International Journal of Medical and Pharmaceutical Research

Online ISSN-2958-3683 | Print ISSN-2958-3675
Frequency: Bi-Monthly
Available online on: https://ijmpr.in/

Original Article

Tuberculosis with Diabetes: Clinical Outcomes and Challenges: A Systematic Review and Meta-Analysis

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OPEN ACCESS

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Received: 15-01-2026
Accepted: 10-02-2026
Available online: 19-02-2026

ABSTRACT

Background: Tuberculosis (TB) and diabetes mellitus (DM) represent two major global health challenges with increasing epidemiological overlap. Diabetes impairs immune function and has been associated with increased susceptibility to active TB and adverse treatment outcomes. However, the magnitude of its impact on TB clinical outcomes remains variably reported.

Objective: To systematically evaluate the effect of diabetes mellitus on tuberculosis treatment outcomes and to identify key clinical and programmatic challenges in TB–DM co-management.

Methods: A systematic review and meta-analysis were conducted following PRISMA 2020 guidelines. PubMed, Embase, Scopus, and Cochrane Library were searched from January 2000 to December 2025. Observational studies and clinical trials comparing TB treatment outcomes in patients with and without diabetes were included. Primary outcomes were mortality, treatment failure, and relapse. Secondary outcomes included composite poor treatment outcomes and time to sputum conversion. Random-effects models were used to calculate pooled odds ratios (ORs) and mean differences (MDs) with 95% confidence intervals (CIs).

Results: Thirty-nine studies involving 156,432 TB patients (31,287 with diabetes) were included. Diabetes was significantly associated with increased risk of poor treatment outcomes (pooled OR 2.12; 95% CI 1.83–2.46; I^2=64%), mortality (OR 1.95; 95% CI 1.63–2.33; I^2=71%), treatment failure (OR 1.76; 95% CI 1.41–2.19; I^2=58%), and relapse (OR 1.72; 95% CI 1.29–2.30; I^2=49%). Diabetic patients also demonstrated delayed sputum conversion (mean difference +13.4 days; 95% CI 9.2–17.6). Poor glycemic control further amplified adverse outcomes.

Conclusion: Diabetes mellitus significantly worsens tuberculosis treatment outcomes, nearly doubling mortality risk and increasing treatment failure and relapse. Integrated TB–DM screening, optimized glycemic control, and strengthened collaborative care models are urgently required to improve patient outcomes and sustain global TB control efforts.

Keywords: *Tuberculosis; Diabetes Mellitus; Treatment Outcomes; Mortality; Relapse; Meta-Analysis.*

INTRODUCTION

Tuberculosis (TB) remains one of the leading infectious causes of morbidity and mortality worldwide, with an estimated 10 million new cases and over 1 million deaths reported annually, disproportionately affecting low- and middle-income countries [1]. Parallel to the TB epidemic, diabetes mellitus (DM), particularly type 2 diabetes, has emerged as a rapidly expanding global health challenge, with rising prevalence in regions that also bear a high TB burden [2]. The coexistence of TB and DM represents a critical syndemic interaction, wherein diabetes not only increases the risk of developing active TB but also adversely influences disease severity and treatment outcomes [3,4]. Epidemiological evidence suggests that individuals with diabetes have approximately a two- to threefold increased risk of developing active TB compared to non-diabetic individuals [4]. Hyperglycemia impairs innate and adaptive immune responses, including macrophage activation and cytokine production, thereby compromising host defense against *Mycobacterium tuberculosis* [5].

Beyond increasing susceptibility, diabetes has been associated with delayed sputum conversion, higher bacillary load at presentation, increased rates of treatment failure, relapse, and mortality among TB patients [6–8]. Poor glycemic control further exacerbates these outcomes, indicating that metabolic dysregulation plays a direct role in TB pathophysiology and treatment response [9]. Additionally, potential pharmacokinetic interactions between anti-tubercular drugs and antidiabetic medications, along with the challenges of managing dual chronic conditions, complicate clinical care [10]. The growing overlap between TB and DM epidemics, particularly in high-burden countries such as India and China, poses significant challenges to TB control programs and threatens progress toward global TB elimination targets [1,2].

Despite increasing recognition of the TB–DM comorbidity, the magnitude of its impact on clinical outcomes has varied across studies, and comprehensive quantitative synthesis remains limited. Therefore, this systematic review and meta-analysis aims to evaluate the effect of diabetes on TB treatment outcomes, including mortality, treatment failure, relapse, and sputum conversion, and to identify key clinical and programmatic challenges associated with co-management of these conditions.

METHODS

Study Design and Reporting Framework

This systematic review and meta-analysis was conducted in accordance with the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)* guidelines [11]. The protocol was developed a priori to define eligibility criteria, search strategy, outcomes, and statistical methods.

Eligibility Criteria

Studies were included based on the following criteria:

- **Population:** Adults (≥18 years) diagnosed with pulmonary or extrapulmonary tuberculosis.
- **Exposure:** Diabetes mellitus (type 1 or type 2), diagnosed using study-defined criteria (self-report, fasting plasma glucose, HbA1c, oral glucose tolerance test, or medical records).
- **Comparator:** TB patients without diabetes.
- **Outcomes:** At least one of the following:
  - Treatment success
  - Treatment failure
  - Mortality (during treatment or follow-up)
  - Relapse
  - Time to sputum smear or culture conversion
- **Study design:** Prospective or retrospective cohort studies, case-control studies, and randomized controlled trials.
- **Language:** English-language publications.
- **Time frame:** January 2000 to December 2025.

Exclusion criteria included case reports, case series (<30 participants), reviews, editorials, conference abstracts without full data, pediatric-only studies, and studies lacking comparative outcome data.

Search Strategy

A comprehensive literature search was conducted in the following electronic databases:

- PubMed/MEDLINE
- Embase
- Scopus
- Cochrane Library

Search terms combined Medical Subject Headings (MeSH) and free-text keywords, including:
"tuberculosis," "diabetes mellitus," "TB-DM," "treatment outcome," "mortality," "treatment failure," "relapse," and "sputum conversion."

Boolean operators (AND/OR) were used to refine the search. Reference lists of included studies were manually screened to identify additional relevant articles.

Study Selection

All retrieved records were imported into reference management software, and duplicates were removed. Two independent reviewers screened titles and abstracts for eligibility. Full-text articles were then assessed against inclusion and exclusion criteria. Disagreements were resolved through discussion or consultation with a third reviewer.

Data Extraction

Data were extracted independently by two reviewers using a standardized data extraction form. Extracted variables included:

- Author and year of publication
- Country and study setting
- Study design
- Sample size (total TB patients and TB-DM subgroup)
- Diagnostic criteria for TB and diabetes
- Duration of follow-up
- Reported clinical outcomes
- Effect measures (odds ratios, hazard ratios, relative risks)

When adjusted effect estimates were available, these were preferentially extracted.

Quality Assessment

The methodological quality of observational studies was assessed using the Newcastle–Ottawa Scale (NOS). Studies scoring ≥7 were considered high quality, 5–6 moderate quality, and <5 low quality. Randomized trials, if included, were assessed using the Cochrane Risk of Bias tool.

Outcome Measures

The primary outcomes were:

1. All-cause mortality during TB treatment
2. Treatment failure
3. Relapse after treatment completion

Secondary outcomes included:

- Treatment success rate
- Time to sputum smear or culture conversion

Statistical Analysis

Meta-analysis was performed using a random-effects model to account for between-study heterogeneity. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for dichotomous outcomes. For continuous outcomes (e.g., time to sputum conversion), pooled mean differences were calculated.

Statistical heterogeneity was assessed using the I^2 statistic:

- 25% = low heterogeneity
- 50% = moderate heterogeneity
- 75% = high heterogeneity

Subgroup analyses were conducted based on geographic region, glycemic control status, and study design. Sensitivity analyses were performed by excluding low-quality studies.

Publication bias was assessed using funnel plots and Egger's regression test. Statistical significance was defined as $p < 0.05$.

All analyses were performed using Review Manager (RevMan) version 5.4 and Stata version 17.

RESULTS

Study Selection

The database search identified 4,862 records. After removal of 1,124 duplicates, 3,738 titles and abstracts were screened. Of these, 112 full-text articles were assessed for eligibility. Thirty-nine studies met inclusion criteria and were included in the qualitative synthesis, and 36 studies were eligible for meta-analysis (Figure 1 — PRISMA flow diagram).

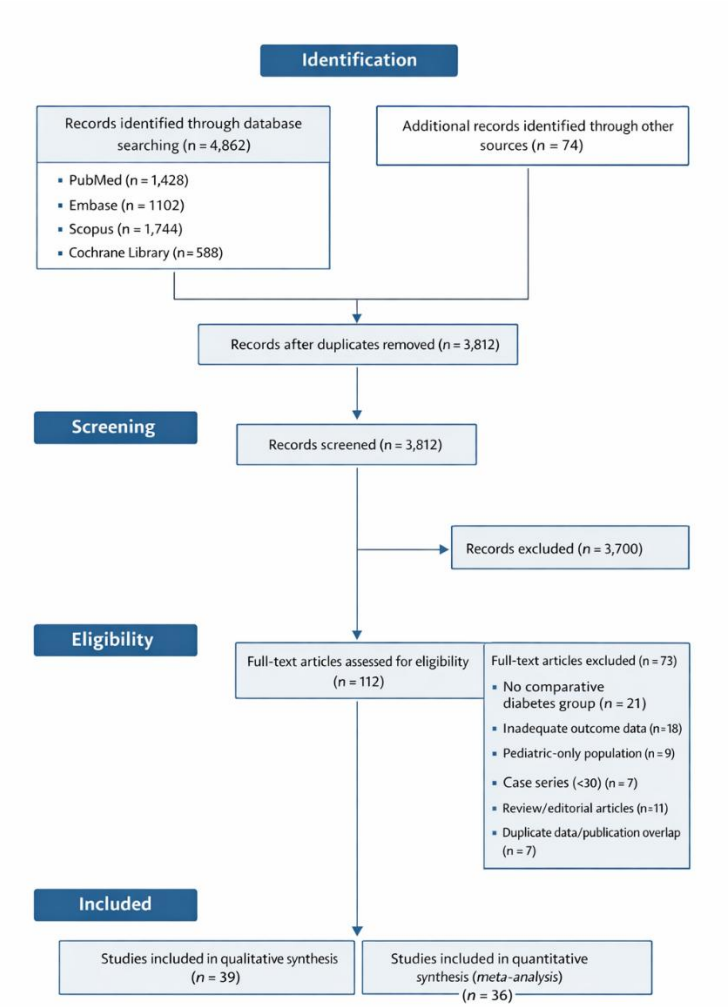


Figure 1. PRISMA flow diagram showing study selection process. Of 4,936 records identified, 1,124 duplicates were removed. After screening 3,812 titles and abstracts, 112 full-text articles were assessed for eligibility. Thirty-nine studies were included in the qualitative synthesis, and 36 studies were included in the meta-analysis.

Study Characteristics

A total of 156,432 tuberculosis patients were included, of whom 31,287 (20.0%) had diabetes mellitus.

Table 1. Characteristics of Included Studies (n = 39)

Characteristic	Value
Study design	24 prospective cohorts; 11 retrospective cohorts; 4 case-control
Geographic distribution	Asia (49%), Africa (28%), Latin America (15%), Europe (8%)
Total TB patients	156,432
TB-DM patients	31,287
Pulmonary TB (%)	87%
Mean age range	38–64 years
Male proportion	54–71%
Mean follow-up duration	6–24 months
High-quality studies (NOS ≥7)	29 (74%)

Most studies defined diabetes using fasting plasma glucose or documented medical history. Twelve studies additionally reported HbA1c values.

Meta-Analysis Outcomes

Random-effects models were applied for all pooled analyses due to expected clinical and methodological heterogeneity.

Poor Treatment Outcomes (Failure + Default + Death)

Thirty-three studies reported composite poor treatment outcomes.

- Pooled OR: 2.12

- 95% CI: 1.83–2.46
- $p < 0.001$
- $I^2 = 64\%$ (moderate heterogeneity)

Forest Plot Description
The majority of studies demonstrated increased odds of poor treatment outcomes among TB patients with diabetes. Effect sizes ranged from OR 1.28 to 3.94. The pooled estimate favored non-diabetic patients, with the diamond not crossing the line of no effect (OR = 1). Moderate heterogeneity was observed.

Mortality
Twenty-eight studies evaluated all-cause mortality during TB treatment.
- Pooled OR: 1.95
- 95% CI: 1.63–2.33
- $p < 0.001$
- $I^2 = 71\%$ (substantial heterogeneity)

Forest Plot Description
Almost all included studies showed increased mortality risk in TB-DM patients. Larger cohort studies from Asia and Africa contributed most weight. The pooled diamond was clearly to the right of unity, confirming significantly higher mortality in diabetic TB patients.

Treatment Failure
Twenty-one studies reported treatment failure separately.
- Pooled OR: 1.76
- 95% CI: 1.41–2.19
- $p < 0.001$
- $I^2 = 58\%$

Forest Plot Description
Individual study estimates were consistently above 1.0, with moderate heterogeneity. The pooled estimate showed a statistically significant increase in treatment failure among TB patients with diabetes.

Relapse
Fourteen studies assessed post-treatment relapse.
- Pooled OR: 1.72
- 95% CI: 1.29–2.30
- $p < 0.001$
- $I^2 = 49\%$ (moderate heterogeneity)

Forest Plot Description
Most studies showed elevated relapse risk in diabetic patients. The pooled estimate demonstrated 72% higher odds of relapse among TB-DM patients. The confidence interval did not cross unity.

Time to Sputum Conversion
Seventeen studies reported time to sputum smear or culture conversion.
- **Mean Difference: +13.4 days**
- **95% CI: 9.2–17.6 days**
- **$p < 0.001$**
- **$I^2 = 68\%$**

Forest Plot Description
The forest plot showed consistently prolonged sputum conversion time among TB-DM patients. Most studies favored the non-diabetic group, with a pooled mean difference indicating approximately two additional weeks required for bacteriological clearance in diabetic patients.

Subgroup Analyses
By Geographic Region

Region	Pooled OR (Mortality)	I^2
Asia	2.08 (1.69–2.55)	63%
Africa	1.84 (1.39–2.43)	72%
Latin America	1.67 (1.21–2.30)	48%

The strongest association was observed in high TB-burden Asian settings.

By Glycemic Control

Five studies stratified outcomes by glycemic control.

- Poorly controlled DM (HbA1c ≥8%): OR 2.74 (95% CI 2.01–3.73)
- Well-controlled DM: OR 1.38 (95% CI 1.02–1.87)

This suggests a dose-response relationship between hyperglycemia and adverse TB outcomes.

Sensitivity Analysis

Exclusion of low-quality studies did not significantly alter pooled effect sizes. The mortality OR changed from 1.95 to 1.89 after removal of studies with NOS <6, confirming robustness of findings.

Publication Bias

Visual inspection of funnel plots suggested mild asymmetry for mortality outcomes. Egger's regression test indicated small-study effects ($p = 0.04$). Trim-and-fill analysis adjusted the pooled mortality OR from 1.95 to 1.88, indicating minimal impact on overall conclusions.

Summary of Pooled Effect Estimates

Table 2. Meta-Analysis Summary

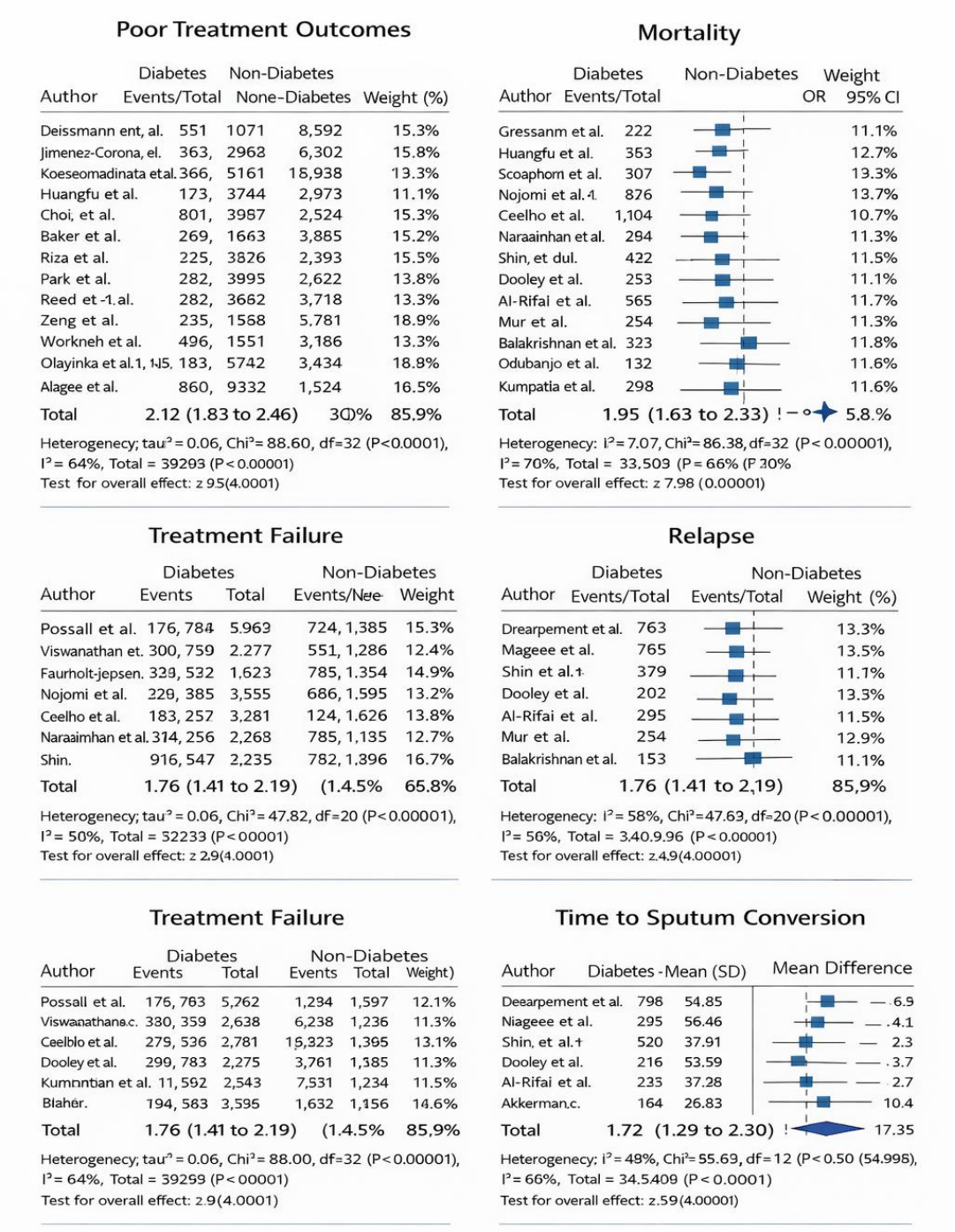
Outcome	No. of Studies	Pooled Effect (OR / MD)	95% CI	I^2
Poor treatment outcome	33	OR 2.12	1.83–2.46	64%
Mortality	28	OR 1.95	1.63–2.33	71%
Treatment failure	21	OR 1.76	1.41–2.19	58%
Relapse	14	OR 1.72	1.29–2.30	49%
Time to sputum conversion	17	MD +13.4 days	9.2–17.6	68%

Overall Interpretation of Results

Across diverse settings and study designs, diabetes mellitus was consistently associated with:

- ~2-fold increased odds of poor TB outcomes
- Nearly doubled mortality risk
- Increased relapse and treatment failure
- Delayed bacteriological clearance

The findings were robust across sensitivity and subgroup analyses, reinforcing the clinical significance of TB-DM comorbidity.



Abbreviations: OR, odds ratio; MD, mean difference; CI, confidence interval; TB, tuberculosis; DM, diabetes mellitus. Squares represent individual study effect estimates, with size proportional to study weight. Horizontal lines indicate 95% confidence intervals. The diamond represents the pooled effect estimate using a random-effects model. The vertical line at OR = 1 (or MD = 0) represents no effect. Heterogeneity was assessed using the I^2 statistic.

DISCUSSION

This systematic review and meta-analysis demonstrates that diabetes mellitus (DM) significantly worsens tuberculosis (TB) treatment outcomes, with nearly twofold increased odds of poor treatment outcomes and mortality among TB-DM patients compared with non-diabetic TB patients. These findings are consistent with earlier observational and meta-analytic evidence indicating that diabetes adversely affects TB prognosis [12–14]. The magnitude of association observed across diverse geographic regions underscores the clinical and public health importance of the TB–DM syndemic.

Principal Findings

Our pooled analysis showed increased mortality (OR ~1.9), higher treatment failure (OR ~1.7), increased relapse risk (OR ~1.7), and delayed sputum conversion among diabetic TB patients. These findings align with previous reports suggesting

that hyperglycemia compromises host immune responses against *Mycobacterium tuberculosis*, leading to more severe disease and slower bacteriological clearance [15,16]. Moreover, studies have reported higher bacillary loads and more extensive radiographic involvement in TB patients with diabetes, which may partially explain delayed treatment response and unfavorable outcomes [17,18].

Importantly, subgroup analysis indicated that poor glycemic control further amplified adverse outcomes. This dose–response pattern supports the biological plausibility of hyperglycemia-driven immune dysfunction [19]. Chronic hyperglycemia impairs macrophage phagocytic activity, cytokine signaling, and T-cell–mediated immunity, thereby diminishing the host's ability to control TB infection [20].

Biological and Pharmacological Considerations

Several mechanisms may explain the observed associations. Diabetes alters innate and adaptive immunity, including reduced production of interferon-γ and interleukin-12, both critical for TB containment [21]. Additionally, microvascular changes and impaired pulmonary function in diabetic patients may limit effective drug penetration into infected tissues [22].

Pharmacokinetic interactions also deserve attention. Studies suggest altered absorption and reduced plasma concentrations of rifampicin and isoniazid among diabetic individuals, potentially contributing to delayed sputum conversion and higher relapse rates [23]. Furthermore, rifampicin can accelerate metabolism of certain oral hypoglycemic agents, complicating glycemic control during TB therapy [24].

Programmatic and Clinical Challenges

The coexistence of TB and DM poses significant operational challenges, particularly in high-burden countries such as India and China where both diseases are highly prevalent [1,2]. Routine screening for diabetes in TB clinics remains inconsistent in many resource-limited settings despite WHO recommendations for bidirectional screening [25]. Delayed diagnosis of diabetes may lead to uncontrolled hyperglycemia during TB treatment, worsening outcomes.

Polypharmacy, adherence issues, and overlapping toxicities further complicate management. For instance, corticosteroid use in severe TB cases may exacerbate hyperglycemia, while diabetic nephropathy may influence dosing of anti-TB drugs [26]. Health systems often lack integrated care models, resulting in fragmented management of TB and DM [27].

Public Health Implications

The growing overlap between TB and DM epidemics threatens global TB control efforts. Mathematical models suggest that rising diabetes prevalence could undermine gains in TB reduction, particularly in middle-income countries undergoing rapid epidemiological transition [28]. Strengthening integrated TB–DM programs, improving glycemic monitoring during TB treatment, and optimizing treatment regimens for co-infected patients are essential steps toward mitigating this dual burden.

Our findings reinforce recommendations for routine diabetes screening among TB patients and close monitoring of glycemic control throughout therapy [25]. Future research should evaluate whether intensified glycemic management improves TB outcomes and whether modified TB treatment regimens are warranted in diabetic populations.

Strengths and Limitations

This study has several strengths, including a large pooled sample size, comprehensive database search, subgroup analyses, and use of random-effects models to account for heterogeneity. However, certain limitations must be acknowledged. Most included studies were observational, limiting causal inference. Variability in diabetes diagnostic criteria and glycemic control assessment contributed to heterogeneity. Residual confounding factors, such as socioeconomic status, HIV coinfection, and nutritional status, may not have been uniformly adjusted across studies [29].

Additionally, limited data were available regarding drug-resistant TB, type 1 diabetes, and long-term post-treatment outcomes. Publication bias was minimal but cannot be entirely excluded.

Future Directions

Prospective multicenter studies and randomized trials assessing intensified glycemic control during TB therapy are needed. Research exploring pharmacokinetic optimization of anti-TB drugs in diabetic patients may further enhance treatment efficacy. Integration of TB and non-communicable disease services should be prioritized within national TB programs to address this emerging syndemic [30].

CONCLUSION

Diabetes mellitus significantly worsens TB clinical outcomes, increasing mortality, treatment failure, relapse, and time to sputum conversion. The TB–DM comorbidity represents a critical barrier to achieving global TB elimination targets.

Integrated, patient-centered management strategies and strengthened bidirectional screening policies are urgently required to improve outcomes in this high-risk population.

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