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Research Article

The Effect of Mortality of Diabetes Tuberculosis Patients Using Meta-Analysis

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Abstract

Objective: To study the mortality of tuberculosis patients with diabetes, compared to tuberculosis patients without diabetes.

Design: We searched papers, including the prospective studies and retrospective studies from 1998 to 2009. All papers must relate to the studies of the mortality of tuberculosis patients with diabetes or without diabetes.

Data sources: We electronically searched the register of the mortality, tuberculosis, and diabetes group from several journals.

Selection of studies: More than 1000 articles we searched, including prospective studies and retrospectives studies. Only 21 papers are related to our subject. After fully screen the data of these papers, 14 papers are completely fit the conditions of our requirements.

Main outcome measures: We meta-analysis the odds ratio of mortality of DMTB patients, compare to TB patients without DM. We selected random affects model to show the results of odds ratio.

Results: This study shows significantly higher mortality in DMTB group. The entire odds ratio is 2.18. 95% CI= [1.50, 3.16], Z=4.09 ($p<0.0001$), I2=63.0% (Figure 1).

Conclusion: Diabetes is one of the risk effects to the tuberculosis patients. Patients who got tuberculosis with diabetes have significantly higher mortality than tuberculosis patients without diabetes. To take care of tuberculosis patients with diabetes is much more critical.

Introduction

Tuberculosis (TB) is an increasing global problem. In 1997, an estimated 32% of the world's population was infected with Tuberculosis (TB), and the disease caused 1.9 million deaths. Several factors are likely to have an impact on mortality from TB infection, including patient age, site and type of disease, treatment delay, *Human Immunodeficiency Virus* (HIV) Infection status, degree of immunosuppressant, virulence of the bacteria, and resistance pattern [1] And the main risk factors for tuberculosis were low accumulated wealth, financial insecurity, consumption of unpasteurized milk, diabetes, living with a relative with tuberculosis, being unemployed, living in overcrowded conditions, illicit drug use, and a history of incarceration in both pretrial detention centers and prison [2] But it was interested, diabetes has always been written among these reasons. According to WHO diagnostic criteria, in 506 consecutive African patients admitted with sputum-positive pulmonary tuberculosis to the tuberculosis wards of Muhimbili Medical Centre, there were 1.8% of patients been known to have diabetes [3]. The prevalence of diabetes for all age-groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030. The total number of people with diabetes is higher in men than women, but there are more women with diabetes than men. Even Saskatchewan Aboriginal people are experiencing epidemics of both Type 2 Diabetes (T2DM) and tuberculosis (TB) [4]. Type 2 Diabetes (DM) is a strong risk factor for Tuberculosis (TB) and is associated with a slower response to TB treatment and a higher mortality rate [5]. If diabetes is a risk factor for bacterial in patients with pneumococcal pneumonia and is associated with increased mortality [6]. Although an association between diabetes and TB has been suggested for more than a thousand years, several studies

have suggested that Diabetes Mellitus (DM) increase the risk of active Tuberculosis (TB) [5,7]. And DM was associated with an increased risk of TB regardless of study design and population. In the paper search, we find the effect of DM on the mortality of TB is not well defined [8]. In our study, we will present the mortality between DMTB patients and TB patients without DM, using meta-analysis.

Methods

Inclusion Criteria

We searched papers in published journals, which included prospective studies and retrospective studies, related to mortality of TB patients. We selected the mortality data of DMTB patients and TB patients. Even patients suffer many other symptoms with tuberculosis, we still collected those data in the papers. Basically, we defined mortality, according to the World Health Organization (WHO) recommendation. WHO recommends that mortality statistics are presented by underlying cause of death, which defines as "the disease or injury which initiated the train of morbid events leading directly to death" or "the circumstances of the accident or violence which produced the fatal injury [9].

Outcomes

The primary outcome is the mortality of DMTB patients, compared to that of TB patients without DM. We define the TB mortality as a ratio of the number of TB death patients and the number of total TB patients. And the DMTB mortality as a ratio of the number of DMTB death patients and the number of total DMTB patients. In our study, the TB patients who were infected by TB, and also possibly infected by other diseases.

Identification of Trials

In the last 20 years, it has witnessed rapid change in infectious diseases practice. At the same time, the revolution in information systems embodied by the Internet has made available at the desktop a dizzying variety of resources for medical information [10]. We electronically searched the register of the mortality, tuberculosis and diabetes group from the journals published. The journals we searched included "American Chemical Society", "HINT", "JAMA: Journal of the American Medical Association", "New England Journal of Medicine", "Pub Med (Free Medline)", "SDOS", and "Tuberculosis Week", et al. We also search from several web sites. There are "Clinical Evidence", "Cochrane Database of Systematic Reviews", "Country health information profiles", "WHO Diabetes Programmed", "World Health Report", "WHO Mortality Fact Sheet", and "World Health Organization" and so on. Computer assisted searches were under taken of "TB versus DM", "Tuberculosis mortality versus diabetes tuberculosis mortality", "Mortality of pulmonary tuberculosis", "Tuberculosis combinative diabetic", and" Mortality, Tuberculosis, Diabetes". All of trials were searched using the same terms.

Data Extraction

Papers were translated into English by a member of staffs, if they were written with other languages, e.g. French, German, Japanese., etc.

Quality Assessment

We didn't assess methodological quality according to the recommendations of the Cochrane Collaboration Handbook. The criteria of the paper qualified for this study is its scope, which must cover TB, DMTB and Mortality.

Statistical Analysis

We use Review Manager (version 4.2.10), a statistical software package for managing and analyzing all aspects of a Cochrane Collaboration systematic review, to analyze our data. For binary outcomes we calculate the odds ratio of mortality between DMTB with/without diabetes TB patients. We select the fixed effect model analysis initially, due to the heterogeneity produced; we change to the random effects model analysis results.

Results

Study Exclusion and Inclusion

There are 7 studies excluded (Table 1). The first one study describes primary cause of death in 494 diabetes patients. It mentions death related to diabetes, but does not describe the relationship between DMTB and TM [11]. The second one evaluates deaths attributed to multiple causes, in which tuberculosis was one of the cause listed [12]. The third one study discusses about tuberculosis, but does not discuss about diabetes [9]. The fourth one study describes of all tuberculosis deaths identified, without mentioning about the mortality between DMTB patients and TB patients without diabetes [13]. The fifth one study shows death certificates without total population [14]. The sixth one study presents that death proportion in single symptom [15]. The seventh one study is associated with tuberculosis and diabetes in the Mexican border region and in non-border regions of Texas. Association between tuberculosis and underlying risk factors is also evaluated [16]. In this study, there are 14 papers, included 13 papers with full text, and 1 review abstract. The year of papers search is extended from 1998 to 2009.

Study	Reason for exclusion
Bhansali, et al. [11]	Mortality in diabetes: a retrospective analysis from a tertiary care hospital in North India. Primary cause of death in 494 diabetes patients. Diabetes related death.
Dye, et al. [12]	Global Burden of Tuberculosis: Estimated Incidence, Prevalence, and Mortality by Country. Estimates of TB Burden by WHO Region.
Hasiak Santo A, et al. [9]	Death attributed to multiple causes and involving tuberculosis in the state of Rio de Janeiro Brazil between 1999 and 2001. To evaluate deaths attributed to multiple causes in which tuberculosis was one of the causes listed.
Lindoso AABP, et al. [13]	Profile of tuberculosis patients progressing to death, city of São Paulo, Brazil, 2002. Of all tuberculosis deaths identified.
Pérez, et al. [14]	Association between tuberculosis and diabetes in the Mexican border and non-border regions of Texas. Evaluated association between tuberculosis and underlying risk factors, in Texas patients hospitalized in the 15 counties along the Mexico border within the remaining non-border counties.
Romon I, et al. [15]	The hurden of diabetes-related mortality in France in 2002: an analysis using both underlying and multiple causes of death. Showed death certificates without total population.
World Health Organization [16]	Mortality Country Fact Sheet 2006. Causes of death in single symptom.

Table 1: The reasons of papers excluded.

Study Characteristics

In one of these14 studies **(**Table 2), Alisjahbana Bachti, et al. included consecutive new patients with pulmonary TB who were aged≧15 years and who presented 3 out-patient TB clinics in Jakarta and Bandung in Indonesia from October 2000 through December 2005. All patients with confirmed TB were screened for DM by measurement of Fasting Blood Glucose (FBG) concentrations. TB treatment consisted of a standard regimen of daily rifampicin, isoniazid, pyrazinamid, and ethambutol for 2 months (the intensive phase) and rifampicin and isoniazid for another 4 months (the continuation phase), patients in whom DM was established initiated oral anti-DM drugs after 2-4 weeks of TB treatment, no patient received insulin. They compared findings for TB patients with DM to TB patients without DM. 737 new TB patients who were screened, 15 were excluded because of HIV seropositivity (n=7), other comorbidity (n=7), or missing data (n=1). 88 patients were excluded because of FBG concentrations indicating impairment or undetermined status of DM. 534 (92.1%) of 580 patients had culture results that were positive for M. tuberculosis. Of 634 patients, 540 had normal FBG concentrations, and 94 patients (14.8%) received diagnoses of concomitant DM. 24 patients (3.8%) defaulted and 11 (1.7%) were transferred during the intensive phase of TB treatment. Among the remaining 599 patients, 2 patients with DM died within 2 months after initiation of treatment. Bashar Mona, et al. conducted a case-control study retrospectively review the records of patients at Bellevue Hospital Center from 1987 to 1997 with a discharge diagnosis of tuberculosis and diabetes mellitus [17,18]. MDR-TB was defined as any case of tuberculosis that was resistant to two or more first-line tuberculosis medications, including at least isoniazid and rifampin. Control cases were randomly selected from nondiabetic patients discharged from Bellevue Hospital between from 1987 to 1997 with a discharge diagnosis of tuberculosis. Sixty-nine patients were identified. Fifty-four percent of the study subjects had type 1 diabetes, while 40% had type 2. Sixty-eight percent of the patients used insulin, 22% used oral agents, and 6% were diet controlled. There were a significantly greater number of MDR-TB cases in the diabetic group (18 cases, 36%) as compared to the control group (10 cases, 10%). More patients in the control group were able to complete therapy (57%) than in the study group (42%). Completion of therapy refers to the patient's ability to comply with the standard length of treatment and to have bacteriologic clearance of sputum cultures. Chiang CY, et al. were setting all individuals reported as being treated for Pulmonary Tuberculosis (PTB) among citizens of Taipei City, Taiwan, in 2003 [18,19]. And to investigate risk factors associated with treatment interruption for least 2 consecutive months and death. Of 1127 PTB patients registered, 824 (73.1%) were successfully treated, 189 (16.8%) died, 65 (5.8%) interrupted treatment, 17 (1.5%) were still on treatment 15 months after commencing treatment and 32 (2.8%) failed. The only significant factor associated with treatment interruption was visits to other health facilities after commencing Tuberculosis (TB) treatment. TB patients had a standardized mortality ratio of 8.7 (95% CI 7.5-10.0). Factors significantly associated with death were age, sputum culture not performed/unknown, and co-morbidity with respiratory disease, infections disease, renal disease or cancer, compared with other patients. Dooley KE, et al. conducted a retrospective cohort study of patients with active, culture-confirmed Tuberculosis (TB)

in Maryland to determine the impact of DM on TB treatment outcome [19]. Their study was approved by Institutional Review Boards of the Johns Hopkins Schools of Public Health and Medicine and the Maryland Department of Health and Mental Hygiene. The primary study outcome was all-cause mortality during TB treatment, comparing patients with diabetes to patients without diabetes. Of 297 TB patients, 42 (14%) had DM. Patients with diabetes had 2.0 times higher odds of death than patients without diabetes (95% Confidence Interval [CI] 0.74-5.2, p=0.18). Adjusting for *Human Immunodeficiency Virus* (HIV), age, weight, and foreign birth, the odds of death were 6.5 times higher in patients with diabetes than patients without diabetes (95% CI 1.1-38.0, P=0.039). In pulmonary TB patients, time to sputum culture conversion was longer in patients with diabetes than patients without diabetes (median 49 versus 39 days, p=0.09). Two-month culture conversion proportions were similar (70% and 69%). Time to sputum culture negative was defined as days from treatment initiation date to date of first of three negative sputum cultures. Treatment failure occurred in 4.1% of patients without diabetes and 6.7% of patients with diabetes (p=0.5). Treatment failure was defined by a sputum culture positive for *M. tuberculosis* at or after completion of 4 months of treatment. They said that DM was a risk factor for death in Maryland TB patients. Dooley, et al., Fielder JF, et al. assessed the case-fatality rate among such patients in Baltimore between January 1993 and June 1998 [20]. Tuberculosis incidence was<17/1000000 population, and 99% of patients received directly observed therapy. Of 174 patients, 42 (24%) died on treatment. Patients who died were older and were more likely to have underlying medical conditions. In multivariate analysis, older age, diabetes mellitus, and renal failure were independently associated with an increased risk of death. Cause of death occurring during the 6-month course of treatment was classified according to the patient's death certificate. Tuberculosis was considered the primary cause of death if it was listed as such on the death certificate. Cases in which TB was not listed on the death certificate were categorized as death not attributable to TB. There were 190 sputum smear-positive tuberculosis causes reported during the study period. Forty-two (24%) of the 174 patients died while them receiving anti-tuberculosis therapy. Patients who died were significantly older than those who survived, but there were no other significant differences in demographic factors between the two groups. The median time from initiation of treatment to death was 32 days. Of the 42 patients who died, tuberculosis was listed on the death certificate as the primary cause of death in 15 (36%), and not listed at all in 11 (26%). During their study period, the annual rate of resistance to at least one anti-tuberculosis medication was 2.6-6.3%. [Fielder, et al. 2002] Lubart Emily, et al. to determine the mortality rate and predictors of mortality among patients hospitalized with TB in Lsrael [20]. They evaluated the medical records of 461 patients with active pulmonary TB who were hospitalized in the respiratory care department during the 5 years' period 2000-2004. Three main ethno-geographic groups were observed: 253 patients from the former USSR, 130 from Ethiopia, and 54 of Lsraeli origin. Most of them, 396 (86%) were successfully treated and discharged to ambulatory treatment in the community after a mean stay of 2.4 months. Six-five patients (14%) died in hospital. Clinical causes of death that may be directly or partially related to tuberculosis were respiratory failure in 12 patients (19%), general deterioration in 9 patients, and a clinical picture of other infections: pulmonary, urinary and others in 23 patients (38%). In one-third of patients, the causes of death were not related to tuberculosis but were described by the attending physicians as related to the aging process. Many other relevant factors such as diabetes, HIV, alcoholism, smoking, positive sputum smear or culture and extra-pulmonary TB were not risk factors for death in this analysis. Mortality rates were 10.4%, 7.8% and 3.7% in the USSR, Ethiopian and Israeli born groups respectively. Lubart, et al. Mathew et al. to identify risk factors and causes of death among TB patients in Russia [21]. They designed a retrospective study conducted to determine the risk factors and causes of death in patients receiving TB therapy in Tomsk, Siberia. They included patients in the study if they (1) were diagnosed with TB by the Central Physicians Committee using clinical, radiological and/or bacteriological criteria, and (2) initiated TB treatment between 1 January 2002 and 31 December 2003. They excluded those patients who were aged<18 years or were receiving care outside of the TOTBS. They used the TOTBS registry to identify subjects and collect information on demographics, date of registration, treatment initiation date, sputum and culture date, Drug Susceptibility Testing (DST) results, and date and status of treatment outcome. The median age was 42 years (range 18-88) and 1326 (69.2%) were male. Seven patients (0.4%) were *Human Immunodeficiency Virus* (HIV) positive and 550 (28.7%) were alcoholic. Of the 856 for whom baseline DST results were available, 152 (17.8%) had MDR-TB. All of 1916 patients who initiated treatment between 1 January 2002 and 31 December 2003, 183 (9.6%) died during treatment, 38 (21%) in the first week of therapy. 25% of deaths were not directly attributable to TB. Risk factors for death included older age, previous treatment for TB, multidrug resistance and alcoholism. Mathew, et al. Oursler Krisk, et al. using restriction fragment-length polymorphism data, they conducted a retrospective cohort study of 139 adult patients with pulmonary tuberculosis to investigate the clinical impact of Mycobacterium tuberculosis infection with a clustered isolate. A "clustered patient" was defined as a patient who was infected with an isolate included in an RFLP cluster. Patients with an M. tuberculosis RFLP pattern that did not match that of ant other isolate were classified as "nonclustered patients". All the patients were followed by Tuberculosis Clinic staff, regardless of whether the patients were treated as out-patients or as inpatients in hospitals or long-tern care facilities. Of the original cohort of 182 culture-positive patients for whom DNA fingerprinting results were available, 43 were excluded from their

study. Of these 43 patients, 11 received a postmortem diagnosis, 22 had isolated extra pulmonary disease, and 3 were unable to provide sputum samples. A total of 29 (21%) of the 139 patients died during treatment; the median time to death among these patients was 39 days. The cumulative all-cause mortality rate during treatment was 21%. Ponce-Leon Alfredo, et al. determined the impact of diabetes on the rates of tuberculosis in a region where both diseases are prevalent. As part of this survey, 1,334 individuals were randomly selected in the state of Vera Cruz to be representative of the civilian, no institutionalized population at the state level [22]. Their study area included 12 municipalities in the Orizaba Health Jurisdiction, state of Vera Cruz, Mexico. They used two definitions of diabetes. In the first diabetes status was considered present among individuals who had received a previous diagnosis by a physician. For the second definition, in addition to previous diagnosis, blood glucose levels (≧126 mg/dl in fasting samples or ≧200 mg/dl for random samples) were considered. They used an established molecular epidemiologic technique to classify patients as having tuberculosis as a consequence of reactivation of a latent tuberculosis infection or recently transmitted infection. They analyzed the ration of rates of tuberculosis among diabetic and non-diabetic populations, modifying the time between diagnosis dates of successive matching fingerprints to 6, 18, 24, 30, and 36 months. Of the 581 patients, 29.6% (172 of 581) had been previously diagnosed with diabetes by a physician. A total of 22% of these patients (38 of 172) had previously used insulin at least once. HIV infection was investigated among 96.9% (563 of 581) subjects; 15 (2.7%) were found to be HIV infected. Rao, Venkatarama K, et al. designs a retrospective cohort study [23,24]. They performed a study to define the factors associated with mortality following the in-hospital diagnosis of tuberculosis in a region with low levels of MDRTB and co-infection with HIV. All 203 patients hospitalized with culture-positive tuberculosis at one of the BJC system hospitals between 1988 and 1996. Follow-up information was obtained by telephone interview and review of medical and public health records. Death was verified through a search of the death certificate registry of Missouri and the records of the Social Security Administration. Mortality was defined as death from any cause during the 14-month following the initial date of hospitalization. Their cumulative all-cause mortality rate for that cohort was 28.1%. That incidence of HIV positively was 7.9% and of MDRTB was 1.5%. Multiple logistic regression analysis demonstrated that respiratory failure requiring mechanical ventilation and the presence of end-stage renal disease requiring dialysis were the largest contributors to mortality. Other variables independently associated with mortality included the presence of malnutrition, age>60 years, drug-induced immunosuppressant, and dyspnea at the time of hospital presentation. Their data suggest that the 14-months mortality rate is high among patients diagnosed as having tuberculosis during hospitalization, despite low incidences of HIV infection and multi-drug resistant disease. Rao, et al. Singal R, et al. want to understand the influence of diabetes on the clinical and bacteriological aspects and treatment outcome of Pulmonary Tuberculosis (PTB) patients [24,25]. So they recorded of 692 consecutive smear-positive PTB patients admitted to a referral hospital in Riyadh, Sudi Arabia, were reviewed retrospectively. The characteristics of 187 patients with diabetes mellitus (PTB-DM group) were compared to 505 patients without DM (PTB group). In the PTB-DM group, 65.2% of the patients had numerous Acid-Fast Bacilli (AFB) on sputum smear examination compared to 54.1% in the control group p=0.008). Among new cases, PTB-DM patients had a lower prevalence of resistance to any anti-tuberculosis drug (6.4% vs. 16.0%, p=0.007) and achieved higher sputum conversion rates at the end of 3 months of treatment (98.9% vs. 94.7%, p=0.013). PTB-DM patients have a higher pretreatment bacillary load, a lower prevalence of anti-tuberculosis drug resistance and achieve slightly higher sputum conversion by the end of 3 months of treatment compared to non-diabetic patients. The associations of diabetes dose not alter the final treatment outcome among PTB patients. A total of 692 sputum-positive PTB patients were included in the study; 187 (27.0%) had co-existing diabetes (PTB-DM group) and 505 (73%) did not (PTB group). After excluding 20 retreatment cases, among the new cases the PTB-DM group had a lower prevalence of drug resistance than the PTB group (6.4% vs. 16.0%, p=0.007). Singal, et al. Sterling TR. et al. to objectives Tuberculosis (TB) patients in North America often have characteristics that may increase overall mortality [25,26]. They evaluated mortality in a large TB treatment trial conducted in the United States and Canada. Persons with culture-positive pulmonary TB were enrolled after 2 months of treatment, treated for 4 more months under direct observation, and followed for 2 years (total observation: 28 months). Cause of death was determined by death certificate, autopsy, and/or clinical observation. All of 1075 participants, 71 (6.6%) died: 15/71 (21.1%) were HIV-infected persons and 56/1004 (5.6%) non-HIV-infected persons (p<0.001). Only one death was attributed to TB. Extents of disease and treatment failure/relapse were not associated with an increased risk of death. Sterling, et al. Touré NO, et al. performed a retrospective case control study for the period between 1 January 1999 and 31 August 2004, comparing the radiological appearances of tuberculosis in 100 diabetics to those in patients matched for age and sex, with pulmonary TB alone presenting to The Chest clinic of the National Hospital of Fann [26,27]. Diabetes was present in 4.7% of the 2116 patients hospitalized for pulmonary tuberculosis during the period of their study and occurred more commonly in men (60%) with an average age of 51years (73%). 82% had type Ⅱ, non-insulin dependent diabetes. Mortality was higher in diabetics (18%) than controls (6%), with death generally occurring within the first 24 hours of hospitalization. Touré, et al. Wang C.S. et al. from the retrospective review 217 consecutive adult patients with PTB from 1 January 2003 to 31 December 2006 [27,28]. They included both out-patients and in-patients. That

patients were included in the PTB-DM group if they had a known history of DM and had been receiving insulin and /or an oral hypoglycemic agent, or were diagnosed as having DM during this hospitalization with subsequent confirmation by two or more fasting plasma glucose levels>126 mg/dl on a different day in an outpatient setting. A total of 217 culture-positive PTB patients were enrolled in their study, there were no type 1 DM patients in this study. The patients' age≧65 years, and gender unknown. Twenty-one patients were excluded in the retrospective study. Patients who did not have DM in the same period were chosen as the control group (PTB group). The characteristics of the 74 type 2 DM patients (PTB-DM group) were compared to those of the 143 non-diabetic patients (PTB group). Mortality for PTB-DM patients was 17.6% in sharp contrast to 7.7% for PTB patients. In subgroup analysis, PTB- related death was significantly more common in the PTB-DM group than the PTB group [28].

Source, year	Incentives and Enablers	Size	Age	Setting	Treatment Outcomes	Mortality Outcomes
Alisjahbana Bachti [17]	Compared findings for patients with TB who had DM with findings for patients with TB who did not have DM.	737	≧15	In a prospective cohort study, included consecutive new patients with pulmonary TB in Indonesia from October 2000 through December 2005.	42 additional patients (7.0%) defaulted, and 11 (1.8%) were transferred.	DMTB: 2/94 TB: 0/540
Bashar M** [18]	To investigate the characteristics of tuberculosis infection in diabetic patients at Bellevue Hospital.	155	1-19: 2 20-30: 23 31-40: 48 41-50: 38 51-60: 28 61-70: 11 >70: 5	conducted a case-control study retrospectively reviewing	More patients in the control group were able to complete therapy (57%) than in the study group (42%).	DMTB: 7/50 TB: 1/105
Chiang C-Y [19]	All individuals reported as being treated for Pulmonary Tuberculosis (PTB) among citizens of Taipei City, Taiwan, in 2003	1127	<25: 82 25-44: 243 45-64: 276 ≧65: 526	The outcome of PTB cases was determined by consulting medical charts.	824 (73.1%) was successfully treated, 198 (16.8%) died, 65 (5.8%) interrupted treatment, 17 (1.5%) were still on treatment 15 month after commencing treatment and 32 (2.8%) failed.	DMTB: 52/241 TB: 137/886
Dooley K.E. 2009	Retrospective cohort study included all patients with culture-confirmed TB diagnosed to determine the impact of DM on TB treatment outcomes.	297	39.8 (18) N=255 56.5 (15) N=42	TB Patients diagnosed in 2004 and 2005 in Montgomery Country, Prince George's County, and Baltimore City in Maryland.	Treatment failure occurred in 4.1% of patients without diabetes and 6.7% of patients with diabetes. (p=0.51) DM was a risk factor for death in Maryland TB patients.	DMTB: 6/42 TB: 20/255

Fielder J.F. [0-20]	Assessed the case-fatality rate among such patients in Baltimore.	174	<49 n=88 ≧49 n=86	Reported to the Baltimore City Health Department (BCHD) between January 1993and June 1998.	Of 174 patients, 42 (24%) died on treatment.	DMTB: 13/22 TB: 29/152
Lubart Emily [21]	To determine the mortality rate and predictors of mortality among patients hospitalized with TB in Israel	461	<65 n=332 >65 n=128	Records of patients with TB, in the Shmuel Harofe Hospital during the 5 year period 2000-2004.	Of the 431 patients 65 (13%) died in hospital.	DMTB: 10/46 TB: 55/415
Mathew T.A. 2006	To identify risk factors and causes of death among TB patients in Russia.	1916	18-29: 12 30-41: 27 42-50: 32 51-88: 67	Patients who initiated treatment between 1 January 2002 and 31 December 2003.	183 (9.6%) died during treatment, 38 (21%) in the first week of therapy. 25% of deaths were not directly attributable to TB.	DMTB: 6/44 TB: 113/1872
Oursler Krisk [22]	Using restriction fragment- length polymorphism data, conducted a retrospective cohort study of adult patients.	139	52.6(17.5)	From 1 January 1994 through 30 June 1996, consecutive cases of culture-confirmed TB were reported to the Baltimore City Health Department Tuberculosis Clinic (Maryland).	A total of 29 (21%) of the 139 patients died during treatment; the median time to death among these patients was 39 days.	DMTB: 8/18 TB: 14/108
Ponce-Leon Alfredo [23]	Report the results of this population-based study from the 2000 National Health Survey (ENSA 2000)	581	44(19-86)	From November 1999 to June 2000, 12 municipalities in the Orizaba Health Jurisdiction, state of Veracruz, Mexico.	Cure 14.23% Failure 0.43% Default 1.70% Retreatment 1.20% All-cause mortality 2.82% Death from tuberculosis 1.36% Death from other causes 1.45%	DMTB: 10/172 TB: 36/409
Rao, Venkatarama k [24]	Retrospective cohort study	203	58 (16-95)	Hospitalized within the BJC Health Syatem, Between January 1988 to December 1996.	57(28.1%) died during the 14-month: 17(29.8%)died during the initial; 26 respiratory failure: 16(61.5%) died during the follow-up period, 7(43.8%) died during the initial	DMTB: 9/29 TB: 48/174

Singla R [25]	To understand the influence of diabetes on the clinical and bacteriological aspects and treatment outcome of (PTB) patients.	692	PTB-DM: 48.2(±12.0) PTB: 32.3 (±12.4)	Retrospective study. Sahary Chest Hospital, Riyadh, Saudi Arabia, the main referral hospital for the central region of Saudi Arabia.	In the PTB-DM group, 62.5% of the patients had numerous acid-fast bacilli (AFB) on sputum smear examination compared to 54.1% in the control group.	DMTB: 1/187 TB: 3/505
Sterling T.R. [26]	Evaluated mortality in a large TB treatment trial conducted in the United States and Canada.	1075	treat 1 weeks: 44.0±14.4 treat 2 weeks: 43.9±14.7	North America.	71 (6.6%) died: 15/71 (21.1%) HIV-infected persons, and 56/1004 (5.6%) non HIV-infected persons.	DMTB: 14/162 TB: 57/913
Toure NO 27]	Retrospective case control study	2116	51 (73%)	From 1 January 1999 to 31 August 2004, Hospitalized	Mortality in diabetics (18%) Mortality in control (6%)	DMTB: 18/99 TB: 121/2017
Wang C.S. [28]	To determine if type 2 DM alters manifestations and treatment outcome of PTB.	217	PTB-DM: 60.8 PTB: 59.1	Records of consecutive culture-proven PTB patients were analyzed retrospectively. From 1 January 2003 to 31 December 2006.	Mortality for PTB-DM patients was 17.6%, for PTB patients was 7.7%.	DMTB: 13/74 TB: 11/143

Table 2: Characteristics of the included studies.

Mortality Comparison

We excluded papers, which contained the high maximum value in confidence interval to low down heterogeneity to less than 50%, and checked change of odds ratio. The study showed a significant higher mortality in DMTB group. The entire odds ratio is 2.18. 95%CI= [1.50, 3.16], Z=4.09 (p<0.0001), I^2=63.0% (Figure 1). When we excluded Alisjahbana B, et al. we found the DMTB group also showed a significantly higher mortality than TB group. Odds ratio is 2.10. 95%CI= [1.46, 3.02], Z=3.98 (p<0.0001), I^2=62.6% (Figure 2). When we more excluded Bashar M et al., DMTB group showed a significantly higher mortality than TB group too. Odds ratio is 1.99. 95%CI= [1.40, 2.83], Z=3.81 (p=0.0001), I^2=60.8% (Figure 3). And then, we excluded Fielder JF, et al. continued. We got DMTB group showed a significantly higher mortality than TB group. Odds ratio is 1.81. 95%CI= [1.30, 2.53], Z=3.48 (p=0.0005), I^2=53.8% (Figure 4). Finally, we also excluded the Ouraler KK, et al. We still find the DMTB group which showed a significantly higher mortality than TB group. Odds ratio is 1.68. 95%CI= [1.22, 2.32], Z=3.18 (p=0.001), I^2=48.2% (Figure 5). We also analyzed the mortality that excluded out patients. We can saw DMTB group showed a significantly higher mortality than TB group. Odds ratio is 2.06. 95%CI= [1.06, 3.99], Z=2.14 (p=0.03), I^2=61.6% (Figure 6). As we excluded papers, one by one, from the highest maximum values of 613.44 in confidence interval, down to the maximum value of 15.7, to low heterogeneity down to less than 50%, the odds ratio, 1.68, is still higher than 1. That indicated that mortality of DMTB patients is much higher than mortality of TB patients without DM.

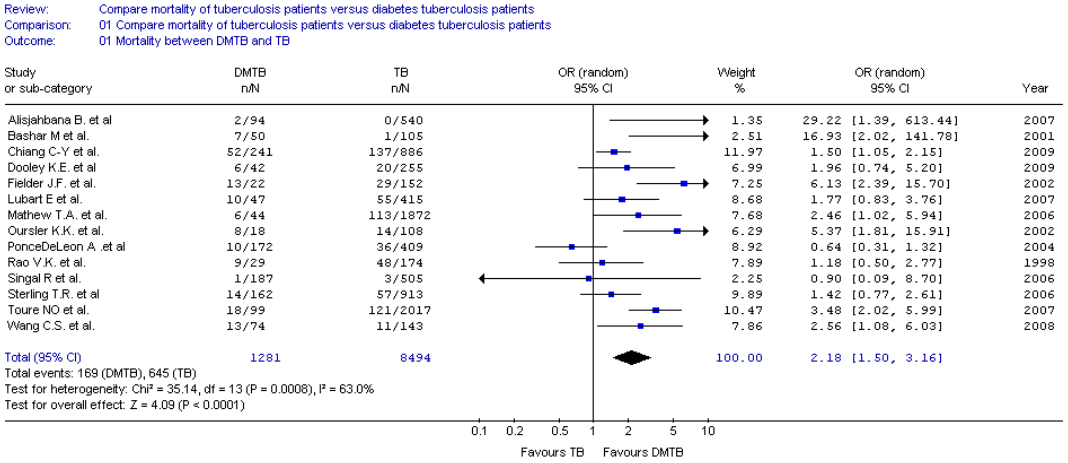

Figure 1: DMTB group show a significant higher mortality than TB group. Odds ratio is 2.18. 95%CI= [1.50, 3.16], Z=4.09 (p<0.0001), I^2=63.0%.

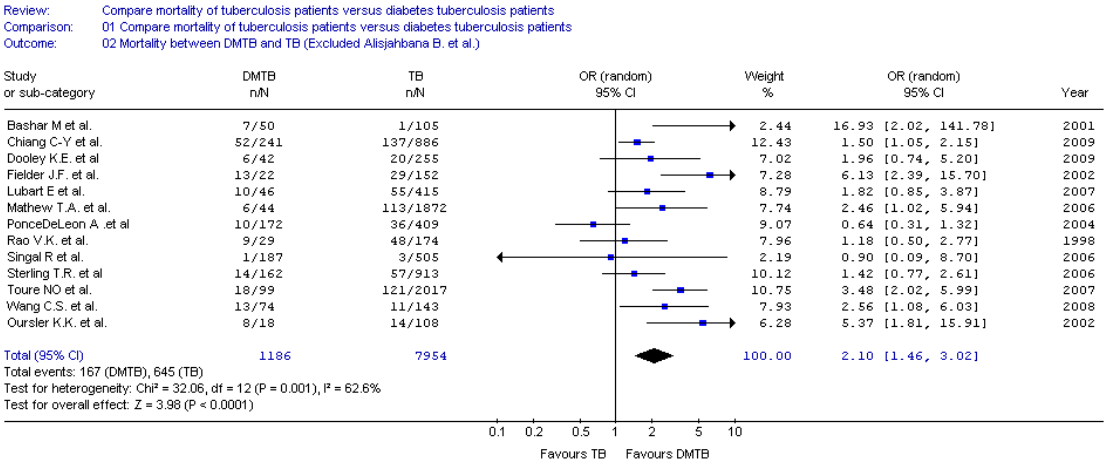

Figure 2: DMTB group show a significant higher mortality than TB group. Odds ratio is 2.10. 95%CI= [1.46, 3.02], Z=3.98 (p<0.0001), I^2=62.6%.

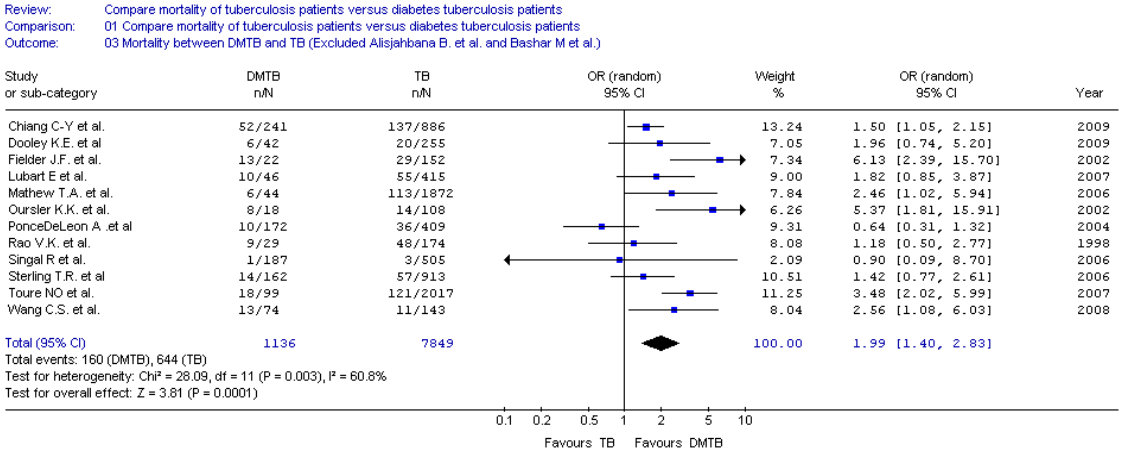

Figure 3: DMTB group show a significant higher mortality than TB group. Odds ratio is 1.99. 95%CI= [1.40, 2.83], Z=3.81 (p=0.0001), I^2=60.8%.

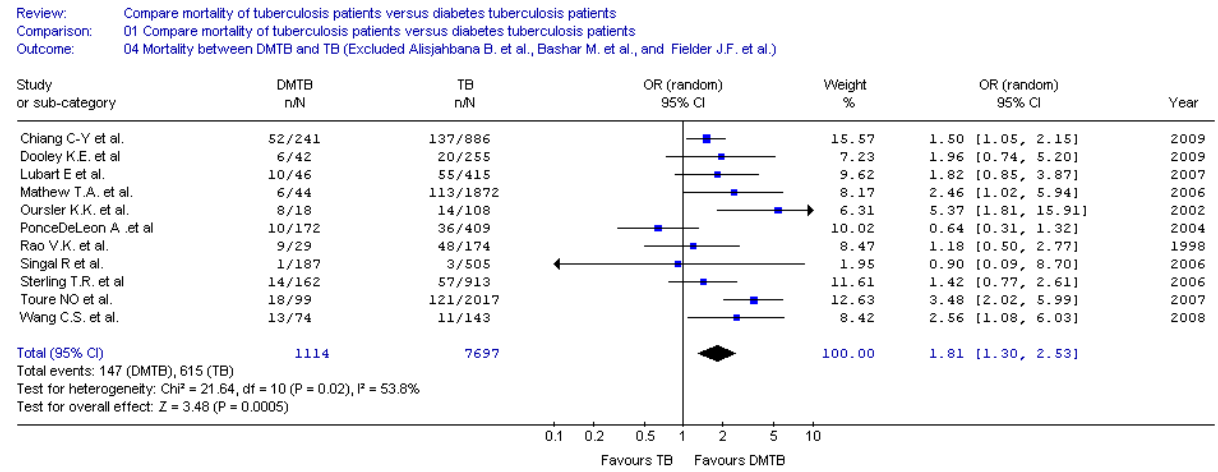

Figure 4: DMTB group show a significant higher mortality than TB group. Odds ratio is 1.81. 95%CI= [1.30, 2.53], Z=3.48 (p=0.0005), I^2=53.8%.

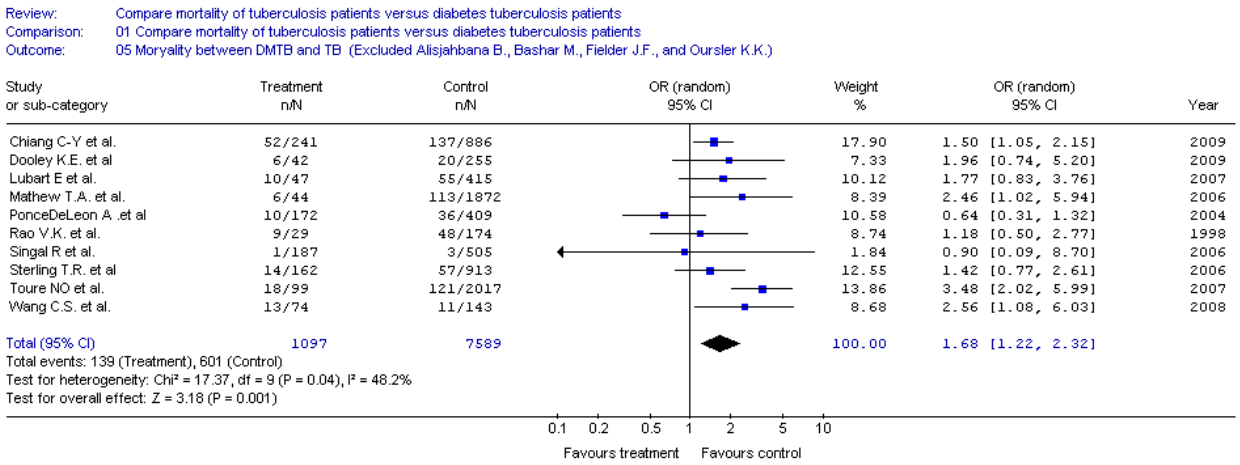

Figure 5: DMTB group show a significant higher mortality than TB group. Odds ratio is 1.68. 95%CI= [1.22, 2.32], Z=3.18 (p=0.001), I^2=48.2%.

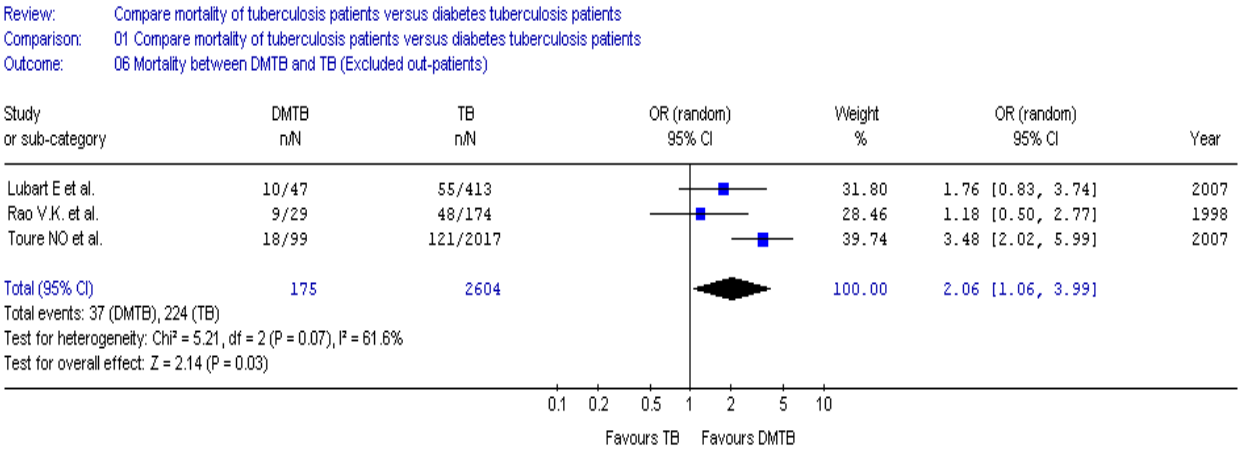

Figure 6: DMTB group show a significant higher mortality than TB group. Odds ratio is 2.06. 95%CI= [1.06, 3.99], Z=2.14 (p=0.03), I^2=61.6%.

Discussion

Diabetes Impact of the Pulmonary Tuberculosis

Diabetic patients were more likely to present with cavitary nodules and lower lung field TB. The PTB-DM group had higher frequencies of fever and haemoptysis than the PTB group. The PTB-DM group also had significantly higher frequencies of consolidation and cavity in terms of lung lesions. Other studies also reported no difference in the symptomatology or clinical presentation of TB patients with or without diabetes. However, there are reports that TB might progress rapidly in diabetic patients [28]. Diabetes may impact the pulmonary tuberculosis treatment and its mortality of tuberculosis [25].

Causes of heterogeneity

When we analyze the data in these selective papers by Review Manager, statistical software, heterogeneity will be generated. Heterogeneity may be due to chance, or unreliable data from the scale used to measure the treatment effect. It may also be due to variety of treatment characteristics, which can be investigated and/or patient-level covariates which can also be investigate it. If none of the above account for it, unexplainable. Rather than explain or explicitly adjust for variation between studies, one can pool studies using a random effects model which allows for variation in the underlying effect size between studies to be taken into account. In our searched papers, there is the difference of the sample sizes among studies [29]. In the four papers, sample size and patient's quantity collected were more than 1000. Only three papers determine the mortality rate and predictors of mortality among patients hospitalized [19,26,27]. In some studies, records of patients are in the period of 5 years [21,24,27]. But in some studies, records of patients are shorter as 2 to 3 years [17,20,21,27]. The parts of papers are related to retrospectively reviewing or retrospective cohort studies [22,23]. This is why the validity of pooling studies will generate heterogeneous treatment outcomes [30-38].

Died Risks of Pulmonary Tuberculosis

In the 14 papers we adopted, there were 8 papers favoring DMTB with a higher mortality and 6 papers without any significant difference between DMTB and TB groups.

Conclusion

There is a paucity of published reports regarding the mortality among TB patients with associated DM. Diabetes is one of the risk effects on the tuberculosis patients, which arises their mortality. Tuberculosis patients with diabetes have the higher mortality than tuberculosis patients without diabetes.

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