panda
- **Writing—review & editing:** Pratyush Mishra; B. Jagadish; Srikanta Panigrahy; Manisha Panda
- **Supervision & project administration:** Suvendu Kumar Panda

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