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Murakami, Risa

Nakazawa, Minato

(Citation)
Bulletin of health sciences Kobe,34:13-25

(Issue Date)
2018

(Resource Type)
departmental bulletin paper

(Version)
Version of Record

(JaLCDOI)
https://doi.org/10.24546/81011894

(URL)
https://hdl.handle.net/20.500.14094/81011894

Risk factors associated with default among TB treatment: a meta-analysis

Risa MURAKAMI[1], Minato NAKAZAWA[1]

Abstract

Objective: In tuberculosis treatment, the ratios of unsuccessful treatment outcome and retreatment cases on males are generally higher. But the results were inconclusive. This study aimed to examine the association between tuberculosis treatment type or treatment outcomes, and sex difference by conducting a meta-analysis.

Methods: Relevant studies compared treatment outcomes with retreatment patients or new patients, and male or female were searched by PubMed and MEDLINE from 1982 to 2012. Both fixed effect model and random effect model were used to calculate the summary risk estimates.

Results: We pooled appropriate data and analyzed using EZR. In total, 20 of 125 studies were identified. Pooled Odds Ratio and its 95%CI of unsuccessful treatment outcomes with retreatment tuberculosis cases compared with new tuberculosis cases was 1.80 (95%CI: 1.34-2.41), and with male for tuberculosis treatment compared with female was 1.31(95%CI: 1.14-1.49).

Conclusion: This meta-analysis revealed an association between unsuccessful treatment outcomes, and retreatment patients and males.

Keywords

Tuberculosis　Treatment outcomes　Default　Meta-analysis

[1] Department of Public Health, Graduate school of Health Sciences, Kobe University

INTRODUCTION

Tuberculosis is a major problem of the global burden of disease and has received considerable attention. According to the recent report by World Health Organization (WHO), there were 6.3 million new cases of tuberculosis and 1.7 million people died from tuberculosis in 2016[1]. Tuberculosis is one of the infectious conditions targeted by a part of Millennium Development Goals. It is important for tuberculosis treatment to take anti-tuberculosis drugs. Directly Observed Treatment, Short-course strategy (DOTS) for tuberculosis control was launched by the WHO in 1995 to provide the treatment for tuberculosis. The strategy, although based on short course treatment regimens, of six months, included practical instruction sets such as political commitment, good management practices, sputum smear microscopy for diagnosis, and the direct observation of doses to ensure adherence.

In many industrialized countries with good treatment facilities and a second supply of drugs free of charge for patients, treatment results have not reached the targets set at 85% by WHO. The main reason for this is the high rate of death as an unfavourable outcome, frequently with much comorbidity from other diseases[2]. Previous studies have shown the association treatment outcomes and intravenous drug use, HIV-infection, high age, alcoholic, male sex and immigration[3].

Recently, the number of tuberculosis cases has been increasing especially in slum areas, which includes not a few number of retreatment cases because there are many patients who previously infected tuberculosis: relapse, and receives re-treatment: treatment after default, treatment after failure. And among them, the number of people who defaulted on the treatment was large. The high failure rate of tuberculosis treatment is partly due to socioeconomic problems[4]. For example, Papua New Guinea (PNG) is one of the countries with the highest burden of tuberculosis with the prevalence of 534/100,000 population in 2011[5]. Tuberculosis is rapidly becoming a severe problem in PNG. And the problem is even more troubling since the successful treatment rate for tuberculosis is lower than the other countries. In 2010, the treatment success rate was 85% among all new tuberculosis cases, and 87% among new cases of sputum smear-positive pulmonary tuberculosis[6]. In contrast, the treatment success rates in PNG in 2010 were only 58% for new smear-positive, 49% for new smear-negative or extra-pulmonary, and 46% for retreatment[5]. In addition, treatment success rate is becoming lower in recent years. The PNG government in cooperation with various groups of other countries such as the Australia Agency for International (AusAID) has started to get involved in the interventions of DOTS or follow-up after the discharge from a hospital[7]. However, the coverage of tuberculosis control is quiet low. Because follow-up after the discharge from a hospital, health education for tuberculosis patients and for the community are not enough. PNG is not the special, but the typical situation in the slum areas of developing countries.

Tuberculosis measures require the standardization of tuberculosis diagnosis, treatment and inspection technology. In addition, as soon as possible, the enforcement of follow up and health

education must be needed. The important thing for tuberculosis treatment is to complete treatment and to minimize the infection to others. The lower successful treatment rate leads the higher default rate for treatment. Considering that the retreatment cases show lower successful treatment rates than new tuberculosis cases, the risk of infecting tuberculosis to others in retreatment cases may subsequently result in the larger number of tuberculosis cases[8].

Several articles have reported the association between treatment outcome and tuberculosis case type or sex. However, the results were controversial. For one, this study identified that successful treatment outcome (cure or treatment completed) was reported for 86% of women and 84% of men who had started treatment. No gender bias was observed in tuberculosis treatment outcome[9]. And few systematic review and meta-analysis have ever been conducted for this topic.[10-12]

Meta-analysis is statistical analysis which combines the results of several studies and provides a broad view in an objective[13]. Its statistical power compared with individual studies is the best as an Evidence Based Medicine. The present study aimed to clarify the association between treatment outcome and tuberculosis case type, and sex by conducting meta-analysis.

MATERIALS AND METHODS

Search strategy

A literature search was conducted in the database MEDLINE and PubMed to identify relevant studies. Key words used in the search were included "tuberculosis" AND "treatment outcome" AND "default", or "treatment" AND "outcome" AND "default". I excluded case reports. Bibliography of full text articles were examined for eligible studies and limited English articles. Articles published from 1982 to 2012 were included. The criteria of tuberculosis patients limited adults (over 19 years). The research was conducted on December, 2012.

Data selection and extraction

Studies identified by the search strategy were reviewed for eligibility based on title and abstract by one investigator (RM). Relevant articles were examined in full text. A second investigator (MN) independently checked the main results of the included studies.

Inclusion criteria were as follows: an original study; reported treatment outcomes and tuberculosis case type on an adult population in English from 1982 to 2012. Exclusion criteria were as follows: a case report; surgical intervention.

Successful treatment outcomes included patients who met the criterion of “Cure” or “Completion” of treatment. Non-successful treatment outcomes included patients whose outcomes were “Failure”, “Default”, “Transfer”, “Died” and “Unknown”. For excluding heterogeneity, outcomes with an intervention were excluded.

This study extracted all relevant data items from each original report. The treatment outcome,

tuberculosis case type and sex extracted from each included study.

Data analysis

A meta-analysis was conducted using EZR (version1.0, R-2.14.1). We extracted the data of successful outcome, unsuccessful outcome, new-case, retreatment, male and female across studies and pooled odds ratio (OR) using a random effect model and a fixed effects model of meta-analysis.

Heterogeneity of studies were evaluated by calculating I^2 and P-value. In the case of being very high heterogeneity (I^2>75%), subgroup analysis was performed for evaluating the variation of the quality.

The biases of this meta-analysis: bias of low quality study, selection bias and publication bias were assessed. Original criteria: sample size was at least 100 participants, it was specified prospective or retrospective study and there was no critical flow, and sensitivity analysis were used for evaluate quality of each study. Funnel plot and linear regression test were used for evaluating publication bias. The inclusion and exclusion criteria were used for protecting selection bias.

RESULTS

Literature search

This study initially identified 125 citations from an electronic database search. Of these, 20 articles[14-33] met the inclusion criteria (Figure 1). Of these, 25 articles excluded based on the title and the abstract, 4articles were unduplicated, 52 articles were inadequate data on patient outcomes, 19articles were not evaluated the association between treatment outcome and tuberculosis case type or sex, and 5 articles were duplicated data.

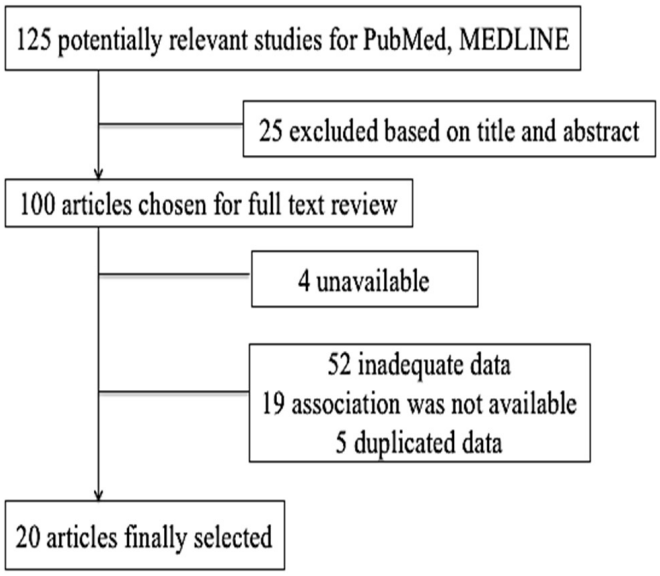

Fig 1. The process of study selection fulfilling eligibility criteria.

Study characteristics

These studies conducted at 15 countries, Zambia, Malawi, Brazil, Kenya, Thailand, India, Taiwan, Estonia, Ethiopia, Vietnam, Russian, Norway, Benin, Switzerland, and Gambia. The study period ranged from 1982 to 2012. Most studies were retrospective or prospective cohort studies. In 17 studies about treatment outcome and sex difference, the total numbers of males were those of 30660 (63%) and females were 18131 (37%). 17articles of these reported on patients with previously tuberculosis history. The total numbers of retreatment were 3969 (10%) and of new-case were 37445 (90%).

Main analysis

Figure 2 showed the rates of sex difference of treatment outcomes. Seven studies showed statistically significant association that males suffered from higher unsuccessful treatment rate than females, though 3 studies showed slight inverse association. The pooled odds ratio was 1.31 and its 95%CI were 1.14-1.49 by a random effects model and a fixed effects model. By test of heterogeneity, I^2 was 67.7%, p-value was lower than 0.0001.

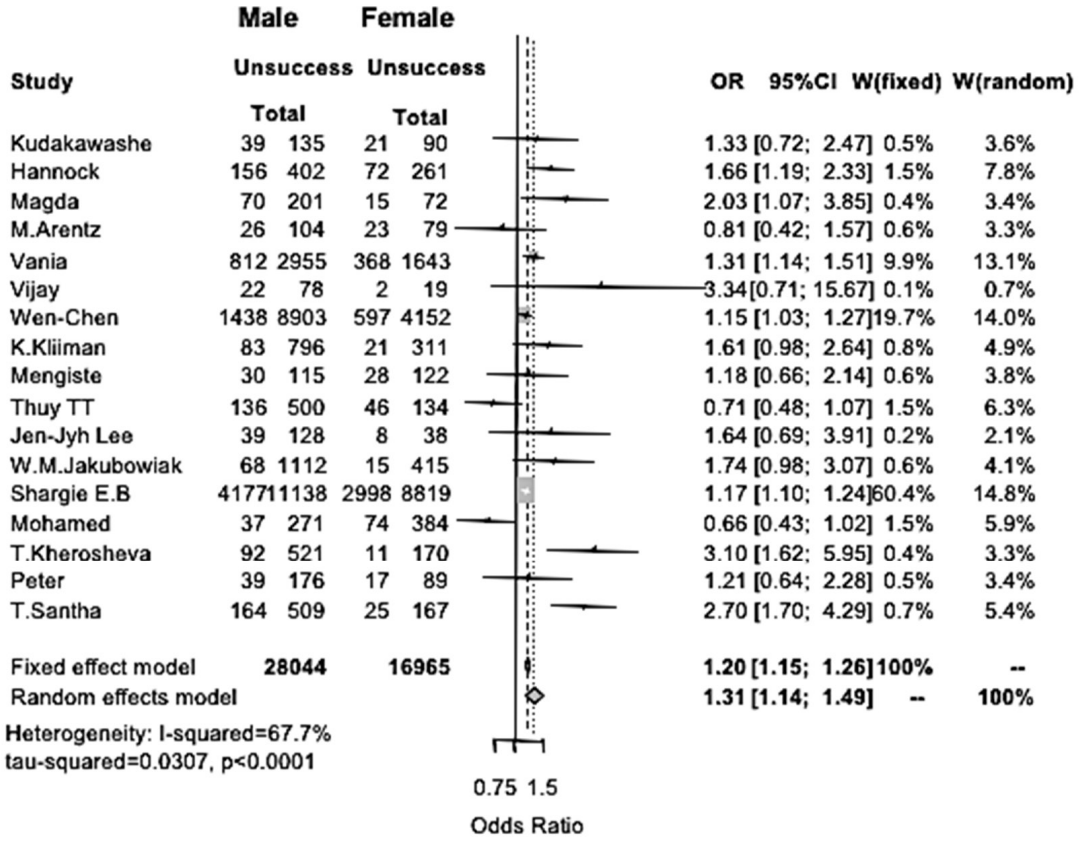

Fig 2. Forest plot of comparison of the ratios of unsuccessful treatment in male vs female.

OR: odds ratio; CI: confidence interval; W: weight.

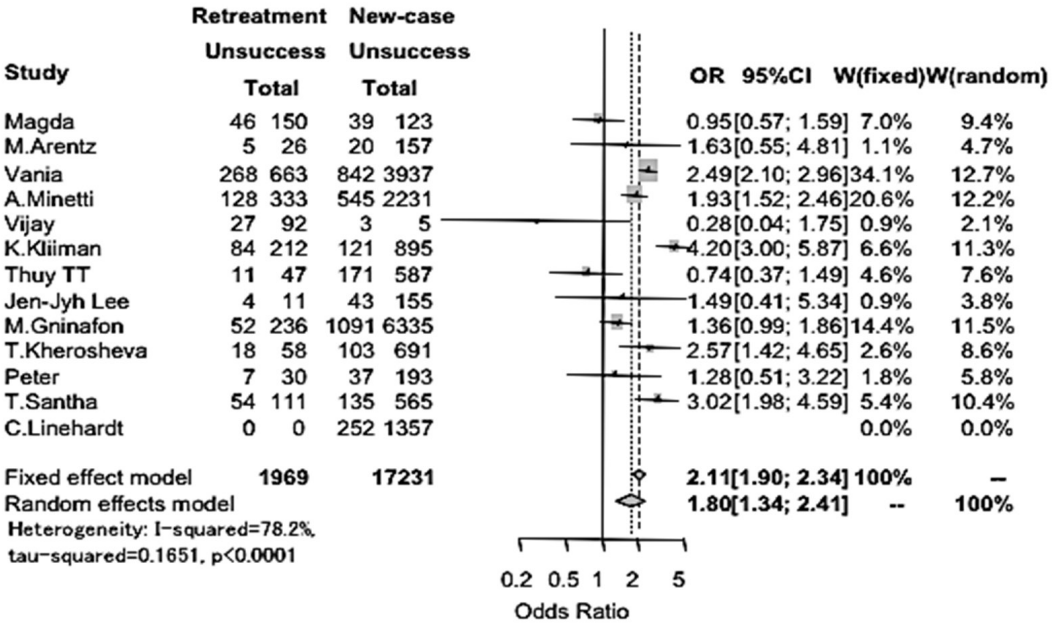

Fig 3. Forest plot of comparison of the unsuccessful treatment ratio in retreatment case vs new-case.

OR: odds ratio; CI: confidence interval; W: weight.

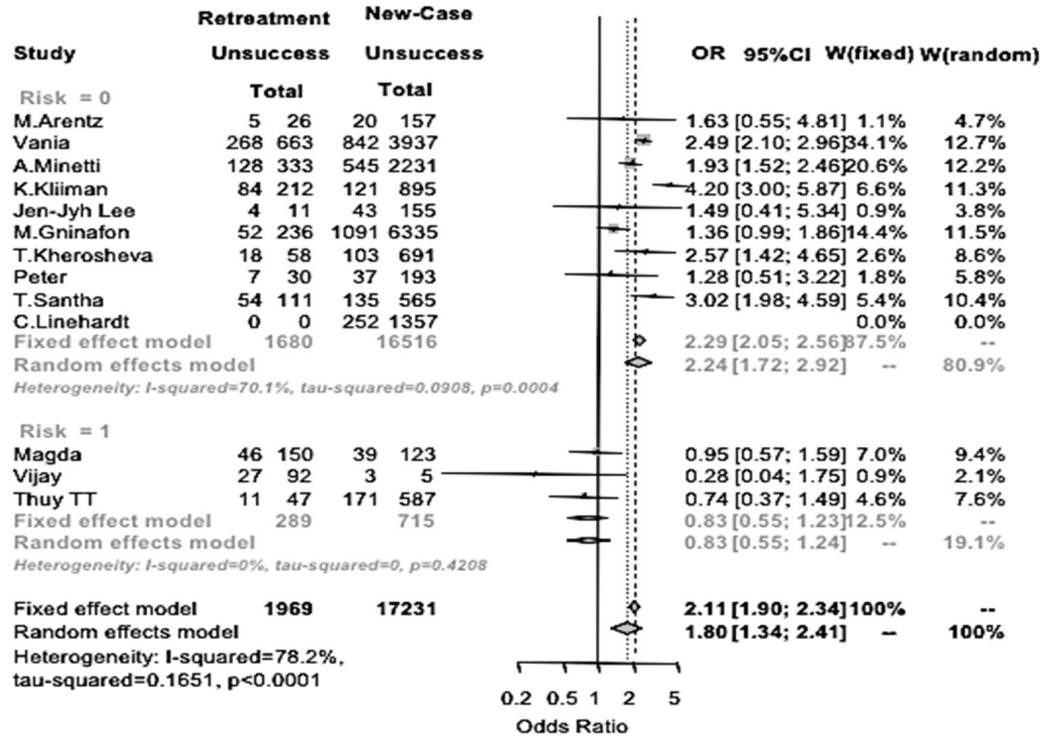

Fig 4. Sensitivity analysis of the unsuccessful outcome ratio in retreatment cases to those in new cases.

OR: odds ratio; CI: confidence interval; W: weight.

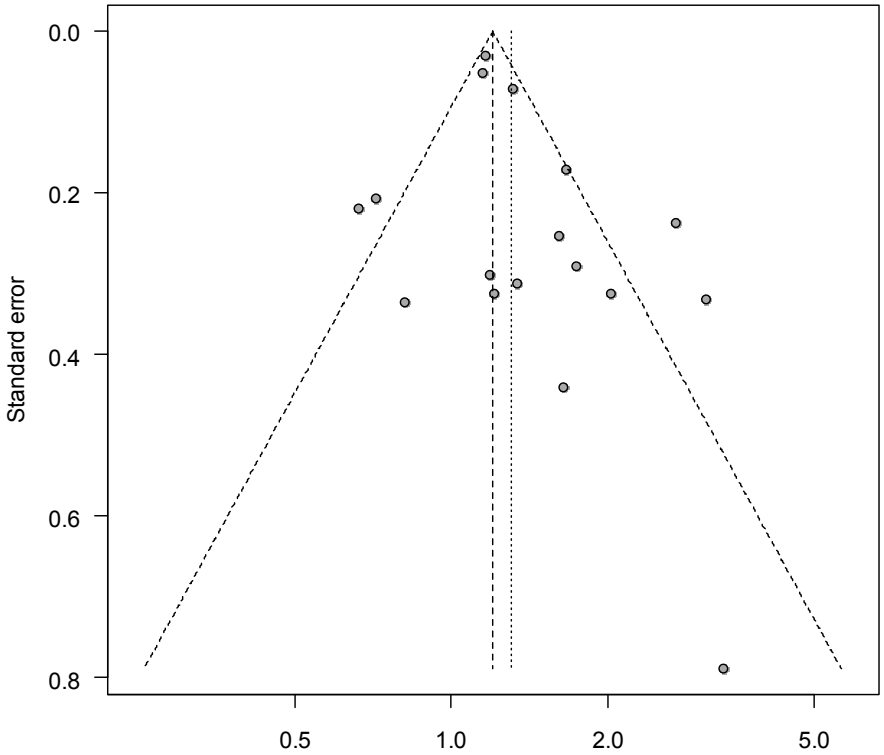

Fig 5. The funnel plot of meta-analysis on unsuccessful outcome and sex.

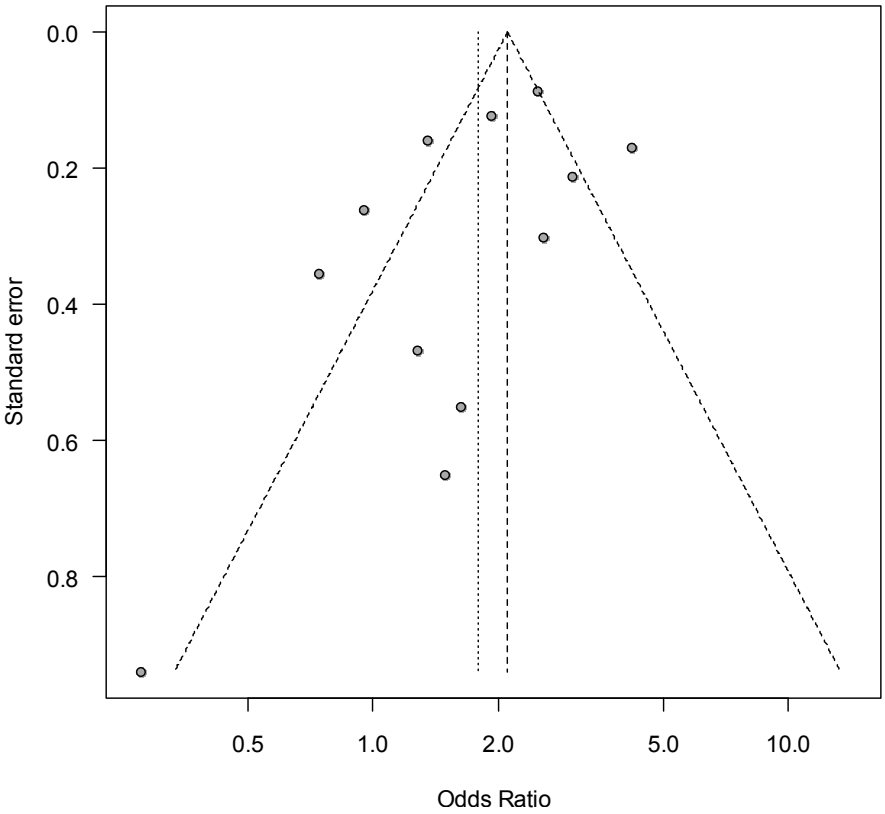

Fig 6. The funnel plot of meta-analysis on unsuccessful outcome and tuberculosis case type.

Sensitivity analyses

Figure 4 shows the rates of retreatment cases to unsuccessful outcome for tuberculosis using sensitivity analysis. This analysis excluded studies which identified heterogeneity was high[16,20,24], thereby I^2 decreased from 78.2% to 70.1% and p-value was 0.0004. Odds ratio was higher compared with before performing sensitivity analysis.

Publication bias

Figure 5 and 6 showed the funnel plot of each meta-analysis. Figure 6 seem to be missing lower right. But they do not look like any substantial asymmetry and P-value was 0.337.

DISCUSSION

In total, 20 publications on the association between tuberculosis treatment outcomes and sex, and treatment type were examined with a meta-analysis. This pooled analysis showed that sex difference and retreatment case were positively associated with an increased risk of unsuccessful treatment rates.

This analysis found significant association between treatment failure and male. Several previous studies discussed the reason why males generally showed higher unsuccessful treatment rate than females; such as males' behavior were highly restricted due to socioeconomic activity compared with females, more common smoking and/or drinking habits in males than in females[34]. This suggests that those reasons are applicable to general population.

Also, this analysis found a significant association between treatment failure and retreatment case. In earlier studies, treatment category was associated with unsuccessful treatment outcome especially for patients who were treated previously[35]. A recent study reported that the high default was consistent with the high default rates observed in the problematic early years of program implementation in the world[32]. For patients' motivation to continue treatment, the prolonged treatment could lend so many burdens and patients need some interventions to support.

There are several limitations of this study. As is expected in meta-analysis, we observed significant heterogeneity of results among the studies. There were some articles which did not match this result. Analyzing pooled data was needed because their associations were defined. The test of heterogeneity of pooled data was high level each analysis. Especially, the heterogeneity was recognized on a meta-analysis about unsuccessful treatment and tuberculosis case type. This study had some reasons why the heterogeneity was high level. One was that the classifications on treatment outcomes could be different in each study. Besides, the reason was to exclude the data of HIV/AIDS positive patients or multi-drug resistant tuberculosis (MDR) patients and extensively-drug resistant tuberculosis (XDR) patients. These may be able to affect the treatment outcomes. Although the heterogeneity of this study was high, most studies were met same outcomes. And

sensitivity analysis was performed. As the result of sensitivity analysis, Odds ratio decreased in excluding studies of high heterogeneity. It was difficult to assess the heterogeneity of this study accordingly and other criteria might be needed. This is the first limitation of this study.

Second, we were unable to collect information about patients' background although lifestyle has been changed in last thirty years. A potential limitation is that our findings are based on the results of observational studies, therefore, we cannot exclude the possibility of confounding by variables that may be associated with each of the exposures.

Third, we have no data to show what kind of treatment for TB each patient in the present study received. Tuberculosis treatment regimens can vary widely, but they require the use of multiple drugs for a minimum of six months. Generally, new patients with pulmonary TB should receive a regimen containing 6 months of rifampicin: 2HRZE/4HR (H: isoniazid; R: rifampicin; Z: pyrazinamide; E: ethambutol).[36] Furthermore, Directly Observed Therapy Short-course: DOTS was used on a nation basis since around 1990s. Any bias by lack of data such as TB treatment could underestimate the association of between treatment outcomes and sex, and treatment type.

This study has implications for future control measures of TB. We recommend for case management policy that monitoring of patients should include further follow-up and support for completing treatment against TB and targeted screening of the risk patients who are males and retreatment case.

In developing countries, it is indicated that lack of knowledge on tuberculosis is problem and intervention such as health education or follow-up is needed now. However, the widespread of facilities or the improvement of the inspection technique or the standardization of treatment of tuberculosis diagnosis leads apparently. Though the interventions like them are important role to improve tuberculosis management, the interventions such as follow-up[37] and health education on tuberculosis are needed with the same precedence for reducing new tuberculosis cases. Without ignoring the perception of patients and citizen, those interventions may not achieve the goals. We need to recognize them as important development challenges as well. Therefore, further research is needed to examine the perception of patients and citizen for beneficial tuberculosis control and treatment.

Conclusion

We examined the association between tuberculosis treatment outcomes and sex, and treatment case using a meta-analysis. This analysis revealed an increase in treatment failure for tuberculosis associated with male and retreatment case.

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Figure legends

Figure 1. The process of study selection fulfilling eligibility criteria.

Figure 2. Forest plot of comparison of the ratios of unsuccessful treatment in male vs female.
OR: odds ratio; CI: confidence interval; W: weight.

Figure 3. Forest plot of comparison of the ratios of unsuccessful treatment in retreatment case vs new-case.
OR: odds ratio; CI: confidence interval; W: weight.

Figure 4. Sensitivity analysis of the ratios of unsuccessful outcome in retreatment cases to those in new cases.
OR: odds ratio; CI: confidence interval; W: weight.

Figure 5. The funnel plot of meta-analysis about unsuccessful outcome and sex.

Figure 6. The funnel plot of meta-analysis about unsuccessful outcome and tuberculosis case type.