Factors predictive of the success of tuberculosis treatment: a systematic review with meta-analysis

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Conflict of interest: none

OBJECTIVE. To produce pooled estimates of the global results of tuberculosis (TB) treatment and to analyze the predictive factors of successful treatment.

MATERIALS AND METHODS. Studies published between 2014 and 2019 that reported the results of the treatment of pulmonary TB and the factors that influenced these results. The quality of the studies was evaluated according to the Newcastle – Ottawa quality assessment scale. A random effects model was used to calculate the pooled odds ratio (OR) and 95 % confidence interval (CI). This review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) in February 2019 under number CRD42019121512.

RESULTS AND DISCUSSION. A total of 151 studies met the criteria for inclusion in this review. The success rate for the treatment of drug-sensitive TB in adults was 80.1 % (95 % CI: 78.4-81.7). America had the lowest treatment success rate, 75.9 % (95 % CI: 73.8-77.9), and Oceania had the highest, 83.9 % (95 % CI: 75.2-91.0). In children, the success rate was 84.8 % (95 % CI: 77.7-90.7); in patients coinfected with HIV, it was 71.0 % (95 % CI: 63.7-77.8), in patients with multidrug-resistant TB, it was 58.4 % (95 % CI: 51.4-64.6), in patients with and extensively drug-resistant TB it was 27.1 % (12.7-44.5). Patients with negative sputum smears 2 months after treatment were almost 3 times more likely to be successfully treated (OR: 2.7; 1.5-4.8), whereas patients younger than 65 years (OR: 2.0; 1.7-2.4), nondrinkers (OR: 2.0; 1.6-2.4) and HIV-negative patients (OR: 1.9; 1.6-2.3) were 2 times more likely to be successfully treated.

CONCLUSIONS. The success of TB treatment at the global level was good, but was still below the defined threshold of 85 %. Factors such as age, sex, alcohol consumption, smoking, lack of sputum conversion at 2 months of treatment and HIV affected the success of TB treatment.

KEY WORDS: tuberculosis, treatment success, predictive factors.

Прогностичні фактори успішності лікування туберкульозу: систематичний огляд із метааналізом

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Конфлікт інтересів: відсутній

МЕТА. Створити об'єднані оцінки глобальних результатів лікування туберкульозу (ТБ) та проаналізувати прогностичні фактори успішної терапії.

МАТЕРІАЛИ ТА МЕТОДИ. Проаналізовано дослідження, опубліковані між 2014 і 2019 рр., в яких повідомляли про результати лікування ТБ легень і фактори, що вплинули на ці результати. Якість досліджень визначали за шкалою оцінки якості Ньюкасла й Оттави. Для обчислення відношення шансів (ВШ) і 95 % довірчого інтервалу (ДІ) використали модель випадкових ефектів. Цей огляд був зареєстрований у Міжнародному проспективному реєстрі систематичних оглядів (PROSPERO) в лютому 2019 р. під номером CRD42019121512.

РЕЗУЛЬТАТИ ТА ЇХ ОБГОВОРЕННЯ. Критеріям включення до огляду відповідало загалом 151 дослідження. Частота успішності лікування ТБ у дорослих становила 80,1 % (95 % ДІ: 78,4-81,7). Америка мала найнижчий рівень успішності лікування – 75,9 % (95 % ДІ: 73,8-77,9), а Океанія – найвищий (83,9 %; 95 % ДІ: 75,2-91,0). У дітей частота успішності терапії становила 84,8 % (95 % ДІ: 77,7-90,7), у пацієнтів із коінфекцією ВІЛ – 71,0 % (95 % ДІ: 63,7-77,8), у пацієнтів із мультирезистентним ТБ – 58,4 % (95 % ДІ 51,4-64,6), у пацієнтів із ТБ із широкою стійкістю до лікарських засобів – 27,1 % (95 % ДІ: 12,7-44,5). Хворі з негативними мазками мокротиння через 2 місяці після терапії мали майже в 3 рази вищу ймовірність успішного лікування (ВШ: 2,7; 95 % ДІ: 1,5-4,8). У 2 рази вищу ймовірність виліковування мали пацієнти віком менш як 65 років (ВШ: 2,0; 95 % ДІ: 1,7-2,4), особи, котрі не вживають алкоголь (ВШ: 2,0; 95 % ДІ: 1,6-2,4), і ВІЛ-негативні хворі (ВШ: 1,9; 95 % ДІ: 1,6-2,5).

ВИСНОВКИ. Успішність лікування ТБ на глобальному рівні є доволі високою, але все ще нижчою за визначений поріг у 85 %. На успішність лікування ТБ впливають вік, стать, уживання алкоголю, куріння, відсутність конверсії мокротиння за 2 місяці лікування та ВІЛ.

КЛЮЧОВІ СЛОВА: туберкульоз, успішність лікування, прогностичні фактори.

Прогностические факторы успешности лечения туберкулеза: систематический обзор с метаанализом

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ЦЕЛЬ. Создать объединенные оценки глобальных результатов лечения туберкулеза (ТБ и проанализировать прогностические факторы успешности терапии.

МАТЕРИАЛЫ И МЕТОДЫ. Проанализированы исследования, опубликованные между 2014 и 2019 гг., в которых сообщали о результатах лечения ТБ легких и факторах, повлиявших на эти результаты. Качество исследований определяли по шкале оценки качества Ньюкасла и Оттавы. Для вычисления отношения шансов (ОШ) и 95 % доверительного интервала (ДИ) использовали модель случайных эффектов. Этот обзор был зарегистрирован в Международном проспективном реестре систематических обзоров (PROSPERO) в феврале 2019 г. под номером CRD42019121512.

РЕЗУЛЬТАТЫ И ИХ ОБСУЖДЕНИЕ. Критериям включения в обзор соответствовало в целом 151 исследование. Частота успешности лечения ТБ у взрослых составляла 80,1 % (95 % ДИ: 78,4-81,7). Америка имела самый низкий уровень успешности лечения – 75,9 % (95 % ДИ: 73,8-77,9), а Океания – самый высокий (83,9 %; 95 % ДИ: 75,2-91,0). У детей частота успешности терапии составила 84,8 % (95 % ДИ: 77,7-90,7), у пациентов с коинфекцией ВИЧ – 71,0 % (95 % ДИ: 63,7-77,8), у пациентов с мультирезистентным ТБ – 58,4 % (95 % ДИ: 51,4-64,6), у пациентов с ТБ с широкой устойчивостью к лекарственным средствам – 27,1 % (95 % ДИ: 12,7-44,5). Больные с отрицательными мазками мокроты через 2 месяца после терапии имели почти в 3 раза более высокую вероятность успешного лечения (ОШ: 2,7; 95 % ДИ: 1,5-4,8). Вероятность излечения была в 2 раза выше у пациентов моложе 65 лет (ОШ: 2,0; 95 % ДИ: 1,7-2,4), лиц, которые не употребляют алкоголь (ОШ: 2,0; 95 % ДИ: 1,6-2,4), и ВИЧ-отрицательных больных (ОШ: 1,9; 95 % ДИ: 1,6-2,5).

ВЫВОДЫ. Успешность лечения ТБ на глобальном уровне довольно высокая, но все еще ниже установленного порога в 85 %. На успешность лечения ТБ влияют возраст, пол, употребление алкоголя, курение, отсутствие конверсии мокроты за 2 месяца лечения и ВИЧ.

КЛЮЧЕВЫЕ СЛОВА: туберкулез, успешность лечения, прогностические факторы.

Introduction

Tuberculosis (TB) remains the leading global cause of death by a single infectious agent; it caused approximately 1.6 million deaths in 2017. An estimated 10 million people developed the disease, of whom 6.4 million (64 %) were notified [1]. Additionally, of the 558,000 estimated cases of rifampicin- and isoniazid-resistant TB (multidrug-resistant TB – MDR-TB) / rifampin-resistant TB (RR-TB), a total of 139,114 people (87 %) received the second-line regimen, and the proportion of MDR-TB cases with extensively drug-resistant TB (XDR-TB) defined as MDR-TB plus resistance to at least one drug in both of the two most important classes of medicines in an MDR-TB regimen: fluoroquinolones and second-line injectable agents (amikacin, capreomycin or kanamycin) was 8.5 % (95 % CI: 6.2-11 %) [1].

The innumerable efforts to end the global TB epidemic have resulted in remarkable developments in research focused on multiple aspects of the disease. Unfortunately, we should rely on poor diagnostic, therapeutic, and preventive options. However, it is estimated that with the current strategies for TB control, the goals of reducing the number of deaths by 95 %, reducing the incidence rate by 90 % and increasing the cure rate of patients receiving first-line treatment to 90 % between 2015 and 2035 will not be reached without intensifying research and development [2]. It is also necessary to strengthen health systems' ability to detect cases early and to improve the quality of care, diagnosis and treatment of people with TB [3].

TB treatment coverage is one of the ten priority indicators for achieving the goals of the End TB Strategy, and it has increased from 51 % in 2013 to 70 % in 2017 [2, 4]. However, the treatment success rate has decreased from 86 % in 2013 to 82 % in 2016; in MDR-TB/RR-TB and XDR-TB cases, the success rate remains low: 55 % and 34 % in 2015 [1]. This situation could be related to the limited evaluation of treatment outcomes in countries with limited resources and to the presence of factors that affect the outcome of TB treatment. Exhaustive estimates of TB treatment outcomes are needed to improve the programmatic management of TB. Therefore, this review with meta-analysis was performed to produce pooled estimates of global TB treatment outcomes and to analyze the predictive factors of successful treatment.

Methods

This review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) in February 2019 under number CRD42019121512.

Search strategy

PubMed, Medline, Embase, ProQuest, Scopus and Scielo were searched for publications of the last 6 years that is, published between January 2014 and November 2019 that reported the results of treatment for pulmonary TB and the factors that influenced these results. We also searched other sources, such as Google and Google Scholar, and bibliographies to obtain additional references. Our search contained the following terms: tuberculosis, predictive factors, risk factors and treatment outcomes (tuberculosis AND (risk factors OR associated factors OR predictive factors OR characteristics) AND (treatment results OR treatment outcome OR successful treatment OR unsuccessful treatment OR unfavorable outcome OR (poverty OR poor)) AND tuberculosis treatment results) in English, Spanish and Portuguese. Trying to include as many publications as possible about our topic of interest. Approval from the ethics committee was not required.

Data extraction and definitions

All article titles and abstracts were evaluated by two investigators (JR and PP), including all the studies that reported quantitative measurements of the results of tuberculosis treatment, and these results were clearly described according to the WHO criteria. For cases of drug-sensitive TB, only studies that clearly described patients receiving the standard treatment for tuberculosis recommended by the WHO known as short-term treatment (6 months) that includes 4 drugs. Studies that reported exclusively on extrapulmonary TB and those that did not allow the adequate extraction of quantitative data were not included. The full text of articles identified as relevant by any of the reviewers was read.

To determine which full-text articles met the inclusion criteria, two investigators (JR and PP) reviewed all full-text articles, and a third investigator (NC) reviewed a random selection of studies. In cases of disagreement, the two investigators discussed the article until they agreed. One investigator (JR) extracted data from all included studies. The second investigator (NC) independently extracted all numerical data regarding the estimation of the main effect to validate the first review. If data from the same cohort were included in several articles, the article with the most complete data was included. For each included study, detailed information was collected on the design, publication year, country, study population, sample size, definition and measurement of treatment outcomes and associated factors.

Validity assessment

The quality of the included studies was evaluated according to the Newcastle – Ottawa quality assessment scale [5]. It evaluates quality based on the content, design and ease of use of the data for meta-analysis. Two investigators (JR and PP) independently evaluated the quality of the studies, classifying each study as being of either good, acceptable or low quality.

Statistical methods and data synthesis

TB treatment outcome measures were evaluated as the percentage of successful and unsuccessful results among all patients who initiated anti-TB therapy. The results of treatment were defined according to WHO criteria [6]. Successful outcomes were those in which patients met the definition of "cure" or "treatment completion". Unsuccessful outcomes were those in which patients met the definitions of death, default, failure or transfer. The subgroup analysis was performed by continent (Africa, America, Asia, Europe and Oceania), people living with HIV, children (1 to 15 years of age) and MDR/XDR-TB.

The associations of different variables, such as age (<65 years – 66 years or older), sex (male – female), area of residence (rural – urban), type of case (new – previously-treated), form of TB (pulmonary – extrapulmonary), alcohol consumption (yes – no), smoking (yes – no), HIV status (positive – negative), diabetes (yes – no), baseline sputum smear (positive – negative), and sputum smear microscopy 2 months after treatment (positive – negative), with the TB treatment outcome were measured. It was not possible to test the association from nutritional status, of educational level or socioeconomic status with TB treatment because these variables were evaluated differently in the studies depending

on the country or region of origin. The influence of the health facility providing treatment on the results of TB treatment was not addressed in the studies included in this review.

Because most of the studies did not examine the association between these variables and successful treatment outcome as the main effect, unadjusted odds ratios (OR) and 95 % confidence intervals (CI) were calculated as estimates of this association. After a table of results was created for each of the analyses, a random effects model was used to calculate pooled ORs and 95 % CIs as there were high levels of heterogeneity in the study populations. Statistical heterogeneity was assessed using the I^2 statistic. Publication bias was assessed using a funnel plot. All statistical analyses were performed in MedCalc® version 19.03.

Results

As indicated in figure, a total of 1,432 articles were identified. Of these, 992 were not duplicated; 807 of those were excluded after the title and abstract were evaluated, and 185 underwent a detailed review of the full text. A total of 151 studies with 1,550,449 patients with TB from 59 countries distributed among 5 continents met the criteria for inclusion in this review (table).

In total, 95 of the 151 studies were retrospective cohort, 28 were cross-sectional, 25 were prospective cohort and 3 were case-control studies. Of the eligible studies, 91 reported treatment results in cases of TB in adults, 7 in children, 15 in patients coinfected with HIV and 38 in MDR/XDR-TB cases.

Results of TB treatment

The success rate for the treatment of drug-sensitive TB in adults was 80.1 % (95 % CI: 78.4-81.7). A high degree of heterogeneity (I^2: 99.8 %) was observed among the studies, but no publication bias was found in the funnel plot. Based on the subgroup analysis, America had the lowest treatment success rate at 75.9 % (95 % CI: 73.8-77.9), followed by Africa

at 78.9 % (95 % CI: 75.5-82.2), Europe at 79.7 % (95 % CI: 76.2-83.0), Asia at 81.6 % (95 % CI: 78.5-84.5) and Oceania at 83.9 % (95 % CI: 75.2-91.0).

The success rate was 84.8 % in children (95 % CI: 77.7-90.7), 71.0 % in patients coinfected with HIV (95 % CI: 63.7-77.8), 58.4 % in patients with MDR-TB (95 % CI: 51.4-64.6) and 27.1 % (95 % CI: 12.7-44.5) in patients with XDR-TB. A high degree of heterogeneity (I^2: 98 %; I^2: 99.8 %; I^2: 99.2 %; I^2: 84.3 %, respectively), was observed in these subgroups, but there was no evidence of publication bias in the funnel plot.

Predictors of TB treatment success

Patients who were smear-negative at 2 months of treatment were almost 3 times more likely to succeed in treatment (OR: 2.7; 1.5-4.8, whereas patients who were younger than 65 years (OR: 2.0; 1.7-2.4), nondrinkers (OR: 2.0; 1.6-2.4) and HIV-negative (OR: 1.9; 1.6-2.3) were 2 times more likely to succeed in treatment. In contrast, diabetes, the TB form and positive baseline sputum smear did not influence the results of treatment.

Discussion

This meta-analysis showed that the success rate for the treatment of drug-sensitive TB in adults was 80.1 % (95 % CI: 78.4-81.7); for those with associated HIV-TB, it was 71.0 % (95 % CI: 63.7-77.8). In patients with XDR-TB it was 27.1 % (95 % CI: 12.7-44.5) and for those with MDR-TB, it was 58.4 % (95 % CI: 51.4-64.6). These values did not differ significantly from those reported by the WHO for 2016 (82 %, 77 %, 34 % and 55 %, respectively) [1]. This result was expected considering that cases of TB require compulsory notification in most countries. A study in Europe (2005), reported a pooled estimate of successful outcomes of 74.4 % (95 % CI: 71.0-77.9 %), this lower estimate than the one reported in this review could be attributed to the fact that the studies analyzed in this work are prior to 2005 [158]. While, another study
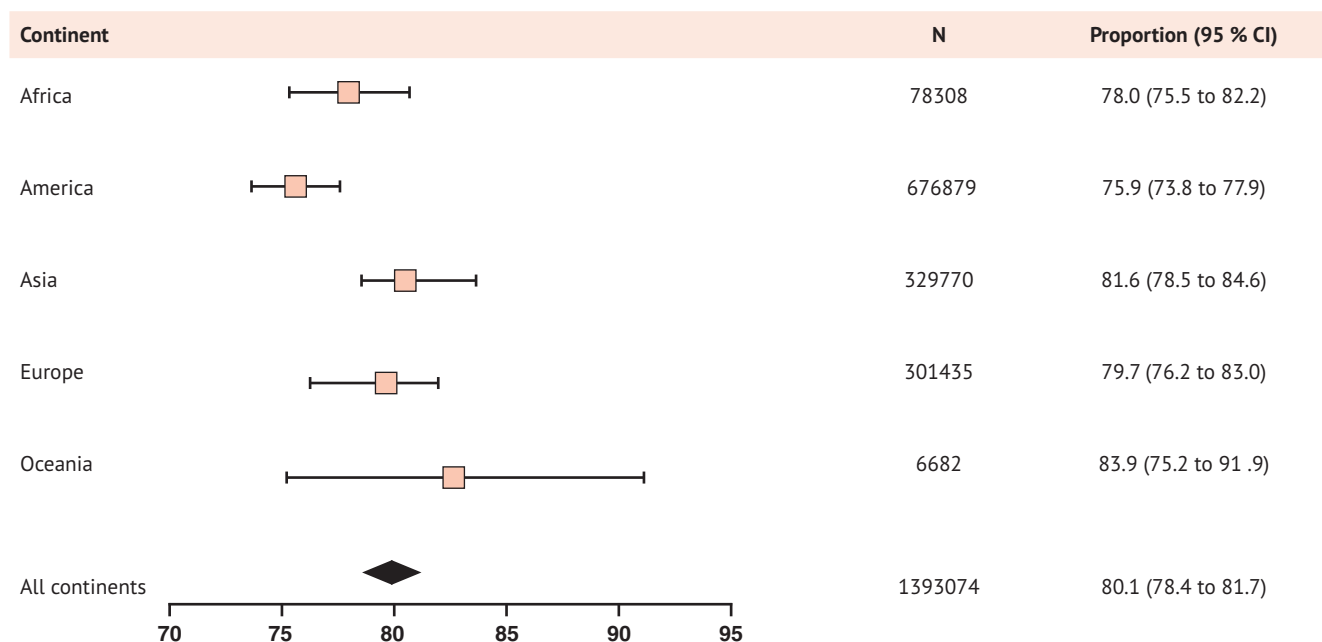
Continent		N	Proportion (95 % CI)
Africa		78308	78.0 (75.5 to 82.2)
America		676879	75.9 (73.8 to 77.9)
Asia		329770	81.6 (78.5 to 84.6)
Europe		301435	79.7 (76.2 to 83.0)
Oceania		6682	83.9 (75.2 to 91 .9)
All continents		1393074	80.1 (78.4 to 81.7)

Fig. Pooled estimate of successful tuberculosis treatment outcome

Table. Factors predictive of favorable outcomes of tuberculosis treatment

	Included studies	Exposed	Not exposed	Odds ratio	95 % CI
Negative smear in the 2nd month	9	8715/12233	4082/7077	2.7	1.5 – 4.8
Age <65 years	15	32384/36587	6937/8127	2.0	1.7 – 2.4
Non-alcoholic	9	18074/30334	4118/7609	2.0	1.6 – 2.4
HIV negatives	35	51769/64024	43781/76845	1.9	1.6 – 2.3
New cases	34	86862/122085	17595/31183	1.6	1.5 – 1.6
No smoking	16	22336/26922	15092/19442	1.5	1.3 – 1.7
Urban residence	27	52617/78278	23016/28380	1.2	1.0 – 1.4
Female sex	61	74645/95809	128387/173218	1.2	1.1 – 1.3
No diabetes	11	34836/53800	4161/5482	1.1	0.9 – 1.5
Pulmonary tuberculosis	34	83906/118231	27509/42250	1.1	0.9 – 1.3
Positive smear on admission	15	39422/57407	31945/46381	1.0	0.8 – 1.2

in Ethiopia, reported a global success rate of combined TB treatment of 86 % (with a 95 % CI: 83-88 %), higher than our estimate of successful treatment [159]. To XDR and MDR TB a review published in 2017 reported pooled treatment success of 26 % and 60 % respectively, which is not different from our results [160]. However, these results should be improved to cure 90 % of patients. The results of TB treatment improve with the use of adherence interventions, such as patient education and counseling, incentives and enablers, psychological interventions, reminders and tracers, and digital health technologies. Therefore, TB control programs should keep in mind that in addition to prescribing TB medications, they need to include resources to help patients overcome individual challenges to complete treatment [161].

In children, the treatment success rate was 83.4 % (95 % CI: 71.0-92.9). The WHO annual Global Tuberculosis Report does not specify a treatment success rate for children. However, studies from varying countries published in 2016 reported success rates for the treatment of children with TB that were both lower and higher than that those estimated in this review, e. g., 61.5 % in Malawi and 91.3 % in the European Union [114, 119]. Although in 2018 a review was published that calculated the success rate of 78 % to MDR TB treatment in children [162], this is the first pooled estimate of treatment of drug-sensitive TB success in children at the global level in the last 5 years.

Sputum smear conversion in the second month of treatment was previously associated with treatment success [163]. This meta-analysis confirmed that a negative sputum smear at 2 months of treatment was a predictor of success (OR: 2.7; 95 % CI: 1.5-4.8). However, sputum smear non-conversion after 2 months of treatment continues to be controversial as a predictor of unfavorable outcomes due to its low sensitivity and specificity for identifying treatment failure [164]. Therefore, further studies are needed to clarify this controversy.

It was also confirmed that factors such as age <65 years (OR: 2.0; 95 % CI: 1.7-2.4), female sex (OR: 1.2; 95 % CI: 1.1-1.3) and a new case type favor the success of TB treatment, as reported in previous studies [8, 9, 17, 48, 68, 69, 86, 138]. Not drinking alcohol was also a predictor of favorable treatment results (OR: 2.0; 95 % CI: 1.6-2.4). Alcohol consumption has been associated with treatment failure and a predisposition toward adverse drug effects, either because those who consumed alcohol skipped more doses during TB treatment or because alcohol may affect the immune response against M. tuberculosis, leading to treatment failure or a late response to treatment [44, 92, 130].

Nonsmokers also had a higher probability of treatment success (OR: 1.5; 95 % CI: 1.3-1.7) according to a study conducted in China that suggested smoking adversely affects the bacteriological response to and the result of TB treatment [53]. In Malaysia, smoking was also identified as a risk factor for unfavorable treatment outcomes [61]. In Poland, smoking did not influence the results of TB treatment [92]. In Brazil patients with a history of smoking increase 2.1 (95 % CI: 1.1-4.1) times, but the possibility of failure in TB treatment. Moreover, having a larger age of 50 years shows that the possibility of failure increases 2.8 (95 % CI: 1.4-6.0) [165].

The HIV-TB association continues to be a challenge for public health. Studies have identified coinfection as a risk factor for unfavorable TB treatment results, and most have attributed these results to the high mortality in these patients [10, 98-100, 105, 109]. We corroborated these results, showing that HIV-negative patients had a higher proportion of favorable treatment outcomes (OR: 1.9; 95 % CI: 1.6-2.3), while in general, the treatment success rate in coinfected patients was low (70.5 %).

In this review, diabetes did not influence treatment outcomes. Our results coincide with those reported in Georgia and Malaysia [40, 61], although it was previously suggested that diabetes was associated with unfavorable TB treatment results [56, 81].

Among the limitations of this study, it is necessary to mention that the use of observational studies for a meta-analysis could induce errors by finding false significant associations when combining small studies affected by confounding [166]. Additionally, it is known that the quality of a meta-analysis depends on the quality of the included studies; in most studies, the quality was classified as low, which may be associated with the fact that most of the studies were retrospective and based on mandatory notification systems, where it is difficult to control due to loss at follow-up and other confounding factors. The degree of heterogeneity was also high among the studies; therefore, the random effects method was used to obtain the pooled results. Finally, the methodological variations among the included studies could also compromise the results of the meta-analysis.

Conclusions

The study findings suggest that the rate of successful TB treatment at the global level is good but is still below the defined threshold of 85 %. Factors such as age, sex, alcohol consumption, smoking, sputum smear non-conversion at 2 months of treatment and HIV affect the results of TB treatment.