**The effects of diabetes on tuberculosis treatment outcomes: an updated systematic review and meta-analysis**

***Running head: diabetes and tuberculosis treatment outcomes***

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**Summary**

**Background**

Previous evidence synthesis has suggested diabetes mellitus (DM) worsens tuberculosis (TB) treatment outcomes. However, these reviews are limited by the number, robustness and conflicting results among the studies included. We conducted a systematic review to update earlier analyses and to explore heterogeneity between studies.

**Methods**

MEDLINE, EMBASE, AIM, LILACS, IMEMR, IMSEAR and WPRIM were searched between 1/1/1980 and 23/07/2018 unrestricted by language or region. All cohort and case-control studies investigating the difference in TB treatment outcomes amongst TB-DM patients compared to those with TB alone were included. Two reviewers independently assessed titles, abstracts, and extracted data. Culture conversion at two/three months, all-cause mortality, treatment failure, relapse, and multi-drug resistant TB (MDR-TB) were evaluated using random effects meta-analysis with generic inverse variance. Heterogeneity was explored using sub-group analyses and meta-regression. [PROSPERO ID: CRD42015026927]

**Results**

One hundred and four publications were identified. Sixty four studies including 56,122 individuals with TB-DM and 243,035 with TB, reported on death. Some outcomes showed substantial heterogeneity between studies which we could not fully explain though confounding adjustment and country income level accounted for some of the differences. TB-DM patients had higher odds of death (Odds ratio(OR)=1.88, 95%CI: 1.59-2.21) and relapse (OR=1.64, 95%CI: 1.29-2.08) compared to TB patients. More limited evidence suggested TB-DM patients had double the risk of developing MDR-TB (OR=1.98, 95%CI: 1.51-2.60).

**Conclusions**

DM is associated with increased risks of poor TB treatment outcomes, particularly mortality, and may increase risk of developing primary MDR-TB. Cost-effectiveness of interventions to enhance TB-DM treatment should be assessed.

**Key words**

Tuberculosis, diabetes, treatment outcomes, epidemiology, public health

**Introduction**

Tuberculosis (TB) remains an important public health issue globally; in 2017 there were an estimated 10 million incident cases and 1.6 million deaths worldwide making TB the primary cause of infectious disease mortality.[1] The International Diabetes Federation estimated that 451 million people were living with diabetes mellitus (DM) in 2017, half of whom were undiagnosed, and that by 2045 this would increase to 693 million.[2, 3] DM prevalence is particularly high and rising in South East Asia, where 58% of incident TB occurs. DM has long been considered to increase infection risk and severity.[4] Furthermore, DM complications such as kidney and cardiovascular diseases may complicate TB treatment.[4] With the rising pandemic of type 2 DM, the relationship between DM and TB has drawn more attention in academic research.[5-11]

An earlier systematic review suggested that DM worsens TB treatment outcomes.[7] However the studies included in this review had many limitations, in particular lacking control of potential confounders.[7] This review also only identified a handful of studies that had been able to assess the associations between DM and longer term TB outcomes (relapse or recurrence), or the development of drug resistance.[7] Many new studies have now been published, but few further comprehensive reviews including multiple outcomes have been undertaken.[12, 13] All earlier reviews have found substantial heterogeneity between studies, but have not attempted to explore this quantitatively, or assess the robustness of the evidence base for each outcome.

We thus performed a new systematic review to estimate the magnitude of the impact of DM on selected TB treatment outcomes, given the recently published data available, and to explore the anticipated heterogeneity between included studies.

**Methods**

We included cohort and case-control studies of patients with newly diagnosed TB. The key exposure was DM (as defined by the individual studies – generally self-reported by patients, abstracted from medical records, and / or through blood glucose / glycated haemoglobin (HbA1c) testing). The main outcomes included were death, treatment failure, recurrence and relapse, all defined according to WHO criteria.[14] Due to the variable and often interchangeable definition used for recurrence and relapse in reviewed studies, we decided to combine these two outcomes as one—relapse.[14] Sputum conversion at two/three months (as an important proxy of treatment outcome) and multi-drug resistant TB (MDR-TB) (as a longer-term treatment outcome) were also investigated.

***Search strategy***

We searched the following electronic scientific journal databases for studies published from the 1/1/1980 up to 23/07/2018: Medline (via PubMed), EMBASE (via Embase.com), African Index Medicus (AIM), Literature in the Health Sciences in Latin America and Caribbean (LILACS), Index Medicus for the Eastern Mediterranean Region (IMEMR), Index Medicus for the South-East Asian Region (IMSEAR), and Western Pacific Region Index Medicus (WPRIM) (all via WHO global index medicus). The start date was chosen as by this point rifampicin was in common use as a mainstay of TB treatment. We used both (Medical Subject Headings) MeSH and keyword terms (tuberculosis, diabetes mellitus, risk factor, outcome) in combination with standard Boolean operators to create a sensitive search strategy (Appendix 1). We also identified potentially relevant titles through conference proceeding searches, contacting specialists in the field and completing a citation search (via Scopus) on an earlier review by Baker et al.[7]

***Inclusion and exclusion criteria***

Cohort and case-control studies examining the difference in TB treatment outcomes between TB-DM and TB only patients were included. Studies were included irrespective of language, study setting, TB type (i.e. pulmonary TB or extra-pulmonary TB), ascertainment method used for TB or DM, DM sub-type (type 1 and type 2 DM), or presence of co-morbidities among the study population.

We excluded: non-research articles, abstracts without sufficient quantitative information, studies with no appropriate control group (i.e. TB only group) or TB-DM group, studies using non-standard TB treatment regimes, studies with no TB treatment recorded, studies conducted among patients with severe conditions or among TB patients with known drug resistance at baseline, studies that did not compare TB treatment outcomes amongst those with and without DM (e.g. studies of the incidence of TB amongst those with DM), studies amongst children, and studies we could not obtain from any sources (i.e. online databases, library request, or by contacting authors).

***Study selection, data extraction***

Titles and abstracts identified through searches were screened for relevance by two of three reviewers independently (CU, JC, or FP). Full text of potentially relevant articles were retrieved and assessed for eligibility. Two of four researchers (PH, CU, JC or FP) independently extracted data into an online data extraction form.[13] Native language researchers assisted in eligibility assessment and data extraction of non-English language papers. Data extracted included study characteristics (study type, study period, country of the study, type of TB, TB/DM diagnosis definition, language, exclusion criteria, and TB treatment regimen), baseline participant characteristics (age, sex, body mass index (BMI) or related measures, fasting blood glucose (FBG) or related measures, HIV status, new TB cases, TB/DM history, TB type, culture positivity, new DM cases, and hypertension status), potential confounders measured or adjusted for.[15] Any discrepancies identified in data extraction were adjudicated by a third researcher (JC or FP).

Where data was not available in publications we contacted study authors to provide more detailed information, out of 33 authors contacted seven replied.

***Statistical analysis***

We pooled studies statistically aiming to summarise conflicting evidence. Random effects meta-analysis, which allows for a distribution of true effect sizes, was chosen due to the likely clinical heterogeneity between the studies included. We conducted meta-analyses for death, treatment failure, relapse, presence of MDR-TB, and sputum culture conversion at two/three month separately. We also combined death and treatment failure as a single outcome in meta-analysis since death is a “competing risk” for treatment failure. All statistical analyses were conducted in Stata 15.[16]

***Sub-group analyses, sensitivity analyses, and meta-regression***

Heterogeneity of effect estimates was assessed using the *I2* statistic. We performed meta-regression to explore the effects of the following pre-specified variables that might explain heterogeneity; income level of study country (low and middle versus high),[17] method of exposure ascertainment (DM defined using glucose or glycated haemoglobin (HbA1c) test versus self-report or medical records or not reported) and adjustment for confounding (none or any).

We were aware of some potentially overlapping studies (i.e. study sample drawn from the same dataset within overlapping time periods), thus some sensitivity analyses were performed by removing these potential overlapping studies, but results were very similar to the main findings (results not shown).

Publication bias was assessed using Begg’s funnel plot by plotting the estimates of effect against standard errors. Where potential publication bias was identified, cumulative meta-analysis was used to assess the individual influence of each study contributing to the pooled assessment of the association.

***Population Attributable Risk (PAR)***

We calculated the PAR of TB death associated with DM using the standard Levin’s formula.[18] We estimated that the prevalence of DM in TB patients was 10—40% from TANDEM[19] and other studies[20, 21]) and estimated the RR (converted from OR) from the meta-analysis of death.

***Risk of bias assessment***

We used the Newcastle-Ottawa Scale to assess risk of bias for each individual study (Supplementary Table 1) and summarised the strength of the overall body of evidence contributing to each outcome in a Grading of Recommendations, Assessment, Development and Evaluations (GRADE) table.[22]

**Findings**

***Search results***

We identified 20,455 articles (Figure 1); after screening, we included 104 publications. One publication[23] included two separate cohorts in the U.S. and Mexico, therefore in analyses it was treated as two separate studies; thus in total 105 studies were included in the review. The previous review included 33 studies; we included 49 studies published over the same time period (i.e. up to the end of 2010). One study reported outcomes using statistical methods (i.e. using survival analysis to explore time to culture conversion) we could not combine with other studies. It showed that DM was associated with delayed culture conversion time (see Appendix 2 for more details).[24]

Most (70) studies used logistic regression and reported outcomes in format of Odds Ratio (OR). Twelve studies reported results using Hazard Ratios (HR),[25-36] but as there was no statistically significant difference between studies reporting results as HR and those as OR (results not shown), we reported OR as the overall estimate.

Of the 104 studies included in meta-analyses, 18 reported culture conversion at two/three months, 72 reported death (including studies reporting only adjusted estimates), 35 reported “death and failure”, 20 reported relapse (i.e. relapse or recurrence), and 19 studies reported MDR-TB (Table 1). Twenty-six studies were prospective cohort studies, ten were case-control studies, and 68 were retrospective cohort studies. Forty-six studies were from high income countries, 38 studies from upper-middle income countries, 14 from lower-middle income countries, and five from a low income country (one study did not report study country). Sample sizes ranged from 50 to 55,883, seven studies had large sample sizes over 12,000.[37-43]

All studies were conducted among both men and women (mainly from hospital or TB tertiary care centres), apart from one study conducted among mostly male prisoners.[40] The average age of the participants was between 30 and 70 years old in the included studies, and TB patients with DM were older than those without. Most studies reported the use of standard TB treatment regimen, but 30 (42.3%) studies did not report the treatment regimen. Twelve studies were conducted among TB patients without a history of prior TB.[30, 32, 43-52] Other studies which reported on TB history found that most patients (generally over 75%) were new TB patients. Methods of identifying DM used in studies included self-report, medical record review, use of anti-DM treatment, measurement of FBG, random blood glucose, or HbA1c test.

Forty seven studies reported on completeness of follow-up which we defined as those with a known outcome (i.e. excluding patients who defaulted, transferred out, abandoned or refused treatment, withdrew due to an adverse drug reaction, with outcome not recorded, or lost to follow-up). For most of these studies, completeness of follow-up was high (over 80%).

Forty eight of 104 studies made adjustment for at least one confounding variable for any outcome measure. Most of these studies adjusted for age and sex, though some adjusted for age only. A few studies adjusted for other socio-demographic factors such as marital status, ethnicity, and education. Only a small number of studies adjusted for HIV status, though most studies excluded patients with HIV or took places in settings where HIV prevalence is relatively low. A number of studies adjusted for other factors associated with either TB treatment outcomes or with DM risk (or both), such as smoking, drug abuse (including alcohol use), homelessness, or incarceration. Some studies also adjusted for clinical variables such as previous TB history, chest X-ray results, cavitation, sputum smear positivity at baseline, time to sputum clearance (i.e. whether there was *Mtb* in a sputum sample), TB symptoms, drug resistance/susceptibility patterns, and co-morbidities. It is plausible that some of these clinical variables, particularly those associated with baseline severity of TB, may be on the pathway between DM and a poor outcome (particularly death during TB treatment); adjusting for them might therefore over-adjust and underestimate the effects of DM, though this is uncertain at present.[7]

***Effect of DM on death***

The pooled OR for death among 64 studies (with unadjusted estimates) was 1.88 (95%CI: 1.59-2.21; *I2*=93%; Figure 2). The association appeared to be slightly stronger among 26 studies that used blood glucose measures (e.g. FBG or HbA1c) (OR=1.97, 95%CI: 1.51-2.59; *I2*=93%) compared to 38 studies using self-reported or medical records (OR=1.70, 95%CI: 1.50-1.93; *I2*=68%; Figure 3), but this was not statistically significant (*b*=1.09, 95%CI: 0.74-1.59, P=0.67, R2=-2.2%; see meta-regression results Appendices 3 and 4). The association was similar in low income countries (34 studies in total; OR=1.80, 95%CI: 1.35-2.40; *I2*=91%) and high income countries (30 studies in total; OR=1.97, 95%CI: 1.64-2.35; *I2*=89%; Figure 4). Twenty-four studies reported adjusted estimates for mortality (see Figure 5).[20, 25-32, 34, 35, 40, 48, 49, 53-62] Six of these studies had adjusted for all key confounders (age, sex, and HIV status) and had not adjusted for any clinical variables (i.e. baseline severity of TB) that might potentially be more likely to lead to early death and hence may overadjust for the effects of DM.[25, 27, 35, 49, 56, 57] The pooled results for this subgroup showed a strong association between DM and death among TB patients (OR=2.83, 95%CI: 1.45-5.52; *I2*=47%; see Figure 6).

However, meta-regression results showed that method of DM diagnosis, study design, confounding adjustment, or country income level could not explain the large heterogeneity among studies (see Appendices 3 & 4).

Overall, the population attributable risk suggested that around 8—25% deaths during TB treatment in entire populations could potentially be statistically attributed to DM.

***Effect of DM on death and treatment failure***

The pooled OR for “death and failure” as a combined treatment outcome was 1.65 (95%CI: 1.39-1.96; *I2*=88%; Figure 7) among 35 studies. The pooled OR for “death and failure” among 18 studies using blood glucose measures to identify DM was 1.53 (95%CI: 1.23-1.89) and it was 1.71 (95%CI: 1.34-2.18) among those using self-report data or medical records (Figure 8). The heterogeneity (*I2*=88%) was high among studies using any blood glucose measures to diagnose DM, possibly due to the different laboratory methods and tests used, but heterogeneity was somewhat lower (*I2*=70%) in the subgroup of studies defining DM based on self-report data or medical records (Figure 8). The association was stronger among 22 studies conducted in low income countries (OR=1.90, 95%CI: 1.43-2.53) compared to 13 studies conducted in high income countries (OR=1.52, 95%CI: 1.17-1.98; Figure 9), P value for difference in OR from meta-regression was 0.03 after accounting for other factors (DM diagnosis and study design) (Appendices 5 and 6). Heterogeneity was however high in both country income level subgroups (84% and 87% respectively). We found two studies which reported an adjusted association for “death and failure”;[63, 64] and another five reported for “failure” only,[20, 37, 45, 48, 61]. We performed sensitivity analysis for these seven studies and results showed higher odds of “death and failure” or failure among TB-DM patients compared to those with TB only (OR=2.19, 95%CI: 1.45-3.31; *I2*=73%; Appendix 7).

***Effect of DM on TB relapse (relapse and recurrence combined)***

The pooled result for combined outcome “relapse” (among 19 unadjusted studies) was 1.64 (95%CI: 1.29-2.08; *I2*=74%, P<0.001; Figure 10). Among five adjusted studies the effect estimates was slightly greater (OR=1.86; 95%CI: 1.51-2.28) and showed no heterogeneity (*I2*=0%) (Figure 11).

***Effect of DM on sputum culture conversion at two/three months***

We found 19 studies investigated the association between DM and culture conversion at two/three month. The pooled OR was 2.06 (95%CI: 1.70-2.49, P=0.01; *I2*=75%; Figure 12). Eight studies reported the adjusted estimates, and the pooled result was 1.75 (95%CI: 1.37-2.24, P<0.001; *I2*=66%; Figure 13)

***Effect of DM on MDR-TB***

MDR-TB was defined as resistance to at least isoniazid and rifampicin in 12 out of 19 studies, while the rest were not clearly defined. One study implied that all MDR-TB patients were from re-treatment cases.[65] Five studies reported the distribution of MDR-TB among new and retreatment/relapse cases, while four found that MDR-TB was more common among retreatment/relapse cases,[23, 66-68] and one found the rate was similar.[40] The pooled analyses showed that DM was associated with a two-fold increased odds of MDR-TB among TB patients (OR=1.98, 95%CI: 1.51-2.60, P=0.01; Figure 14). Moderate heterogeneity (*I2*=48%) was found in these studies.

Among the 19 studies, ten[23, 37, 39, 40, 46, 50, 61, 66, 69] reported adjusted estimates. The pooled adjusted OR was 2.22 (95%CI: 1.54-3.20; P=0.004 *I2 =62%*; Figure 15).

***Publication bias***

Begg’s test showed no evidence of publication bias for the association between DM and “death and failure” (P=0.10), relapse (P=0.14), sputum culture conversion (P=0.65), or MDR-TB (P=0.33); whereas there was publication bias for the association between DM and death (P=0.03). Therefore, we performed cumulative meta-analysis sorted by sample size and standard error, and assessed the individual influence of each study towards the pooled result for death. This demonstrated that smaller studies (sample size<500) had little influence on the overall effect size (Appendix 8), providing some assurance that smaller studies, more likely to be at risk of publication bias,[70] were not substantially affecting the pooled results.

***Risk of bias and certainty of the body of evidence synthesised***

Sixty eight studies used either medical records or self-report to identify the exposure of interest (DM) resulting in a high potential for non-differential misclassification of the exposure, potentially underestimating associations between DM and TB treatment outcomes. Fifty six studies did not adjust for key confounders in analyses and ten adjusted for confounders we considered potentially on the pathway to a poor TB outcome (particularly death) in their analyses, which could potentially result in over-adjustment (Table 1, Appendices 2 and 3).

As only observational studies were identified the overall Cochrane GRADE scores were limited as being of adequate quality or below without any upgrading of evidence (e.g. for large magnitude of effects or presence of dose-response gradient). In general, data pooled for each outcome was not impacted by bias, inconsistency, indirectness, or imprecision. For “death and failure” as outcomes, we could explain some of the heterogeneity in the unadjusted studies, and considering the large number of studies, consistent results, lack of strong evidence of publication bias, and evidence of stronger associations in better designed studies, we rate the quality as “moderate”. The quality of evidence contributing to the pooled analysis for MDR-TB was downgraded for risk of bias due to the high potential of variability between the study defined outcomes measured. Quality of evidence was also downgraded for outcomes where confounding and lack of adjustment was deemed to impact upon pooled estimates derived. The overall certainty is considered moderate in studies reporting death and “death and failure”, low among studies reporting relapse, MDR-TB, and sputum culture conversion at 2-3 months (see Table 2).

**Discussion**

***Key Strengths***

This updated review identified 106 studies (compared with the 33[7] and 54[12] included in previous systematic reviews) providing more robust evidence for the detrimental effects of DM on TB treatment outcomes. To reduce the risk of publication bias, we developed a more sensitive search strategy, screening far more records than previously identified (20,455 compared with 3,623[7] and 2,131[12]). This review is therefore larger than any other we are aware of to date, and brings together all major relevant TB treatment outcomes, as well as the effects of DM on MDR-TB.

We found similar association between DM and TB treatment failure and death with both previous reviews (1.61 (95%CI: 1.36-1.91) compared with 1.69 (95%CI: 1.36-2.12))[7] and 1.96 (95 % CI: 1.64-2.33).[12] Studies with improved control of confounding showed a somewhat stronger association, up to a three-fold increased odds of death (OR=2.83, 95%CI: 1.45-5.52).

This review presents substantial new evidence that DM affects a number of longer term TB treatment outcomes, particularly a doubling of the risk of relapse. Most importantly, we found that DM is associated with a two-fold increased odds of MDR-TB, given the rising global burden of MDR-TB (a 20% increase in cases treated has been reported over the past year).[1]

No previous reviews have examined heterogeneity between studies in depth, we demonstrate that heterogeneity can partly be explained by differences in adjustment for confounding, and country income level. Country income level may itself represent different TB incidence or possibly differences in diagnosis and management of DM. We did not find strong evidence of publication bias except for one outcome (death) which we investigated further using cumulative meta-analysis finding no evidence that smaller studies more prone to this type of bias were influencing results.

***Key limitations – study design and analysis***

This review has important potential limitations, mostly concerning the variable quality of the evidence base available, and heterogeneity which we could only partially explain. The newer evidence for associations with TB relapse and MDR-TB is important, but most included studies were based on retrospective data sources; thus were often limited by lack of measurement of confounding variables and case definitions based on data collated. Therefore, many included studies could not adjust for key confounders. Most studies included used multivariate logistic regression, but this method is potentially biased since it cannot take into account the fact that some patients (both with and without DM) have experienced adverse events such as death, treatment failure, or may be lost to follow-up before they have time to develop longer-term outcomes. This survivor bias is likely to attenuate the magnitude of associations between DM and TB outcomes. Of the studies included, only 12 used survival analyses techniques which are able to account for variant follow up time in their risk estimations. [25-36]

We excluded studies where it was clear that drug resistance was present at baseline, but the timing of drug susceptibility testing was not always reported; therefore, it is difficult to distinguish with certainty whether MDR-TB was primary or due to retreatment. However, one study attempted to adjust for a history of TB and showed an increased and significant magnitude of odds of having MDR-TB among TB-DM patients.[23] Other reviews, with somewhat different inclusion criteria, have reached similar conclusions but did not highlight the uncertainty in the evidence base.[12, 13] Recent pharmacokinetic studies have shown that the concentration of main anti-TB drugs may be lower in TB patients with DM, suggesting a possible mechanism by which such patients could be at higher risk of developing MDR-TB.[71-73] Although some drugs are adjusted for weight, there are concerns that DM patients may experience more weight change during TB treatment, therefore potentially require more frequent re-adjustment of dosage.

Other limitations of the evidence based include lack of information on cause-specific mortality. It, therefore, cannot be assumed that the increased mortality represents death from TB; other causes especially cardiovascular disease may also be common. The proportion of patients with “unknown outcomes” were relatively low in studies reporting this figure, but some studies did not report on such loss to follow-up. Given the very large size of the review, it is less likely that substantial differences to pooled estimates would result from new studies reporting on death or “death and failure”. However, the estimates for the association between DM and TB relapse and MDR-TB are less certain, and could potentially alter with newer, better designed studies.

***Heterogeneity of results***

The pooled analyses used the random effects model to take into account heterogeneity, the remaining moderate-high heterogeneity between studies could not be fully explained by our pre-specified variables including exposure ascertainment method, control of confounding, or study country income level. Adjustment for confounding was absent from some studies, very variable, and may sometimes include variables (baseline severity of TB disease) that could be on the pathway to death during TB treatment and hence potentially result in over-adjustment. This may also explain heterogeneity between studies, and some of our adjusted analyses (e.g. TB relapse) showed much reduced or no heterogeneity. Other explanations maybe that studies include highly variable populations in terms of severity and nature of the TB epidemic, DM prevalence and control, and health care systems, as well as having ethnic and racial variation. Importantly, we found that an association with poor outcomes remained in high income countries (where DM is generally well controlled and TB incidence low), in disagreement with some earlier reports.[74]

***Public health importance and need for further research***

The magnitude of the association identified is clearly very important in public health terms. This is because in many parts of the world, DM is highly prevalent in TB patients,[75, 76] and it roughly doubled the risk of a poor treatment outcome among TB patients. We estimated that up to 25% of TB deaths might be attributable to DM in some areas. Further pragmatic trials are thus needed to optimise treatment for both TB and DM among such patients. Some observational studies have suggested that prolonged TB treatment may improve outcomes, compared to the standard six-month treatment.[42] Higher drug dosages may also be of benefit,[77, 78] given the pharmacokinetic evidence showing lower concentrations in DM patients,[71-73] although this might also increase the risk of toxicity in older and frailer patients with DM. Very limited evidence from two out of three studies in this review [79-81] and another recent review[82] suggested that lower HbA1c or fasting/random blood glucose levels and optimal glycaemic control were associated with improved TB outcomes. Recently, a large cohort study from Taiwan showed good glycaemic control could modify the risk of TB among DM patients, suggesting this hypothesis should be investigated further.[4, 83] Despite this high need, only two small trials of DM and TB appear to be currently registered and underway.[79]

**Conclusion**

This large systematic review and meta-analysis showed that DM plays a salient role among TB-DM patients. Our results showed that even a doubling risk for poor treatment outcome would have substantial population impact – up to 25% of deaths in TB patients could be attributable to DM. These findings are not only important for low-middle income countries that have high TB incidence and high DM prevalence, but also important for high income countries with sub-populations that have higher risks of both conditions. Screening programmes for DM among TB patients should be implemented in primary care especially in regions that have high incidence of TB. Further studies are needed to explore the optimal treatment plan and glycaemic control among TB-DM patients to improve their treatment outcomes.

**List of abbreviation**

TB—tuberculosis

DM—diabetes

Medline—Medical Literature Analysis and Retrieval System Online

EMBASE—Excerpta Medica dataBASE

AIM—African Index Medicus

LILACS—Literature in the Health Sciences in Latin America and Caribbean

IMEMR—Index Medicus for the Eastern Mediterranean Region

IMSEAR—Index Medicus for the South-East Asian Region

WPRIM—Western Pacific Region Index Medicus

MeSH—Medical Subject Headings

MDR-TB—multi-drug resistant TB

FBG—fasting blood glucose

HbA1c –glycated haemoglobin

OR—odds ratio

RR—risk ratio

HR—hazard ratio

GRADE—Grading of Recommendations, Assessment, Development and Evaluations

U.S.—United States of America

K.S.A.—Kingdom of Saudi Arabia

R.O.K.—Republic of Korea

**Declarations**

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Availability of data and material**

All our data is held online in the Systematic Review Data Repository (SRDR).[84]

**Competing interests**

There are no competing interests to declare.

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**Authors’ contributions**

CU, FP, JG, and JC developed the initial concepts for the review. CU, FP, and JC implemented search strategies and screened manuscripts for inclusion of studies. PH, JC, FP and CU extracted data from studies and performed quality assessments. PH performed statistical analyses and wrote the first draft of the manuscript with input from FP, JC, CU, and JG. All authors read and approved the final manuscript.

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**Figure legend**

Figure 1: Flow chart of study screening, selection, and eligibility assessment in the systematic review

Figure 2 Association between DM and death among TB patients in unadjusted studies

Figure 3 Association between DM and death among TB patients by method of identifying DM

Figure 4 Association between DM and death among TB patients by country income level

Figure 5 Association between DM and death among TB patients among studies adjusted for any confounders

Figure 6 Sensitivity analysis: association between DM and death among TB patients among adjusted studies without potential for over-adjustment

Figure 7 Association between DM and treatment failure and death among TB patients

Figure 8 Association between DM and treatment failure and death among TB patients by method of identifying DM

Figure 9 Association between DM and treatment failure and death among TB patients by country income level

Figure 10 Association between DM and relapse (relapse and recurrence) among TB patients

Figure 11 Association between DM and relapse (relapse and recurrence) among TB patients in adjusted studies

Figure 12 Association between DM and culture remaining positive at 2-3 months of treatment among TB patients

Figure 13 Association between DM and culture remaining positive at 2-3 months of treatment among TB patients in adjusted studies

Figure 14 Association between DM and MDR-TB among TB patients

Figure 15 Association between DM and MDR-TB among TB patients in adjusted studies

**Table 1 Characteristics of studies included in the systematic review of the association between DM and TB treatment outcomes**

| **Study** | **Study type** | **Country**  **Study period (end year)** | **Total N** | **DM N** | **Male%** | **Age**  **(Mean or median)** | **New TB (%)** | **% with known outcome (%)[[1]](#footnote-2)** | | **Type of TB** | **DM diagnosis** | **Exclusion criteria** | **Outcome** | **Confounders** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Abdelbary[20] | Retrospective Cohort | Mexico 2013 | 6310 | 2121 | 65.5 | 43 (SD 16.6) | NR | NR | | Pulmonary TB & Extra-pulmonary TB | Glucose testing (unclear whether fasting or not). Not all patients were tested | <18 yrs; repeated TB episodes excluded, as were re-entry, treatment failure, relapse and referred cases. | Death/ failure | Age, gender, education level, unemployment status |
| Alavi-Naini[58] | Retrospective Cohort | Iran  2011 | 715 | 108 | 52.4 | TBDM: 56.6(SD12.7) TB only: 44.8(SD18.3) | 75.4 | NR | | Pulmonary TB | FBG | <15yrs, incomplete data | Death | Smoking, drug abuse, drug induced hepatitis, TB history, +ve sputum smear, anemia. Age and sex not included as limited effect in univariate analyses |
| Alisjahbana[85] | Prospective Cohort | Indonesia  2005 | 634 | 94 | 52.4 | TBDM 45.0 (IQR 39.8 to 52.0); TB only 27 (IQR 22-35.0)[[2]](#footnote-3) | 95 | NR | Pulmonary TB | | FBG | <15yrs, HIV | Death,  culture conversion | Age, sex, BMI, study site, chest radiograph abnormalities before starting treatment |
| Alo[86] | Retrospective Cohort | Fiji  2012 | 388 | 53 | 57 | 36.1[[3]](#footnote-4) | NR | 86.9 | Undifferentiated TB | | FBG | NR | Death/ failure | None |
| Altet[87] | Retrospective Cohort | NR 2014 | 1622 | 100 |  |  |  | NR |  | | Not stated | NR | Culture conversion | None |
|  |  |  |  |  |  |  |  |  |  | |  |  |  |  |
| Ambrosetti[88] | Prospective Cohort | Italy  1995 | 769 | 32 | 59.2 | NR | 82 | 85.7 | Undifferentiated TB | | Medical records/ self-report | NR | Death/ failure | None |
| Ambrosetti[89] | Prospective Cohort | Italy  1996 | 823 | 50 | 56 | NR | 84 | 85.3 | Undifferentiated TB | | Medical records | NR | Death/ failure | None |
|  |  |  |  |  |  |  |  |  |  | |  |  |  |  |
| Ambrosetti[90] | Prospective Cohort | Italy  1997 | 707 | 41 | 56 | NR | 89 | 84.7 | Undifferentiated TB | | Medical records/ self-report | NR | Death/ failure | None |
| Amnuaiphon[91] | Prospective Cohort | Thailand  2006 | 4478 | 290 | 65 | 44.82 | NR | NR | Undifferentiated TB | | Medical records | Transferred in, registration status as "other" (i.e. patients with chronic TB), defaulted, transferred out, changed diagnosis | Death | Age, sex, marital status, nationality, residency, cavity on chest radiograph, directly observed therapy, previous TB treatment, treatment facility, drug resistance, network sites (NS in univariate: cohort period, type of TB, ever received INH prophylaxis, cough lasting>2 weeks at diagnosis, ever used IV drugs, incarcerated, abnormal chest radiograph, initial treatment regimen) |
| Anunnatsiri[63] | Retrospective Cohort | Thailand  2001 | 226 | 38 | 66.4 | 47.2 (SD 17.7) | 86.3 | 37.2 | Undifferentiated TB | | Medical records/ self-report | <15 yrs, incomplete medical records, AFB not identified in the sputum | Death/ failure | Age, HIV, previous TB treatment, under non-pulmonary physician |
| Atif[59] | Retrospective Cohort | Malaysia  2011 | 336 | 131 | 70.24 | 49.1 (SD 16.6) | NR | NR | Undifferentiated TB | | Medical records | NR | Death | Age, sex, history of >=4 weeks cough, lung cavities, high-grade sputum, smoking, alcoholism |
| Baghaei[46] | Prospective Cohort | Iran 2013 | 64 | 62 | 57.2 | 52.3 (SD 19.9) | 100 | 79.2 | Pulmonary TB | | FBG and HbA1c | NR | Death, MDR-TB, | Age, sex, smoking, drug use, Hx imprisonment, TB contact, Co-morbidity, Smear grade, lesions |
|  |  |  |  |  |  |  |  |  |  | |  |  |  |  |
| Banu Rekha[92] | Retrospective Cohort | India  2002 | 190 | 92 | 78 | TBDM 48.0;  TB only 31.01 | NR | NR | Pulmonary TB | | FBG and HbA1C | Patients in moribund state or with major systematic illnesses or with abnormal biochemical profile | culture conversion | None |
| Barss[93] | Retrospective Cohort | Canada 2012 | 638 | 150 | NR | NR | NR | NR | NR | | Medical records and anti-DM treatment | <18 yrs; inadequate chart data | Death/ failure relapse | None |
| Bashar[66] | Retrospective Cohort | U.S.  1997 | 155 | 50 | 84.5 | TBDM 47.1  TB only 41.62 | NR | NR | Undifferentiated TB | | Medical records | NR | Death, MDR-TB, relapse | For MDR-TB only: HIV and homelessness |
| Burgielski[94] | Retrospective Cohort | Poland  1982 | 137 | 65 | 50 | NR | 50 | NR | Pulmonary TB | | Medical records | NR | Death | None |
| Burgielski[95] | Retrospective Cohort | Poland  1978 | 180 | 90 | 50 | NR | NR | NR | Pulmonary TB | | Medical records | NR | Death | None |
| Cavanaugh[96] | Prospective Cohort | Kiribati  2012 | 275 | 101 | 52.4 | TBDM 49 (IQR 39-56); TB only 26 (IQR 20-40) 1 | 94.2 | 96.0 | Undifferentiated TB | | HbA1c | Pregnant women, <18 yrs | Death/ failure | None |
| Centis[97] | Prospective Cohort | Italy  1998 | 1100 | 41 | 61.7 | NR | 76.6 | 65.7 | Undifferentiated TB | | Medical records | NR | Death/ failure | None |
|  |  |  |  |  |  |  |  |  |  | |  |  |  |  |
| Centis[98] | Prospective Cohort | Italy  1999 | 892 | 40 | 61.1 | NR | 78.8 | 79.3 | Undifferentiated TB | | Medical records | NR | Death/ failure | None |
|  |  |  |  |  |  |  |  |  |  | |  |  |  |  |
| Chang[68] | Prospective Cohort | Taiwan  2005 | 192 | 60 | 74.8 | TBDM 57.9 (SD12.8) TB only 57.2 (SD18.8) | 61.4 | NR | Pulmonary TB | | FBG | HIV, previously treated TB, interrupted treatment for 2+ consecutive weeks, died during treatment, transferred out after registration | MDR-TB | None |
| Chiang[99] | Retrospective Cohort | Taiwan  2003 | 1127 | 241 | 66.0 | 52.92 | 93.3 | NR | Pulmonary TB | | Medical records | NR | Death/ failure | None |
|  |  |  |  |  |  |  |  |  |  | |  |  |  |  |
| Chiang[81] | Retrospective Cohort | Taiwan  2010 | 1473 | 705 | 74.3 | TBDM 59.6  TB only 54.62 | 86.4 | 98.2 | Pulmonary TB | | Medical records/ self-report | Patients with transient hyperglycemia at TB treatment initiation | Death/ failure | Age, sex, smear +ve, retreatment, smoking, drug resistance, non-DM-related co-morbidity, DM-related co-morbidity (adjustment only for unfavourable outcomes, not outcomes analysed) |
| Choi[64] | Prospective Cohort | R.O.K.  2012 | 569 | 149 | 84.2 | 40.1 | 33.5 | NR | Pulmonary TB | | Medical records | <20 yrs | Death/ failure | Age, sex, BMI, drug susceptibility pattern |
| Da Costa[100] | Retrospective Cohort | Portugal 2013 | 10465 | 706 | 70.4\* | 47 (mean calculated) | 90.2 | NR | Pulmonary TB | | Not stated | NR | Relapse | None |
| Degner[62] | Retrospective Cohort | Taiwan 2013 | 1717 | 699 | 68.3 | 61.2 (SD 20.0) | NR | NR | Pulmonary TB | | FBG, RBG, HbA1c, medical records and anti-DM treatment | <13 yrs; only drug susceptible PTB were included | Death, culture conversion | Age, sex, chronic kidney disease, cancer, hepatitis C virus infection, history of tobacco use, cavitary disease, treatment adherence |
|  |  |  |  |  |  |  |  |  |  | |  |  |  |  |
| Delgado-Sánchez[37] | Retrospective Cohort | Mexico 2012 | 114248 | 29534 | 64.51 | 46 (IQR 32-60) | 90.8 | 79 | Undifferentiated TB | | FBG, OGTT | <20 yrs; other type of TB | Death/ failure MDR-TB | For failure and MDR-TB only: age, sex, previous TB treatment, malnutrition |
| De Oliveira[101] | Case-control | Brazil  1994 | 361 | 27 | 42.9 | 42.62 | NR | NR | Pulmonary TB | | Medical records | Abandon, inmates, relapse after 5 years, patients who did not use H, R, Z, E | Relapse | None |
| Dooley[56] | Retrospective Cohort | U.S.  2005 | 297 | 42 | 52.9 | TBDM 56.5 (SD 15) TB only 39.8 (SD18) | NR | NR | Undifferentiated TB | | RBG | Patients not alive at the time of TB diagnosis, initiated TB treatment outside of Maryland, died before DM status could be obtained | Death, culture conversion | Age, sex, foreign birth, HIV (for death only) |
| Dos Santos Feltrin[102] | Retrospective Cohort | Brazil 2014 | 4141 | 306 | 71.3 | 49.4 (mean calculated) | 89.3 | 83.0 | Undifferentiated TB | | Not stated | excluded all cases with diagnosis changes, without closure, or those in which the patient was transferred to another state. Also excluded open cases of TB notifications where the municipality was not in the range area. 541 cases without closure were excluded out of 5361 in total therefore 4820 included | Death | None |
| El Sahly[103] | Case-control | U.S.  2000 | 744 | 85 | NR | 39.3 | NR | NR | Undifferentiated TB | | Medical records | NR | Recurrence | None (DM was not included in the adjusted multivariate model due to insignificant findings in the univariate analysis) |
| Faurholt-Jepsen[28] | Prospective Cohort | Tanzania  2008 | 1205 | 197 | 59.2 | 36.5 (SD12.9) | NR | NR | Pulmonary TB | | FBG | <15 yrs, pregnant/ lactating women; terminally ill from TB or HIV (judged unlikely to survive >48h), suffering from other severe diseases and non-residents of Mwanza City | Death | Age, sex, HIV, culture -ve PTB, BMI |
| Fielder[53] | Retrospective Cohort | U.S.  1998 | 174 | 22 | 71.3 | 49 | NR | NR | Pulmonary TB | | Medical records | If smear for acid-fast bacilli was from sputum induction or bronchoalveolar lavage; patients with unavailable medical records, or those lost to follow-up | Death | Age |
| Fisher-Hoch[23] | Retrospective Cohort (Texas part) | U.S.  2003 | 1442 | 401 | 68.6 | TBDM 54.4  TB only 45.82 | 94.4 | NR | Undifferentiated TB | | Self-report | Incomplete DM, culture, or sensitivity data | MDR-TB  recurrence | Age, sex, drug abuse, alcoholism, HIV, history of previous episode of TB |
| Fisher-Hoch[23] | Retrospective Cohort (Mexico part) | Mexico  2003 | 1436 | 287 | 72.1 | TBDM 51.2  TB only 40.62 | NR | NR | Undifferentiated TB | | Self-report | Incomplete DM, culture, or sensitivity data | MDR-TB | Age and sex |
| Guler[44] | Retrospective Cohort | Turkey  2000-05 | 306 | 44 | 63.1 | 42.8 (SD 16.4) | 100 | NR | Pulmonary TB | | Medical records | Patients with TB history, HIV | Culture conversion | None |
| Gullón Blanco[104] | Retrospective Cohort | Spain  2005 | 98 | 13 | 78.6 | 40.5 (SD 1.67) | NR | NR | Pulmonary TB | | Medical records | Drug resistance, HIV, lost to follow up, death during TB treatment | Culture conversion | None |
| Hara[105] | Case-control | Japan  1994 | 394 | 93 | NR | NR | NR | NR | Pulmonary TB | | Medical records | NR | Culture conversion | None |
| Hasibi[106] | Retrospective Cohort | Iran  2006 | 50 | 6 | 62 | 39 (SD 17) | NR | NR | Disseminated TB | | Medical records | Patients with single organ involvement | Death | None |
| Horita[26] | Retrospective Cohort | Japan  2011 | 432 | 92 | 68.7 | 64.9 (SD19.7) | 88.2 | NR | Pulmonary TB | | Medical records | HIV, MDR-TB, discharged alive before negative infectivity confirmed (including refused treatment or transferred out) | Death | Age, sex, performance status, comorbidities (heart disease, respiratory disease, liver disease, kidney disease, active malignancy), non-standard drug regimen |
| Hongguang[65] | Prospective Cohort | China  2011 | 1126 | 182 | 66.7 | TBDM 53 (IQR 45-64); TB only 34 (IQR 21-45) 1 | 92.2 | 97.8 | Pulmonary TB | | FBG, OGTT | patients with incomplete medical records | Death/  failure,  MDR-TB | None |
|  |  |  |  |  |  |  |  |  |  | |  |  |  |  |
| Hung[107] | Nested case control | Taiwan 2010 | 595 | 165 | 67.9 | 52.9 | 0 | N/A | Undifferentiated TB | | Medical records | all patients with TB before 1998, HIV, or < 18 were excluded. | Relapse | Age, gender, socio-economic status, and comorbid diseases |
| Jiménez-Corona[36] | Prospective Cohort | Mexico  2010 | 1262 | 374 | 57.84 | TBDM 53.5(SD12.8); TB only 41.9 (SD19.0) | 87.9 | 91.1 | Pulmonary TB | | Medical records and self-report | NR | Death/ failure, culture conversion, relapse, recurrence | Recurrence and relapse were both adjusted for joint resistance to isoniazid and rifampicin. Recurrence was also adjusted for failure or default and HIV; relapse was also adjusted for smoking and sputum grading. |
| Kanda[33] | Retrospective Cohort | Japan 2002 | NR | NR | 69.8 | 57 (IQR 40-67) | NR | 100 | Pulmonary TB | | History of DM | <18 yrs; retreatment/relapse cases; cases with no positive AFB smear or culture of Mtb; and those with drug resistant strains were excluded. | Culture conversion | Age, sex, smoking status, drinking habit, chest x-ray, sputum smear grading |
| Karachunskiĭ[108] | Prospective Cohort | Russia  NR | 210 | 110 | NR | NR | NR | NR | Pulmonary TB | | Medical records | NR | Culture conversion | None |
| Kitahara[109] | Retrospective Cohort | Japan  1991 | 520 | 71 | 70.8 | NR | NR | NR | Pulmonary TB | | Medical records | NR | Death, culture conversion | None |
| Ko[30] | Retrospective Cohort | Taiwan 2010 | 6412 | 2333 | 67.1\* | 60.1 (mean calculated) | 100 | 100 | Undifferentiated TB | | Medical records, health insurance claims | incomplete information on age or sex; relapse/retreatment cases | Death | Age, sex, comorbidities, site of tuberculosis infection |
| Kourbatova[110] | Case-control | Russia  2003 | 460 | 20 | 71 | 43 (range 18-88) | NR | NR | Undifferentiated TB | | Medical records/ self-report | <18 yrs, re-treatment cases and TB patients in prison | Death | None |
| Lee[111] | Case-control | Taiwan  2007 | 600 | 170 | 72 | 48.12 | NR | NR | Pulmonary TB | | FBG | Defaulted, transferred out, died during anti-TB treatment, still on treatment or found to be MDR-TB | Relapse | Age, BMI, sex, indigenous population, history of alcohol use, history of smoking, cancer, ESRD, coexisting extra-pulmonary lesion, initial cavitation, suboptimal regimen, DOT>=60% |
| Lee[47] | Retrospective Cohort | R.O.K.  2012 | 764 | 238 | 62.5 | 56 (IQR 30-94) | 100 | 86.4 | Pulmonary TB | | 2012 ADA diagnostic criteria history or RSG ≥11.1 mmol/L at time of TB diagnosis. For general population history or FPG ≥7.0 mmol/L | NR | Death/ failure, culture conversion | Age, sex, BMI, cavitary disease, retreatment |
| Leung[38] | Prospective Cohort | Hong Kong 2012 | 17488 | 3206 | 63.6 | 54.2 (SD 20.6) | 90 | NR | Pulmonary TB & Extra-pulmonary TB | | Not stated | patients with baseline drug resistance | Death/ failure, relapse, culture conversion | Age, gender, Chinese ethnicity, permanent residency, employment status, homeless/overcrowded, alcohol dependence, drug abuse, smoking status, HIC, previous TB treatment |
|  |  |  |  |  |  |  |  |  |  | |  |  |  |  |
| Lin[60] | Retrospective Cohort | Taiwan  2007 | 747 | 182 | 71.1 | 59.3 (range 0.3-96) | NR | NR | Undifferentiated TB | | Medical records | NR | Death | Matched by age, sex, and site of TB |
| Liu[31] | Retrospective Cohort | China 2015 | 2459 | 282 | 70.5 | 32.3% were aged 60+ | 12.3 | 96.4 | Pulmonary TB | | Medical records | patients registered twice during the study period | Death | Age, sex |
| Lo[32] | Retrospective Cohort | Taiwan 2008 | NR | NR | 69.1 | 66 (IQR 46-77) | 100 | 93.7 | Pulmonary TB & Extra-pulmonary TB | | Medical records, ICD 9 codes from health insurance claims | patients were previously treated, those  with incomplete information, and cases reported after death. | Death | Age, sex, sputum bacteriology, types of TB, residential place, comorbidity (including HIC, chronic kidney disease, stroke, cancer, chronic liver disease and cirrhosis, COPD) |
|  |  |  |  |  |  |  |  |  |  | |  |  |  |  |
| Ma[48] | Prospective Cohort | China 2010 | 1156 | 157 | 69.7 | NR | 100 |  | Pulmonary TB | | Repeated FBG | <15 yrs; no other comorbidity. | Death/ failure, culture conversion | Age, sex, education, smoking status, BMI |
|  |  |  |  |  |  |  |  |  |  | |  |  |  |  |
| Maâlej[112] | Case-control | Tunisia  2000-06 | 142 | 60 | 52.8 | TB-DM 54.0 (SD 14.4); TB only 32.0 (SD 13.0) | NR | NR | Pulmonary TB | | Medical records | Immunosuppression (e.g. HIV, corticosteroids long course, immunosuppressive treatment) | Death, relapse | None |
| Magee[29] | Retrospective Cohort | U.S.  2012 | 1318 | 151 | 66.5 | TB-DM 57.4 (SD14.4); TB only 44.3 (SD17.8) | 93.8 | NR | Undifferentiated TB | | Medical records | <16 yrs | Death | Age, sex, ethnicity, occupation, foreign born, alcoholism, HIV status, and baseline TB culture |
| Magee[49] | Retrospective Cohort | U.S. 2012 | 327 | 42 | 60.8 | 41.5 (IQR 30-57) | 100 | 100 | Extra-pulmonary TB | | Self-report, medical records, random blood glucose. | <16 yrs | Death | Age, sex, foreign-born status, HIV, EPTB site, and ESRD |
| Mathew[54] | Retrospective Cohort | Russia  2003 | 1916 | 44 | 69.2 | 42 | 86.4 | NR | Undifferentiated TB | | Medical records | <18 yrs, receiving treatment outside of local TB service | Death | Age, sex, TB treatment, MDR, prior incarceration, HIV, alcoholism, narcotic use |
| Mboussa[113] | Retrospective Cohort | Congo  1998 | 132 | 32 | 60.6 | TBDM 46.3  TB only 35.02 | NR | 90.9 | Undifferentiated TB | | FBG | HIV | Death/ failure, relapse | None |
| Mi[114] | Retrospective Cohort | China  2012 | 580 | 97 | 65.6 | TBDM 47.4  TB only 35.52 | 91.4 | 89.3 | Undifferentiated TB | | FBG | NR | Death/ failure | None |
|  |  |  |  |  |  |  |  |  |  | |  |  |  |  |
| Moosazadeh[34] | Prospective Cohort | Iran  2012 | 964 | 140 | 56 | 42.63 | 94.3 | NR | Pulmonary TB | | Medical records/ self-report | Non-Iranian, unsuccessful treatment outcome (treatment failure/discontinued treatment due to death/ wrong diagnosis/ absence of treatment) | Death | Age, previous TB treatment, result of sputum smear after 2 months of treatment, renal disease, cancer |
|  |  |  |  |  |  |  |  |  |  | |  |  |  |  |
| Morsy[45] | Case-control | Egypt  2002 | 238 | 40 | 66.4 | 30.42 | 100 | NR | Undifferentiated TB | | Medical records and self-report | Patients with previous TB history | Failure | Age, sex, family knowledge of TB, missed doses, family size, distance to TB center, walking disability, satisfaction with care, household members <15 years, health education received, patient knowledge of TB |
| Mundra [35] | Retrospective Cohort | India 2014 | 187 | 12 | 62.9 | 35 (IQR 25-50) | 77.5 | 91.4 | Undifferentiated TB | | Limited screening for DM (details not given) but 61% of patients were not screened | NR | Death | Age, sex, area of residence, site of TB, retreatment, HIV status, |
| Nakamura[115] | Retrospective Cohort | Japan  2012 | 260 | 69 | 65.8 | TBDM 64.5 (SD15.0) TB only 61.3 (SD21.6) | NR | NR | Pulmonary TB | | HbA1c | Incomplete data on sputum bacteriology or DM | Culture conversion | Age, sex, and cavitation |
| Namukwaya[116] | Case-control | Uganda  2007 | 150 | 6 | 61.3 | NR | NR | NR | Pulmonary TB | | Surrogate measures | <13 yrs, incomplete records | Failure | None |
|  |  |  |  |  |  |  |  |  |  | |  |  |  |  |
| Nandakumar[80] | Retrospective Cohort | India  2011 | 2794 | 667 | 67.9 | 46 (SD17) | 86.9 | 94.0 | Undifferentiated TB | | Various objective and subjective measurements | <14 yrs, transfer-in cases | Death/ failure, MDR-TB | Age group, sex, site and type of TB, smear result and HIV status (adjustment was only in all unfavourable outcomes |
| Nissapatorn[117] | Retrospective Cohort | Malaysia  2002 | 1651 | 241 | 65.7 | TBDM 51.5 (SD12.0) TB only 37.5 (SD15.4) | 92.9 | 80.0 | Undifferentiated TB | | FBG | < 14 yrs, HIV | MDR-TB | None |
| Orofino[118] | Retrospective Cohort | Brazil  2006 | 308 | 14 | NR | 39 | NR | 81.2 | Undifferentiated TB | | Medical records | Discontinued follow-up during the first 15 days of treatment for any reason | Death/ failure | None |
| Oursler[25] | Retrospective Cohort | U.S.  1996 | 126 | 18 | 72 | 52.6 (SD 17.5) | NR | NR | Pulmonary TB | | Medical records | Patients with isolated extra-pulmonary TB | Death | Age, COPD, renal disease, HIV (race, sex, and homelessness, were not associated with death in univariate analyses) |
| Pérez-Navarro[119] | Prospective Cohort | Mexico  2009 | NR | NR | 66 | TBDM 50.7(SD12)  TB only 40.7(SD19) | 86 | NR | Undifferentiated TB | | Medical records | <15 yrs, HIV | Relapse | None |
| Pérez-Navarro[69] | Prospective Cohort | Mexico  2013 | 409 | 146 | 65 |  | 87 | NR | Pulmonary TB | | FBG | <15 yrs, HIV | MDR-TB | Age |
| Perez-Navarro[61] | Retrospective Cohort | Mexico 2014 | 324 | 183 | 64 |  | 90 | 85 | Pulmonary TB | | Medical records, FPG test | <15 yrs; patients with T1DM or HIV; relapse patients or those with previous treatment history. | Death/ failure, MDR-TB, relapse | Age, sex, smoking and overcrowding, smear positivity at two months |
| Pina[120] | Retrospective Cohort | Spain  1997 | 1511 | 73 | 64.4 | 38.63 | NR | NR | Undifferentiated TB | | Medical records | Patients with TB diagnosis after death, death from non- adherence, failures, transfer and incomplete medical records | Death | None |
| Reed[27] | Prospective Cohort | R.O.K.  NR | 657 | 162 | 83.9 | 44.5 | 33.5 | NR | Pulmonary TB | | FBG | HIV and pregnant women | Death | Age, sex, education, alcohol use, previous TB |
| Reis-Santos[39] | Retrospective Cohort | Brazil  2009 | 17750 | 703 | 67.1 | TBDM 49.2  TB only 37.62 | 87.7 | 81.1 | Undifferentiated TB | | Medical records | HIV, missing information on DM and HIV | Death, MDR-TB | Age,  institutionalization, TB form, initial smear, treatment type |
| Ribeiro Macedo[40] | Retrospective Cohort | Brazil  2011 | 12795 | 323 | 90.7 | 18+ (NR) | 79.5 | 87.5 | Undifferentiated TB | | Medical records | Patients who transferred, had a change of diagnosis, aged<18 yrs, subjects with missing outcome information (only included the prisoners) | Death, MDR-TB | Age, sex, ethnicity, education, alcoholism, mental disease, other co-morbidities, type of treatment, chest X-Ray, tuberculin skin test, form of TB, sputum smear, sputum culture, histopathology, sputum smear microscopy for the second month of treatment and DOT |
| Salindri[50] | Prospective Cohort | Georgia 2014 | 232 | 36 | 75.4 | 49 (IQR 42-58) | 100 | 69 | Pulmonary TB | | Medical records, HbA1c | <15 yrs; retreatment cases or patients with prior TB history | MDR-TB | Age, sex, socioeconomic status, smoking status, alcohol use, HIV status, kidney disease |
|  |  |  |  |  |  |  |  |  |  | |  |  |  |  |
| Sangral[121] | Retrospective Cohort | India  2010 | 280 | 23 | 65.3 | 41.83 | NR | 90.7 | Undifferentiated TB | | Medical records | <15 yrs, pregnant women | Death/ failure | None |
|  |  |  |  |  |  |  |  |  |  | |  |  |  |  |
| Satung[51] | Retrospective Cohort | Thailand 2012 | 7250 | 555 | 72 |  | 100 | 94 | Pulmonary TB | | Medical records | relapse/retreatment cases | Death/ failure | None |
|  |  |  |  |  |  |  |  |  |  | |  |  |  |  |
| Shahrezaei[122] | Retrospective Cohort | Iran 2011 | 508 | 38 | 49.7 |  | 89.2 | 94 | Undifferentiated TB | | Medical records | cases that had changes of disease diagnosis | Death | None |
|  |  |  |  |  |  |  |  |  |  | |  |  |  |  |
| Siddiqui[123] | Prospective Cohort | India 2014 | 150 | 36 | 44.6 | 33 | 80.7 | 98.7 | Pulmonary TB & Extra-pulmonary TB | | Medical records | <15 yrs; suspected or known MDR TB patients; patients who were not willing to participate; patients with other comorbidity | Death/ failure, MDR-TB | None |
| Singla[124] | Retrospective Cohort | K.S.A  1999 | 692 | 187 | 64.6 | TBDM 45.8  TB only 30.12 | NR | 73.0 | Pulmonary TB | | FBG | Patients with extra-pulmonary or miliary TB | Death/ failure, relapse | None |
|  |  |  |  |  |  |  |  |  |  | |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  | |  |  |  |  |
| Subhash[125] | Retrospective Cohort | India  1999 | 361 | 72 | 77 | TBDM 49.5  TB only NR | NR | NR | Undifferentiated TB | | FBG | <12 yrs | MDR-TB | None |
| Sulaiman[126] | Retrospective Cohort | Malaysia  2007 | 1256 | 342 | 72.3 | TBDM 50.7 (SD 13.0) TB only 41.4 (SD 16.5) | 92.7 | 93.6 | Undifferentiated TB | | Medical records/ self-report | HIV, hepatitis B/C or both, ESRD, immunosuppression due to organ transplantation, cancer, and patients with incomplete medical records | Death | None |
| Tabarsi[79] | Prospective Cohort | Iran  2013 | 104 | 37 | 51.4 | TBDM 62.9 (SD13.6) TB only 45.3 (SD22.3) | NR | 100 | Undifferentiated TB | | FBG HbA1c | <15 yrs | Death/ failure | None |
| Tatar[127] | Retrospective Cohort | Turkey  2003 | 156 | 78 | 62.8 | TBDM 53.6 (SD 12.7) TB only 34.2 (SD 14.8) | NR | 91.0 | Undifferentiated TB | | BG | TB-non DM group included patients without any other underlying disease | Death | None |
| Tipayamongkholg-ul [128] | Retrospective Cohort | Thailand 2012 | NR | NR | NR | NR | NR | N/A | Pulmonary TB | | Medical records | patients with TB drug resistance and uncompleted comorbidity data | Relapse | Age, sex sputum conversion, treatment outcome of previous treatment |
|  |  |  |  |  |  |  |  |  |  | |  |  |  |  |
| Touré[55] | Retrospective Cohort | Senegal  2004 | 174 | 86 | NR | 51.5 (Range 19-80) | NR | NR | Pulmonary TB | | FBG | HIV, previous PTB, immunosuppressive treatment (including long term use of corticosteroids) | Death | Matched for age and sex |
| Uchimura[41] | Retrospective Cohort | Japan  2010 | 33699 | 5622 | 63.2 | 691 | NR | 92.1 | Pulmonary TB | | Various objective and subjective measurements | Treatment outcome unevaluated | Death/ failure | None |
| Vasankari[129] | Retrospective Cohort | Finland  1996 | 629 | 92 | 61.4 | 54.12 | 90.6 | NR | Pulmonary TB | | Medical records/ self-report | NR | Death | None |
|  |  |  |  |  |  |  |  |  |  | |  |  |  |  |
| Vasankari[130] | Retrospective Cohort | Finland  1996 | 230 | 25 | 42.0 | 70.11 | NR | 81.8 | Extra-pulmonary TB | | Medical records | Previous TB treatment, PTB patients | Death | None |
|  |  |  |  |  |  |  |  |  |  | |  |  |  |  |
| Velayutham[52] | Prospective Cohort | India NR | 885 | 223 | 72 | 41 | 100 | 91.6 | Pulmonary TB | | FCG, self-report | <18 yrs; patient with previous treatment, unavailable smear results, and those with refused consent. | Relapse | None |
|  |  |  |  |  |  |  |  |  |  | |  |  |  |  |
| Viswanathan[131] | Retrospective Cohort | India  2011 | 245 | 96 | 74.3 | TBDM 49.9 (SD11.3); TB only 37.5 (SD13.6) | NR | 99.6 | Pulmonary TB | | FBG, HbA1c | Pre-DM | Death/ failure, MDR-TB | None |
| Viswanathan[132] | Prospective Cohort | India  2012 | 209 | 89 | 76.1 | TBDM 50  TB only 481 | 84.7 | 97.6 | Undifferentiated TB | | OGTT | HIV, impaired glucose test or impaired fasting glucose on OGTT | Death/ failure | Age, sex, smoking, alcohol, adherence |
| Wada[133] | Retrospective Cohort | Japan  1997 | 726 | 143 | 75.8 | TBDM 46.5  TB only 41.6 | NR | NR | Undifferentiated TB | | Medical records | >80 yrs | Culture conversion,  Relapse | None |
| Wang[67] | Retrospective Cohort | Taiwan  1999 | 453 | 75 | 73.3 | NR | NR | NR | Pulmonary TB | | Medical records | NR | MDR-TB | None |
| Wang[57] | Retrospective Cohort | Taiwan  2006 | 217 | 74 | 72.4 | TBDM 60.8 (SD 9.9) TB only 59.1 (SD 17.2) | 88.5 | 92.6 | Pulmonary TB | | FBG and treatment | <18 years old, non-Taiwanese, already diagnosed with TB in another hospital, if chest radiograph done at presentation missing or no clear data on bacteriology and DM history | Death | Age and sex |
| Wang[42] | Retrospective Cohort | Taiwan  2010 | 55883 | 12688 | NR | TBDM 65.8 (SD13.5) | NR | NR | Pulmonary TB | | Medical records | Patients received any non-first line anti-TB drugs for > 14 days (to avoid inclusion of patients with drug-resistant TB or adverse reaction due to first line anti-TB drugs); DM visit claim within 270 days before parturition | Recurrence | None |
| Workneh[134] | Prospective Cohort | Ethiopia 2015 | 1205 | 109 | 52.7 | 35.74 (SD 15.2) | NR | 98.9 | Undifferentiated TB | | Medical records, self-report, RBG or FBG | <15 yrs; retreatment cases, patients who could not offer informed consent, known or suspected MDRTB cases, those with malignancy and patients who were on immunosuppressive therapy | Death/ failure | None |
|  |  |  |  |  |  |  |  |  |  | |  |  |  |  |
| Wu[43] | Retrospective Cohort | Taiwan  2008 | 33851 | 7637 | 74.6 | NR | 100 | NR | Undifferentiated TB | | Medical records | Previous treatment | Death | Stratified by age groups. Sex, residence of living (eastern or not), comorbidity (HIV, chronic kidney diseases, stroke, cancer, liver disease) |
| Wu[135] | Retrospective Cohort | China 2008 | 161 | 40 | 64.2 | 45.8% were aged 50+ | NR | 100 | Pulmonary TB | | Medical records | patients who were infected with non-tuberculosis mycobacteria | Culture conversion | None |
|  |  |  |  |  |  |  |  |  |  | |  |  |  |  |
| Zerbini[136] | Case-Control | Argentina 2013 | 305 | 31 | 65 | 58 | 85.9 | NR | Undifferentiated TB | | Medical records | <18 yrs | Death | None |
|  |  |  |  |  |  |  |  |  |  | |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  | |  |  |  |  |
| Zhang[84] | Retrospective Cohort | China  2009 | 2141 | 203 | 76.2 | 42.7 | NR | 75.0 | Pulmonary TB | | FBG | NR | MDR-TB, relapse | None |

**Table 2 Summary of findings for the effect of DM on TB treatment outcomes among TB patients and GRADE assessment across studies for each outcome**

| **Certainty assessment** | | | | | | | **№ of patients** | | **Effect** | | **Certainty** | **Importance** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **TB-DM** | **TB** | **Relative (95% CI)** | **Absolute (95% CI)** |
| Death (Majority of studies followed up for 1 year. Assessed with study defined measures; all cause or TB-specific) | | | | | | | | | | | | |
| 64 | observational studies a | not serious | serious b | not serious | not serious | none | 7356/56122 (13.1%) | 29117/243035 (12.0%) | **OR 1.88** (1.59 to 2.19) | **84 more per 1,000** (from 58 more to 110 more) | ⨁⨁⨁◯ MODERATE | CRITICAL |
| Death and Failure (Majority of studies followed up for 1 year. Assessed with study defined measures; for failure majority follow WHO definition) | | | | | | | | | | | | |
| 35 | observational studies c | not serious | serious b | not serious | not serious | none | 4854/40029 (12.1%) | 22716/166815 (13.6%) | **OR 1.65** (1.39 to 1.96) | **70 more per 1,000** (from 44 more to 100 more) | ⨁⨁⨁◯ MODERATE | CRITICAL |
| Relapse and recurrence (Majority of studies follow up for 1 year. Assessed with study defined measures; majority follow WHO definition) | | | | | | | | | | | | |
| 19 | observational studies d | not serious | not serious | not serious | not serious | none | 755/17905 (4.2%) | 2787/74686 (3.7%) | **OR 1.64** (1.29 to 2.08) | **22 more per 1,000** (from 10 more to 37 more) | ⨁⨁◯◯ LOW | CRITICAL |
| MDR-TB (Majority of studies follow up during treatment. Assessed with study defined measures)e | | | | | | | | | | | | |
| 19 | observational studies f | serious e | not serious | serious e | not serious | none | 270/4216 (6.4%) | 712/41108 (1.7%) | **OR 1.98** (1.51 to 2.60) | **16 more per 1,000** (from 9 more to 26 more) | ⨁⨁◯◯ LOW | CRITICAL |
| Sputum culture conversion at 2-3 months (Outcome informs follow up from baseline to 3 months. Assessed with objective lab measure, however, any culture method included)ghi | | | | | | | | | | | | |
| 18 | observational studies c | not serious | not serious | not serious | not serious | none | 685/3054 (22.4%) | 1675/15099 (11.1%) | **OR 2.07** (1.63 to 2.62) | **0 fewer per 1,000** (from 106 fewer to 136 more) | ⨁⨁◯◯  LOW | IMPORTANT |

**CI:** Confidence interval; **OR:** Odds ratio

#### Explanations

a. Any observational study reporting this outcome of interest was included. However, only four studies identified were not cohort studies and were all case-control studies.

b. Heterogeneity denoted by the I2 statistic is high and only partially explained.

c. Any observational study reporting this outcome of interest was allowed for. However, only two non-cohort studies were identified and all were case-control studies.

d. Any observational study reporting this outcome of interest was allowed for. However, only five non-cohort studies were identified and all were case-control studies.

e. May not indicate new cases of MDR-TB

f. Any observational study reporting this outcome of interest was allowed for. For this outcome, only cohort studies were identified.

g. Not an outcome, on the pathway to a poor outcome

h. Culture is the gold standard for laboratory confirmation of active TB disease, although diagnosis can be made using clinical judgement alone. Differing culture techniques are available. Broth culture (BACTEC, MGIT, VersaTREK, MBBACT) allows detection in 4-14 days, solid media in 3-6 weeks. Here, papers report culture conversion at 2-3 months detected by serial bacteriologic exam using any culturing system.

i. Majority of cohort studies continue follow up for 1 year, however, data for this outcome was collected for each study participant at a specific time-point. Thus, limited deviation in time during which events can occur is seen between studies.

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1. % Known outcome is defined as the proportion of the initial study group with a known TB treatment outcome includes cured, treatment completed, treatment failure, death, relapse, MDR-TB; unknown outcome includes default, transferred out, not recorded, abandonment/refusal of treatment, loss to follow up, withdrawals due to adverse drug reaction. [↑](#footnote-ref-2)
2. Median age [↑](#footnote-ref-3)
3. Mean age calculated from age-group distribution

   Abbreviation: IV-intravenous; NR-not reported; NS-not significant; +ve-positive; -ve-negative; ESRD-end stage renal disease; AFB- acid-fast bacillus; DOT-Directly Observed Treatment; COPD- chronic obstructive pulmonary disease; OGTT- oral glucose tolerance test; U.S.-United States of America; R.O.K.-Republic of Korea; K.S.A.-Kingdom of Saudi Arabia. [↑](#footnote-ref-4)