Pulmonary resection for patients with multidrug-resistant tuberculosis: systematic review and meta-analysis

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Objectives: Multidrug-resistant tuberculosis (MDR-TB) has become an emerging global public health crisis. Several studies have suggested that pulmonary resection has efficacy in the treatment of MDR-TB. A systematic review of the available therapeutic studies was conducted to determine the treatment outcome among patients with MDR-TB who underwent pulmonary resection.

Methods: To evaluate pulmonary resection for MDR-TB, a random-effect meta-analysis of the available studies was used to assess the overall treatment outcome. Subgroup analyses were also conducted by separating studies based on each characteristic independently.

Results: After screening 4996 articles, 15 clinical reports with a mean of 63 patients per report met the inclusion criteria. Analysis of the studies showed that the estimated pooled treatment success rate of pulmonary resection for patients with MDR-TB was 84% [95% confidence interval (CI) 78%–89%]. The rates of failure, relapse, death and default were 6% (95% CI 4%–8%), 3% (95% CI 1%–4%), 5% (95% CI 2%–8%) and 3% (95% CI 1%–5%), respectively. The proportion of patients treated successfully did not differ significantly on the basis of any of the individual study characteristics.

Conclusions: Substantial heterogeneity in the study characteristics prevented a more conclusive determination of what factors had the greatest effect on the proportion of patients that achieve treatment success and limited the validity of this analysis. Some important variables, including patient HIV status, were inconsistently reported between studies. These results underscore the importance of strong patient support and treatment follow-up systems to develop successful MDR-TB treatment programmes.

Keywords: pulmonary surgical procedures, MDR-TB, treatment outcome

Introduction

Tuberculosis (TB) is a major global health problem, with 9 million new cases and almost 2 million deaths per year. Most patients with TB can be successfully treated using short-course medical chemotherapy, which consists of a four-drug regimen including isoniazid, rifampicin, pyrazinamide and ethambutol. However, a small proportion of patients with pulmonary TB require surgical treatment. The indications for surgery usually include the management of complications of TB (including haemoptysis, bronchiectasis, bronchial stenosis, bronchopleural fistula and aspergiloma) and the management of drug-resistant forms of the disease. A wide variety of procedures have been reported, including surgical resection and thoracoplasty. Patients usually do well with surgery, with cure rates of 60%–100% being achieved.

Multidrug-resistant TB (MDR-TB), a major indication for surgery, is defined as having in vitro resistance to at least both isoniazid and rifampicin, the two most powerful existing anti-TB agents, and has become an emerging global public health crisis. Strains of MDR Mycobacterium tuberculosis are often resistant to other anti-TB agents in addition to isoniazid and rifampicin. When such an isolate is resistant to any second-line injectable agent (e.g. amikacin, capreomycin or kanamycin) and any fluoroquinolone, the strain is termed extensively drug-resistant TB (XDR-TB). In many countries the rates of drug-resistant TB are increasing and more international efforts have been mobilized to confront this emerging infectious disease. An estimated 489000 cases of MDR-TB occurred worldwide in 2006. The management of drug-resistant TB requires extended treatment and expensive and potentially toxic drug regimens, and often results in higher rates of treatment failure.
and death compared with the drug-susceptible disease.\textsuperscript{16–18} Reported cure or treatment completion rates for MDR-TB using second-line agents have ranged from 44% to 83%.\textsuperscript{19–24} Treatment failure is especially common in patients co-infected with XDR-TB and HIV, where mortality approaches 100%.\textsuperscript{25}

Medical treatment for drug-resistant TB with anti-TB drugs does not achieve satisfactory outcomes. However, in several studies, the resection of cavitary lesions or destroyed lobes that harbour great numbers of the TB organism improved patient outcome in cases with MDR-TB. Pulmonary resection combined with antituberculous chemotherapy for MDR-TB has shown success rates of 89%–96%.\textsuperscript{16,26–29} Recently, treatment guidelines for MDR-TB were published. The role of surgery in the treatment of MDR-TB continues to be controversial.\textsuperscript{30,31} We conducted a systematic review and meta-analysis of the available therapeutic studies to determine the outcome among patients with MDR-TB who were treated with pulmonary resection.

**Methods**

The meta-analysis was conducted in accordance with QUOROM guidelines.\textsuperscript{32}

**Data sources**

PubMed, Embase and the Cochrane Library were searched for studies through July 2010. There was no limit put on the earliest date of publication. The search terms included were as follows: ‘tuberculosis’; ‘pulmonary resection’; ‘pneumonectomy’; ‘surgery’; ‘surgical treatment’; ‘lung resection’; ‘drug-resistant’; ‘multi-drug resistant’; ‘multidrug resistant’; ‘MDR’; and ‘multiple drug-resistant’. In addition, the online archives of the International Journal of Tuberculosis and Lung Disease were reviewed for applicable studies not found in the previous search. The reference lists of identified original articles and reviews were searched for other relevant articles. Abstracts, chapters of books, conference proceedings or correspondence were not included. The initial search had no language restrictions, but studies not published in the English language were excluded from the data extraction process. As very small studies may be vulnerable to selection bias, only studies including ≥10 patients were selected for inclusion in the analysis.

**Study selection**

Two reviewers (H.-B. X. and R.-H. J.) selected articles in the following two stages: titles and abstracts; and then full-text articles. Discrepancies between the two reviewers were resolved by consensus or through discussion with a third reviewer (L. L.). Two reviewers (H. B. X. and R. J. H.) independently performed data extraction for all the articles and a third reviewer (L. L.) independently performed data extraction for one-third of the articles to assess accuracy in the data extraction. Studies were required to meet the following inclusion criteria: (i) confirmation that patients had MDR-TB using drug-susceptibility testing of cultured \textit{M. tuberculosis}; (ii) treatment outcome definitions specified by mycobacterial culture endpoints; and (iii) outcomes reported according to WHO classifications of success (cure or treatment completion), failure, relapse, death and default (treatment interruption).\textsuperscript{30} Because this study was a systematic review, ethics committee approval or written informed consent from the participants was not required. The methodological quality of the eligible studies was assessed mainly according to Cochrane-based criteria.

**Data extraction**

We recorded treatment outcomes according to WHO classifications of treatment success (cure or treatment completion), failure, relapse, death and default (treatment interruption).\textsuperscript{30} Patients still on treatment who were classified as ‘probable cure’ or ‘probable failure’ were added to the success and failure categories, respectively. Patients who remained on treatment but were not assigned an interim outcome were not included in this analysis. All patients who were classified as ‘transfer out’ were added to the default category.

For each study, data were gathered on patients’ characteristics, treatment protocols and study definitions. Patients’ characteristics included previous TB treatment history, HIV prevalence, and the mean number of drugs to which patients’ isolates were resistant. Data on treatment protocols included the indication for surgery, pre-operative lung lesion type and type of pulmonary resection. In addition, the length of follow-up and definition of cure were recorded, if available. If no data on the above-mentioned characteristics were reported in the primary studies, the information was requested from the original authors.

**Data synthesis and analysis**

For each study, the yield of treatment outcomes including success, failure, relapse, death and default was calculated. Pooled percentages for each outcome from every study were included in a Bayesian random-effects meta-analysis.\textsuperscript{33} A Bayesian model was chosen because of its appealing nature, such as full allowance for all parameter uncertainty in the model, the ability to include other pertinent information that would otherwise be excluded and the ability to extend the model to accommodate more complex, but frequently occurring, scenarios. The Bayesian method overcomes some of the difficulties encountered with other traditionally used methods, such as wide variation in sample sizes and estimates, the presence of covariates, and response rates near 0 or 1. The Bayesian method directly interprets the credible intervals of the posterior-effect estimates.\textsuperscript{34,35} The heterogeneity across the studies was estimated by calculating $I^2$, an index of the proportion of total variation across studies that is due to heterogeneity rather than to chance.\textsuperscript{36} A $P$ value of <0.05 indicated that heterogeneity among the group of studies being analysed was significant. The $I^2$ statistic was >50% (with $P<0.05$) for each treatment outcome (success, failure, relapse, death and default). Therefore, a random-effects analysis, incorporating the impact of both chance and heterogeneity among study populations and study design, was chosen over the fixed-effects alternative, which assumes that differences among study outcomes are due entirely to chance.

To examine the influence of each study characteristic individually on the treatment success, subgroup analyses were also conducted by separating studies based on each characteristic independently. The individual factors were ranked by the difference in treatment success between reports that met the cut-off compared with all other reports. The differences in the proportion of patients achieving treatment success among studies that met the cut-offs compared with those that did not were then examined. Statistical analyses were done with WinBUGS and R. As publication bias is a risk in meta-analyses, the potential presence of this bias was tested for by using the Egger test.

**Results**

**Study characteristics**

As summarized in Figure 1, 15 studies (Table 1) were selected for inclusion in the analysis,\textsuperscript{16–29,37–46} including 12 studies of pulmonary resection for patients with MDR-TB\textsuperscript{25–29,37–40,43–46} and 3 studies for patients with MDR-TB or XDR-TB.\textsuperscript{41,42,47} Because...
of language problems, four studies published in Lithuanian and Chinese were excluded. The reports came from several countries and included treatment outcomes for a mean of 63 patients per report (range 19–172). Of the 15 studies, all reported data on post-operative cure, 13 reported failure rates, 26–29,37–44,46 11 reported relapse rates, 26,27,29,37–39,42–46 8 reported death rates 26,28,29,37,41,43,44,47 and 5 reported default rates. 26,28,37,41,46 Thirteen studies reported data on follow-up 26,27,29,37–40,42–47 and only 4 (27%) reported <10% of patients lost to follow-up after surgery in the analysis. 29,42,43,47 The length of follow-up after pulmonary resection often varied and ranged from 3 to 204 months. Twelve studies reported varied post-operative medical therapy regimens. 26,27,29,37–40,42,44–47

Characteristics of the patient population and the cure definition differed among the included studies (Table 1). The number of patients previously medically treated for TB ranged from 95% to 100% in the 15 reviewed reports and in five studies patients received a fluoroquinolone. 41,44–47 Six (40%) of the studies reviewed were published before 1995 26,28,37–39,43 and nine (60%) were published in 1995 or later. 27,29,40–42,44–47 By the World Bank classification system, six (40%) studies were from developing countries 37,39,40,43–45 and nine (60%) were from developed countries. 26,27,29,37–39,41,42,44–47 Fourteen studies reported post-operative complications. 26,27,29,37–47 The pre-operative lung lesion type was not consistent in the 11 studies in which it was reported and was therefore inappropriate for analysis. 26,27,29,38,39,41,43–47

Major complications included empyema in 9 studies, bleeding in 12, bronchopleural fistula in 8, air leakage in 8 and wound infection in 6. The results of methodological quality assessment of the studies are described in Table 2. All studies are case series. Thirteen studies were retrospective 26,27,28,37–41,43–47 and 2 were prospective. 29,42 The statistical analysis methodology was well described in seven studies, 28,29,37,38,41,45,47 but was not reported in eight studies. 26,27,39,40,42–44,46

Treatment outcomes

Across all studies, the estimated pooled treatment success rate, defined as the proportion of patients who were cured or completed treatment, was 84% [95% confidence interval (CI) 78%–89%]. The pooled treatment failure, relapse, death and default rates were 6% (95% CI 4%–8%), 3% (95% CI 1%–4%), 5% (95% CI 2%–8%) and 3% (95% CI 1%–5%), respectively (Figure 2). However, the heterogeneity in the study characteristics led to significant variation in the reported treatment outcome. Among the 12 reports of pulmonary resection for patients with MDR-TB (mean 69 patients; range 23–172), the mean proportion of patients achieving treatment success was 83% (95% CI 77%–89%; Figure 3 and Table 3). Among the three studies involving patients with MDR-TB or XDR-TB (mean 42 patients; range 19–72), the mean proportion achieving treatment success was higher than that for the studies with MDR-TB patients, but the difference was not significant at 89% (95% CI 86%–92%; Figure 3 and Table 3).

We also analysed the effect of each of the other study characteristics independently (Table 3). The analysis showed that the proportion of patients treated successfully did not differ significantly on the basis of any of the following individual study characteristics: start year of the study; cure definition; national income status; geographic region; or type of pulmonary resection (Table 3). Differences in population characteristics, including
<table>
<thead>
<tr>
<th>Study location</th>
<th>Years</th>
<th>Sample size</th>
<th>Proportion previously treated (%)</th>
<th>HIV prevalence</th>
<th>Median resistance [n drugs (range)]</th>
<th>Pulmonary resection (type, n)</th>
<th>Definition of cure</th>
<th>Follow-up (months)</th>
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</thead>
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<tr>
<td>Pomerantz et al.</td>
<td>USA</td>
<td>1983–2000</td>
<td>172</td>
<td>100</td>
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<td>South Korea</td>
<td>1995–1999</td>
<td>49</td>
<td>100</td>
<td>0</td>
<td>pneumonectomy 12, lobectomy 35, wedge resection 1, cavernoplasty</td>
<td>3 months of consecutive negative cultures</td>
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<td>USA</td>
<td>1984–1998</td>
<td>130</td>
<td>100</td>
<td>NR</td>
<td>pneumonectomy 66, lobectomy 64</td>
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<td>121</td>
<td>95</td>
<td>1%</td>
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<td>6 months of consecutive negative cultures</td>
<td>19–103</td>
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<td>Leuven et al.</td>
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<td>1990–1995</td>
<td>61</td>
<td>100</td>
<td>≥4</td>
<td>pneumonectomy 35, lobectomy 26, segmentectomy 1</td>
<td>3 months of consecutive negative cultures</td>
<td>24</td>
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<tr>
<td>Sung et al.</td>
<td>South Korea</td>
<td>1994–1998</td>
<td>27</td>
<td>100</td>
<td>NR</td>
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<td>3 months of consecutive negative cultures</td>
<td>3–45</td>
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<td>China</td>
<td>1990–1999</td>
<td>26</td>
<td>100</td>
<td>3.9 (3–6)</td>
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<td>culture negative</td>
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<td>South Africa</td>
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<td>17%</td>
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<td>18 months of consecutive negative cultures</td>
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<td>South Korea</td>
<td>1995–2004</td>
<td>35</td>
<td>100</td>
<td>NR</td>
<td>pneumonectomy 14, lobectomy 20, segmentectomy 1</td>
<td>Laserson definition</td>
<td>NR</td>
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<td>South Korea</td>
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<td>culture negative for ≥18 consecutive months</td>
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<td>1995–2005</td>
<td>23</td>
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<td>1995–2006</td>
<td>56</td>
<td>100</td>
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<td>2 months of consecutive negative cultures</td>
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<td>Japan</td>
<td>2000–2007</td>
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<td>100</td>
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<td>culture negative</td>
<td>8–105</td>
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<td>Kang et al.</td>
<td>South Korea</td>
<td>1996–2008</td>
<td>72</td>
<td>100</td>
<td>0</td>
<td>pneumonectomy 23, lobectomy 38, segmentectomy 10, wedge resection 1</td>
<td>Laserson definition</td>
<td>18–24</td>
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</table>

NR, not reported.
prevalence of HIV, and mean number of resistant drugs also did not lead to significantly different outcomes.

**Publication bias**
The result of the Egger test for publication bias was significant \((P=0.020)\). The funnel plots for publication bias (Figure 4) also showed asymmetry. These results indicate a presence of potential for publication bias.

**Discussion**
MDR-TB ultimately develops from the inadequate treatment of active pulmonary TB. There are multiple reasons for inadequate therapy; poor prescribing practices with insufficient treatment duration and poor drug selection are well-recognized contributors.48,49 Systemic problems, through inadequate public health resources and unpredictable drug supplies, also play a role.50 In addition, irregular medication intake—whether due to insufficient patient education, adverse events or socioeconomic determinants—contributes to resistance. Also, a significant proportion of patients acquire the drug-resistant disease because they live in an environment with a high prevalence of drug-resistant TB.

The medical treatment of MDR-TB is complex and costly, and is associated with relatively low cure rates, high relapse, increased toxicity, and high morbidity and mortality. Two previous systematic reviews evaluated the existing evidence regarding medical treatment regimens for MDR-TB. The authors used a meta-analysis of the available therapeutic studies to assess treatment outcomes. The results of the two reviews showed that the pooled treatment success estimate, defined as the

<table>
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<th>Study location</th>
<th>Sampling method</th>
<th>Incomplete outcome data addressed</th>
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<tr>
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<td>South Korea NR</td>
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</tbody>
</table>

NR, not reported.

The medical treatment of MDR-TB is complex and costly, and is associated with relatively low cure rates, high relapse, increased toxicity, and high morbidity and mortality. Two previous systematic reviews evaluated the existing evidence regarding medical treatment regimens for MDR-TB. The authors used a meta-analysis of the available therapeutic studies to assess treatment outcomes. The results of the two reviews showed that the pooled treatment success estimate, defined as the

**Figure 2.** Treatment success and other treatment outcomes for pulmonary resection of multidrug-resistant tuberculosis. Treatment effects and summaries were calculated using a random-effects model weighted by study population. The 95% confidence intervals (95% CI) are shown.
proportion of patients who were cured or completed treatment, was only 62%, while the pooled default, death, and transferred out rates were 13%, 11% and 2%, respectively. Because anti-TB medical therapy occasionally proves inadequate to cure MDR-TB, adjunctive pulmonary resection has been advocated in selected patients who have localized disease, such as a cavitary lesion or a single destroyed lobe. The rationale for pulmonary resection is based on the belief that pulmonary cavities harbour millions or billions of the resistant organisms. The infection in these locations cannot be controlled by the host-specific immunity and, consequently, the surgical removal of these cavities may permit cure. Here, a systematic review and meta-analysis is reported that evaluated the treatment outcomes of pulmonary resection for patients with MDR-TB. The results showed that the pooled success rate was 84%, and the pooled failure, relapse, death and default rates were 6%, 3%, 5% and 3%, respectively. Although pulmonary resection was an adjunct to medical treatment for patients with MDR-TB, it seemed that the overall treatment success rate of pulmonary resection was better than that for medical treatment regimens. The overall incidence of failure, relapse, death and default with pulmonary resection was also relatively lower. To date, there has been no randomized study to address the comparative efficacy of chemotherapy versus surgery combined with chemotherapy in the management of MDR-TB. This type of study is urgently needed in the future. Prospective randomized controlled trials comparing different treatment strategies for MDR-TB will provide greater insight into the improvement of MDR-TB treatment protocols.

To determine which patient and programme characteristics facilitate the greatest treatment success, data from the reviewed 15 studies that included treatment outcomes for a total of 949 patients receiving pulmonary resection were analysed. Among the studies that included MDR-TB and XDR-TB patients receiving pulmonary resection, the treatment success was relatively better than in studies including MDR-TB patients, but the difference was not significant. In fact, no individual patient or programme characteristic was associated with a

![Figure 3. Treatment success by type of study. (a) Treatment success for studies with multidrug-resistant tuberculosis patients. (b) Treatment success for studies with multidrug-resistant and extensively drug-resistant tuberculosis patients. Treatment effects and summaries were calculated using a random-effects model weighted by study population. The 95% confidence intervals (95% CI) are shown.](https://academic.oup.com/jac/article-abstract/66/8/1687/675861)
significantly greater proportion of patients achieving treatment success. However, substantial heterogeneity in the patient populations, study designs and reporting limit the scope of this analysis. It prevents a more conclusive determination of what factors have the most effect on the proportion of patients that achieve treatment success and limits the validity of this analysis. The treatment protocols, and the reporting of key patient and study characteristics were found to be inconsistent across studies. Several studies omitted the pre-operative lung lesion type and the average number of drugs to which each patient’s TB isolate was resistant. HIV infection, which has been associated with poor outcomes among patients receiving treatment for MDR-TB and XDR-TB, was not assessed in five of the studies reviewed. This absence, despite the confluence of the HIV and TB epidemics, exemplifies the heterogeneity in TB epidemics and associated treatment strategies. Thus, the lack of significant findings associated with certain variables in this analysis may be due to reporting insufficiency, rather than the absence of a real association. Furthermore, these variations in the recording of data necessary for assessing treatment outcomes underscore the need for standardized data collection and reporting in programmes and studies of MDR-TB, possibly through the use of an international registry of treatment outcomes. The absence of a registry of individual treatment outcomes or outcome studies precluded the possibility of estimating publication bias in this meta-analysis. Standards in outcome reporting are particularly important in light of the emergence of XDR-TB.

Our systematic review and meta-analysis had several strengths. The comprehensive search strategy enabled us to...
review articles from multiple databases though July 2010. Moreover, two reviewers independently and reproducibly completed screening, study selection and data extraction. An additional strength was the subgroup analysis to examine the impact of each study characteristic individually on treatment outcome. This review also had several limitations. First, the most important is our inability to identify any randomized control trials. Instead, observational data were relied on exclusively for treatment outcomes. This likely introduced confounding to our pooled analysis, since crude outcomes, rather than adjusted odds ratios, were reported for most trials. Second, although our search strategy was systematic, we were not able to include non-English-language papers, thereby limiting the scope of the included studies. Analyses were limited by the small number of included studies for a particular outcome. Third, there was substantial variability in study characteristics, which resulted in substantial heterogeneity, even in stratified analyses. The pooled treatment outcome estimates should be viewed with caution. Additionally, the pre-operative lung lesion type was not reported precisely in most studies; thereby, the influence of lesion type on treatment outcome could not be analysed.

As in any systematic review, publication bias was a concern. However, existing methods such as funnel plots and regression asymmetry tests for publication bias were designed for the meta-analysis of randomized controlled trials. To our knowledge, they cannot be used to detect publication bias in a meta-analysis of diagnostic studies or rates. 57

The ‘Stop TB’ strategy developed by WHO set the goal of curing 85% of all detected TB cases by 2005. 58 MDR-TB has presented challenges to achieving this objective in many areas. Nonetheless, appropriate pulmonary resection might lead to treatment success more readily and should be further investigated in current trials of MDR-TB therapy. In the absence of randomized clinical trials, more systematic documentation of programmatic components and outcomes of MDR-TB treatment can strengthen the evidence base for treatment. The comprehensive treatment of MDR-TB is of vital importance in promoting public health to slow the spread and reduce the impact of drug-resistant TB around the world.

Figure 4. Funnel graph for the assessment of potential publication bias. The funnel graph plots the log of the odds ratio (OR) against the standard error (SE) of the log of the OR (an indicator of sample size). Circles represent each study in the meta-analysis. The result of the Egger test for publication bias was significant (P=0.020).

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## Transparency declarations
None to declare.

## References


